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Cost-effectiveness of screening for Severe Combined Immunodeficiency (SCID) in the NHS Newborn Blood Spot Screening Programme.

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EXECUTIVE SUMMARY

Background

Severe combined immunodeficiency (SCID) is a rare treatable genetic disorder that affects the development of functional T cells and B cells in infants and if left untreated results in repeated severe infections and death within the first few years of life. Patients are currently identified symptomatically through presentation with repeated infections or pre-symptomatically if there is a known family history of the condition, in the UK around 30%.

The standard treatment for SCID is hematopoietic stem cell transplantation (HSCT) which restores immune function. Gene therapy has also been shown to be successful and is currently used on a clinical trial basis for two of the genetic forms of SCID. Patients with the second most common form of SCID, ADA-SCID can also be treated with enzyme replacement therapy which is not curative but can stabilise patients. Analysis of the outcomes of HSCT have shown survival rates are higher in those who are transplanted in the first 3.5 months of life, due to a family history of the disorder, compared to those transplanted later. There is also evidence that long term outcomes are also improved from an early diagnosis and treatment. Due to the benefits of an early diagnosis there has been an interest in developing a newborn screening test that can be used in a population based screening programme.

A screening method that measures the number of T-cell receptor excision circles in a dried blood spot has been developed that accurately diagnoses affected SCID individuals. This method is currently used in the US to screen for SCID. A pilot conducted in the UK has also shown the test to have a high sensitivity to SCID in line with the results from the US. However, the screening test also identifies infants without SCID that potentially have other immunological problems.

Methods

A decision model has been developed to assess the incremental costs and health benefits and cost-effectiveness of including screening for SCID in the NHS Newborn Blood Spot Screening Programme compared to no SCID screening. The analysis is undertaken from the perspective of the NHS and Personal Social Services. The analysis focuses on the health benefits to the child expressed in quality adjusted life years. Costs and benefits are discounted at the standard rate of 3.5% in the base case.

The parameters used in the economic model are derived from the published literature obtained from reviews of the economic and clinical evidence relating to SCID screening. Systematic reviews undertaken in support of this assessment are reported in a companion report "Systematic reviews of screening for Severe Combined Immunodeficiency (SCID) in the NHS Newborn Blood Spot Screening Programme: Incidence, screening test characteristics and the effectiveness of treatments". Evidence from the literature is supplemented by routine data sources, NHS reference costs, expert judgement and with access to data supplied from the two specialist childcare centres that currently treat SCID patients in the UK, Great Ormond Street Hospital for Children (GOSH) and the Great North Children's Hospital in Newcastle.

Probabilistic sensitivity analysis, scenario analyses, threshold analyses and expected value of information analysis are used to generate estimates of cost and health outcomes and investigate the impact of uncertainty and assumptions in the model.

Results and conclusions

Screening for SCID as part of the NHS Newborn Blood Spot Screening Programme is predicted to prevent early mortality in affected infants. For the UK as a whole and with complete uptake of screening, it is estimated that 17 (14, 22) newborns with SCID may be detected annually, leading to a reduction in

mortality of 6.4 (4.0, 9.7) newborns per year and a total gain of 184 (118, 274) discounted quality adjusted life years (QALY). It is estimated that screening for SCID would cost approximately £3.0 million per year, with discounted lifetime health and social care costs increasing by an estimated total of £3.2 (£2.3, £4.4) million for each annual cohort (inclusive of the above immediate screening cost). The baseline estimate of cost effectiveness of screening for SCID is £17,600 per QALY gained, with a 71% and 99% probability of this being better than a cost effectiveness threshold of £20,000 and £30,000 respectively.

It is estimated that screening will identify 260 (25, 764) true false positive cases who will undergo confirmatory testing followed by an all clear result. The evidence concerning impact of false positives on quality of life and parental preferences is mixed, therefore the baseline cost effectiveness estimates make no quality of life adjustment for this group.

The programme would also be expected to identify approximately 7 (1, 21) preterm newborns with TCL and 26 (9, 50) newborns with non-SCID TCL of other causes. Many of these newborns may be expected to show symptoms or be otherwise diagnosed in the absence of screening. However it is estimated that 7 (2, 16) newborns might be identified by screening that would otherwise be healthy at birth. There is currently no evidence to suggest that early diagnosis can benefit these children and no relevant UK evidence on incidence. In the Californian SCID screening programme, around half had resolved within the one to 5 year follow up period and half were either still being followed up or had been lost to follow up.

The results of the analysis are highly sensitive to the discount rate used. The use of a 1.5% discount rate for both benefits and costs results in a lower cost effectiveness of £11,700 per QALY, whilst mixed discounting of 1.5% for health benefits and 3.5% for costs improves cost effectiveness further to £10,300 per QALY gained. In both cases the probability that cost effectiveness is better than £20,000 per QALY rises to over 99%. This improved cost effectiveness is due to the majority of costs for screening and transplantation occurring in the first year

and not being subjected to discounting. Whereas the QALY benefits of the intervention are spread over the patient's life and are discounted less with a reduced discount rate. NICE recommends that public health interventions use 1.5% for both costs and benefits for this reason. NICE also recommends that appraisal committees can consider a sensitivity analysis with a discount rate of 1.5% for benefits and 3.5% for costs when the intervention has a substantial and sustained impact on health.

The key uncertainties highlighted by sensitivity analysis are the cost of the TREC test, the incidence of SCID, post HSCT mortality rates in the early diagnosed population, the length of stay in hospital of the early diagnosed SCID patients and the proportion detected by family history in the absence of screening.

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1 INTRODUCTION

Severe combined immunodeficiency (SCID) is a rare treatable genetic disorder that affects the development of functional T cells and B cells in infants and if left untreated results in repeated severe infections and death within the first few years of life. Estimates of UK incidence have been suggested at between 1:40,000 and 1: 48,000 newborns. SCID is caused by a number of different genetic mutations which can affect the treatment and outcomes of treatment. Patients are currently identified symptomatically through presentation with repeated infections or pre-symptomatically if there is a known family history of the condition. In the UK around 30% of cases are currently identified due to a family history of the disorder (1, 2).

The standard treatment for SCID is hematopoietic stem cell transplantation (HSCT) which restores immune function. Gene therapy has also been shown to be successful and is currently used on a clinical trial basis for two of the genetic forms of SCID. Patients with the second most common form of SCID, ADA SCID can also be treated with enzyme replacement therapy which is not curative but can stabilise patients. Gene therapy has also recently been licensed for ADA SCID patient and offers an alternative curative treatment for patients without a well matched family donor (MFD). Analysis of the outcomes of HSCT have shown survival rates are higher in those who are transplanted in the first 3.5 months of life compared to those transplanted later (3, 4).These patients have often been diagnosed before they are symptomatic due to a family history of the disorder. There is also evidence that long term outcomes are also improved from an early diagnosis and treatment (5). Due to the benefits of an early diagnosis there has been an interest in developing a newborn screening test that can be used in a population based screening programme.

A screening method that measures the number of T-cell receptor excision circles (TRECs) in a dried blood spot has been developed. Studies have shown it to accurately diagnose affected individuals from newborn dried bloodspots (DBS) and to have a high sensitivity and specificity (6). This method is currently used in

32 states in the US to screen for SCID in their newborn screening programmes. There is however, a lack of uniformity on the TREC assay protocols and test algorithms among individual newborn screening programmes in the US as most have been locally developed laboratory tests (7). A test has been developed by PerkinElmer which would be used in the UK. A pilot conducted on newborn DBS from normal and SCID patients in the UK have shown the test to have a high sensitivity to SCID in line with the results from the US (6).

The screening test also identifies infants without SCID that have low TREC levels and T-cell lymphopenia (TCL) for other reasons. These include other congenital syndromes such as DiGeorge, Trisomy 21, and Ataxia-Telangiectasia, cases where the low TREC levels are due to other conditions such as cardiac or gastro-intestinal conditions, cases where the low TREC levels are due to the infants being pre-term and finally a group that have been identified as variant SCID or idiopathic SCID (7, 8).

A decision model has been developed to assess the cost-effectiveness of including TREC screening for SCID in the NHS Newborn Blood Spot Screening Programme. The analysis is undertaken from the perspective of the NHS and Personal Social Services (PSS) with health impacts incurred by patients with SCID expressed as quality adjusted life years (QALYs). Evidence to inform the model parameters was found from systematic reviews of the literature, expert opinion and evidence from routine data sources. Systematic reviews of SCID incidence, treatment effectiveness and screening test characteristics are presented in a companion report (9).

2 REVIEW OF ECONOMIC ANALYSES

Four economic analyses of newborn screening for SCID were identified in a topic search which included citation searching (10-13). The four economic analyses are summarised in Table 1.

In addition a non-peer reviewed white paper by Chan (10) presents cost minimisation analysis of screening for SCID in the UK using the T-cell receptor excision circle (TREC) test. A review of this white paper (10) undertaken by the authors prior to the economic analysis presented here and commissioned by PHE on behalf of Anne Mackie and the UK National Screening Committee is summarised below.

The paper compares the costs of treatment and management of non-screen detected SCID with the costs of screening, treatment, and management of screen detected SCID. The analysis suggests that screening for SCID would be cost saving in the UK. This cost benefit of screening is derived from projected lower treatment and management costs for patients detected early before they develop the symptomatic infections compared to being detected later and it is estimated that these savings offset the costs of the screening programme.

While the paper suggests that screening for SCID would be cost-saving in the UK there are a number of methodological issues that undermine the reliability and credibility of the results:

1. In the absence of screening a proportion of SCID cases are detected through a family history of SCID. These patients will tend to be diagnosed early before they develop infections. The Chan analysis (10) assumes all non-screened patients are diagnosed late and incur the associated higher costs. If a proportion of patients are diagnosed early because of a family history the costs of not screening are likely to be lower than those estimated by Chan and therefore the marginal benefit of screening in terms of both costs and effects will be lower.

2. The Chan analysis (10) used an incidence rate of 1 in 66,000. This was derived from the reported incidence in the screening programme in California (8) . However, an incidence rate without screening of 1 in 48,000 has been estimated for the UK based on the number of patients seen in the two UK treatment centres (2). A higher incidence rate is likely to increase the benefit of screening as more cases will increase the total cost differential between those diagnosed early and those diagnosed late
3. It is unclear how the cost estimates used in the Chan analysis (10) for the UK screening programme are derived as they are not referenced or described in detail. Therefore it is not clear whether the £7 for a screening test and £250 for the confirmatory test are realistic estimates of the cost if screening were to be implemented in the UK. In addition no set up costs have been included.

4. It is unclear how the costs of clinical care for a SCID patient were calculated. Compared to a previous study by Chan et al (12) the difference between costs for screened and unscreened patients seems to be higher. In the Chan et al study (12) the cost of a late HSCT was estimated to be 3 times as expensive as an early HSCT. In the UK study the cost of a late HSCT was between 4 and 6 times as expensive as an early HSCT. Based on a survey of parents with children with SCID a symptomatically detected patient was estimated to spend twice as long as an inpatient identified early (12). In the Chan analysis (10) the non-screened patient is estimated to spend 3-4 times as long as an inpatient as a screened (or early diagnosed) patient.
5. Productivity costs were also included which were to represent "the loss of productivity represents the loss of an average monthly salary (or Gross Domestic Product (GDP)) of one parent due to care-taking. This value may vary accordingly to the parent employment status". The cost of a parent taking time off are estimated at £4,000 per month. This is substantially higher than estimates of the mean yearly salary of £26,500 compared to the £48,000 implied by a £4,000 a month salary.

6. The experience of screening for SCID using TREC has shown that it also identifies a number of different conditions. This is not adequately dealt with in the Chan analysis (10). The potential costs and benefits of this should be included in order to estimate the potential cost-effectiveness of screening for SCID.

Table 1. Summary of published health economic studies of screening for SCID

Study	Country	Type	Model Type	Outcome		ICER (life years)	ICER (QALYs)	Additional life years (US)	Total screenig programme costs (US)
Ding et al (2016)	US	CEA	Decision tree	ICER	Cost per life year saved	$35,311	N/A	555	$32,624,000
Chan et al (2011)	US	CEA	Decision tree & Markov model	ICER	Cost per QALY	$25,429	$27,907	880	$22,377,000
McGhee et al (2005)	US	CEA	Decision tree	ICER	Cost per QALY	Threshold analysis		760	$23,920,000
Chan et al	UK	Cost minimisation analysis		Total costs		N/A	N/A	-	-

The other three economic analyses were full cost-effectiveness analyses and were all US based (11, 12, 14). They all looked at the inclusion of TREC screening for SCID in the US newborn screening programme. Two were decision trees (11, 14) and one used a decision tree for the screening part of the analysis and a markov model for the longer term outcomes (12). Two of the studies used cost per QALY as the outcome (12, 15) and one presented cost per life years gained as the outcome (11). In the two studies that used QALYs, these were estimated from published values for bone marrow transplants for oncologic disease and gave a value of 0.95 for a successful HSCT and 0.8 if IG was required (15). The second study that uses QALYs estimated them from published studies on cystic fibrosis, sickle cell anaemia, paediatric HIV-AIDS, MCAD and leukaemia. The actual QALY figures used are not reported (12). The McGhee et al study (15) does not provide an incremental cost effectiveness ratio (ICER) but provides a threshold analysis of the probability of screening being cost-effective against willingness to pay (WTP).

No studies included any set-up costs associated with including a new test in the screening programme. Only one study specified that the cost per test included labour costs (12). All studies assume that treatment costs (HSCT costs) are lower

in the earlier identified group. The difference ranged from about double the costs to six times the cost. The study with the biggest difference was the Chan cost minimisation study. However, it is unclear how these costs were calculated (10). No studies, apart from the Chan cost minimisation analysis, included productivity costs. One study (11) included the costs of treatment with enzyme replacement therapy for ADA-SCID patients.

As shown in Table 2, two of the full cost-effectiveness analyses included a proportion detected due to a previous family history (11, 15). This is an important parameter to include as without it the benefits of screening will be overestimated as those detected by a family history already benefit from an earlier diagnosis in the absence of screening. All studies used both a high sensitivity and specificity for the screening test. Only one of the cost-effectiveness analyses included prevalence of non-SCID TCL (11). All studies assumed that survival was improved in the early identified patients compared to the later identified patients but the survival rates varied between the studies.

Table 2. Included parameter values

	Ding et al	Chan et al 2011	McGhee et al	Chan (UK)
Birth prevalance of SCID	1/58,000	1/75,000	1/50,000	1/66,000
Proportion of SCID cased etected without NBS	0.203	-	Included but not reported	
Birth prevalance of non-SCID TCL	1/14,000	-	-	1/20,000
Sensitivity of the overall screen process	0.995	0.99	0.99	0.99
Specificity of the overall screen process	0.9997	0.99	0.96	0.99
Cumulative surivial early identified	0.88	1	0.95	-
Cumulative survivial late identified	0.54	0.375	0.72	-

Both the McGhee (14) and the Chan et al study(12) report results for the whole of the US. The Ding et al study (11) is only for Washington State but the results have been multiplied by the US birth rate to allow comparison between the three

studies. Overall screening costs are higher and the incremental life years gained are lower than in the two other studies. This accounts for the higher ICER in the Ding et al study (11) compared to the Chan et al study (12) ($35,000 vs $25,000). Only the Ding et al study (11) has been conducted since screening has been implemented in the US and provides the most complete economic analysis.

3 HEALTH ECONOMIC MODELLING METHODS

3.1 Health economics overview

A cost-effectiveness model was built to estimate the impact of including SCID in the NHS Newborn Blood Spot Screening Programme. A cost-effectiveness model provides the framework that enables evidence from a number of sources to be brought together to estimate the costs and benefits of a new intervention. The output of the model includes the incremental costs and health benefits of screening versus not screening which are used to calculate the incremental cost-effectiveness ratio (ICER). This analysis focuses on health impacts for SCID patients expressed in quality adjusted life years (QALYs). The model takes an NHS/PSS perspective, whereby only costs that accrue to the NHS or PSS are included. Costs and benefits are discounted at the standard rate of 3.5% in the base case (16, 17) and costs are at 2014/15 prices unless otherwise specified. Costs were inflated where necessary by the hospital and community health services index (18).

The primary motivation for screening for SCID is to enable earlier diagnosis and treatment. Earlier treatment has been associated with improved survival, improved long term quality of life and a reduction in the short term costs of treating patients primarily due to reduced length of stay (19, 20). Screening however incurs additional costs and also has the potential to identify non-SCID cases, impacting on diagnosis, management and treatment costs and effects in these patients (8). This analysis seeks to clarify some of the trade-offs inherent in screening for SCID.

The model consists of a decision tree, a simplified version of which is presented in Figure 1 together with a full tree presented in APPENDIX A that shows the separate handling of ADA-SCID. For patients that survive transplantation a lifetable with a horizon of 100 years is used to estimate lifetime costs and QALYs. In Figure 1 the decision to screen or not is represented by the square node at the extreme left. The no screen (status quo) is represented by the lower branch,

where newborns have a chance of having SCID or not equal to the SCID birth prevalence. Newborns with SCID and no prior known family history will present symptomatically with a late diagnosis with a high risk of mortality prior to and post HSCT. Survivors will have long term costs and quality of life outcomes associated with a late HSCT. A proportion of SCID patients may be diagnosed asymptomatically, primarily by family history, these may have an early diagnosis, may still die pre HSCT with HSCT survivors having cost and QALY outcomes associated with the early diagnosis. SCID patients are further separated into two groups – those with ADA-SCID and those with all other types of SCID. Patients with ADA-SCID have an additional option for gene therapy if no matched family donor is available for HSCT and their survival outcomes differ to those in the (non-ADA) SCID arm. The full decision tree showing options for ADA-SCID patients is included in Appendix A.

The screening option is represented in the upper branch of the decision tree where the TREC test is applied to the DBS sample obtained from newborns with an associated cost. For newborns with SCID, those with a true positive screening result (SCID screening sensitivity) will receive an early SCID diagnosis and treatment with outcomes assumed to be as for the 'no screening, family history' branch. Newborns with SCID that are not identified by screening (1-sensitivity) are assumed to arise symptomatically with outcomes as for a late diagnosis, that is 'no screening, no family history' branch. This is a conservative assumption as a proportion of these screen missed cases might be expected to be identified through family history. Newborns with no SCID and a true negative screening test result will have normal health outcomes and incur no other additional costs or resources. Newborns with no SCID and an initial false positive for SCID screening result will undergo further confirmatory testing that is assumed to identify patients as either healthy (true false positive for SCID) or with a range of other non-SCID TCL.

The parameters used in the economic model are presented in Table 3 and Table 4 together with references. Costs are given in the text with further details given

in APPENDIX B. The assumptions and data used to inform each model parameter are further described below.

Figure 1. Screening for SCID decision tree

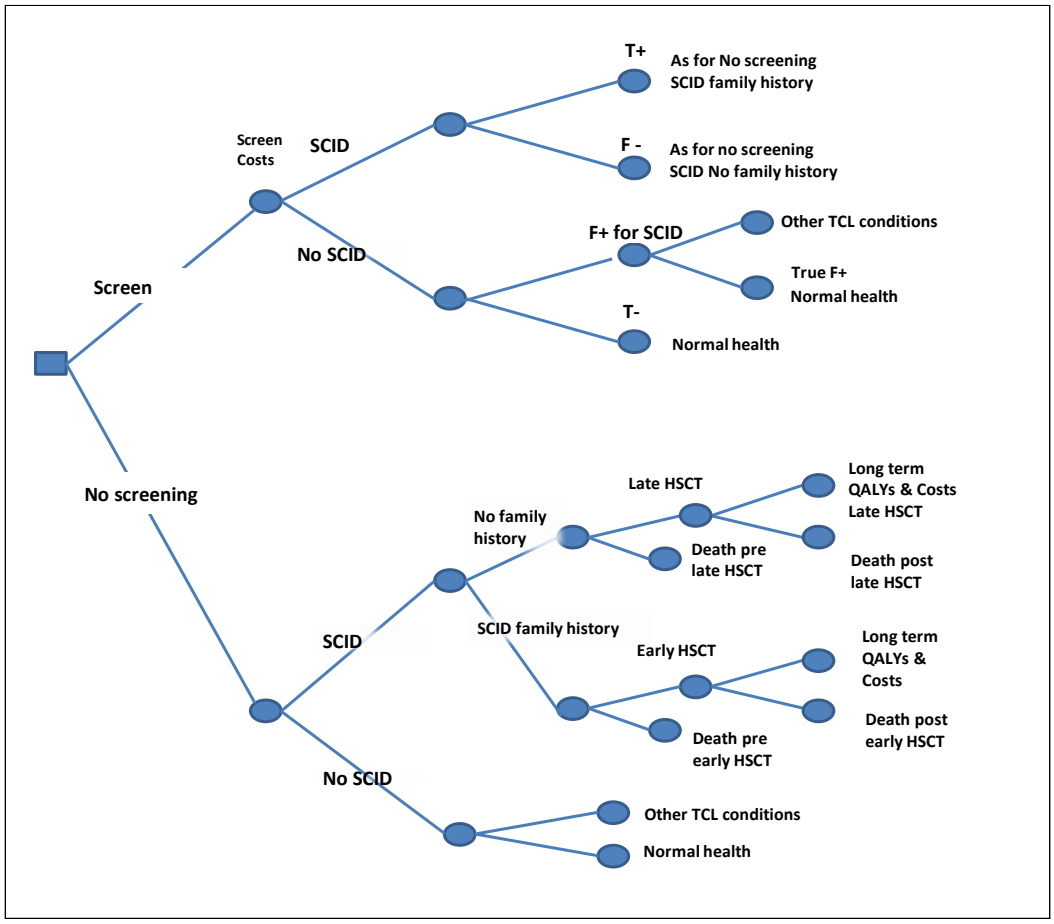


Table 3. Model parameters

Parameter	Value	Distribution	Reference
Number of births (UK)	780835	N/A	(21-23)
Incidence of SCID	1: 49000	Beta (82; 4,012,522)	(2)
Incidence of undiagnosed SCID	1: 521000	Beta (1.5; 780,833)	(2)
Incidence of syndromes	1: 51000	Beta (##)	(8)
Incidence of secondary conditions	1:134000	Beta (##)	(8)
Incidence of variant SCID	1: 174000	Beta (##)	(8)
Incidence of preterms	1:116000	Beta (##)	(8)
Specificity of the screening process	1	N/A	
Sensitivity for SCID	0.99	Beta (1567.17; 15.83)	(6)
Presumptive positives (20 copies/µl)	0.034%	Beta (1.71; 5079)	(6)
Proportion of variant and syndromes not diagnosed at birth	0.33	Beta (7; 14)	(8)
Proportion of SCID patients with a family history	0.30	Beta (25; 57)	(2)

Proportion of SCID ADA-SCID	0.17	Beta (14; 82)	(2)
Proportion of SCID patients with a matched family donor available	0.25	Beta (3.5,10.5)	(24)
Pre HSCT mortality (late diagnosed)	0.35	Beta (31; 17)	(4)
Pre HSCT mortality odds ratio (early diagnosed)	0.03	Lognormal (-4.03; 1.05)	(4)
HSCT mortality (late diagnosed)	0.39	Beta (19; 12)	(4)
HSCT mortality odds ratio (early diagnosed)	0.15	Lognormal (-2.1; 0.6)	(4)
ADA-SCID pre HSCT morality (late diagnosed)	0.21	Beta (38, 10)	(4, 24)
ADA-SCID pre HSCT mortality odds ratio (early diagnosed)	0.06	Lognormal (-3.31; 1.07)	(4)
ADA-SCID HSCT mortality (matched family donor) (late diagnosed)	0.33	Beta (8; 4)	(4)
ADA-SCID HSCT mortality odds ratio (matched family donor) (early diagnosed)	0.11	Lognormal (-2.91; 1.2)	(4)
ADA-SCID Gene therapy mortality	0.05	Beta (18; 1)	(4)
Number of days HSCT	54.0	N/A	(25)
Early diagnosis - Total days non-critical care	82.6	Gamma (19.73; 4.19)	(26)
Early diagnosis - Total days critical care	3.96	Gamma (1.35; 1.92)	(26)

Late diagnosis - Total days non-critical care	144	Gamma (55.39; 2.6)	(26)
Late diagnosis - Total days critical care	8.19	Gamma (8.9; 0.92)	(26)
Early diagnosis - Gene therapy - Total non-critical care preGT	12.25	Gamma (22.97; 0.53)	(26)
Early diagnosis - Gene therapy - Total critical care preGT	0.25	Gamma (1.94; 0.13)	(26)
Late diagnosis - Gene therapy - Total non-critical care preGT	45.7	Gamma (69.72; 0.66)	(26)
Late diagnosis - Gene therapy - Total critical care preGT	4.37	Gamma (5.93; 0.74)	(26)
QALYs - early diagnosis	0.955	Beta (212.39; 6.62)	(27)
QALYs - late diagnosis	0.825	Beta (165.35; 21.89)	(27)
## - Academic in confidence			

3.2 Epidemiology of SCID

The annual number of births for England and Wales, Scotland, and Northern Ireland was estimated from the average of 10 years, 2005-2015, for both sexes from the relevant authority (21-23)

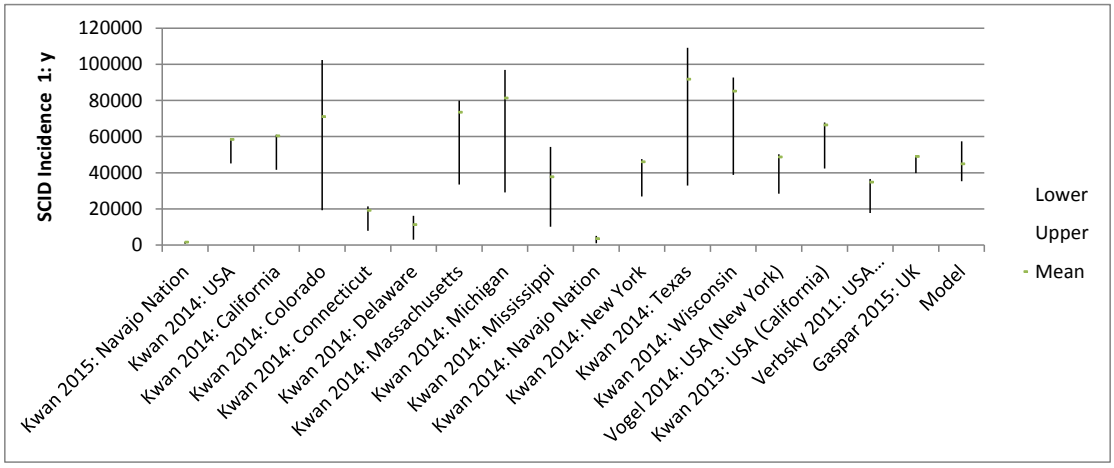
A systematic review of SCID incidence is presented in the companion report (9). The incidence of SCID found in US newborn screening programmes demonstrates a high degree of variability between different states, with an overall average of 1 in 58,000 varying between 1 in 11,000 in Delaware to 1 in 92,000 in Texas. In the Navajo Nation with a known founder mutation gene the incidence is much higher at 1 in 3,500 (8). In the California screening programme the SCID incidence is 1:54,000 (1:83:000, 1:40,000) (2, 8).

The only information concerning the incidence of SCID in the UK population is from an unpublished study, based upon the number of cases referred to the two specialist centres in the UK that treat SCID, namely Great Ormond Street Hospital for Children (GOSH) and the Great North Children's Hospital in Newcastle. Eighty two cases were referred to the two UK centres between 2008-2012 giving an incidence of 1 in 48,000 (2). It is conjectured that the true incidence of SCID in the UK may be higher if infants die due to SCID before they are diagnosed and referred to the specialist centres. There is no empirical evidence available to estimate the extent of this ascertainment bias. The economic model assumes a mean of 1.5 SCID cases might be missed each year (Beta distribution B(1.5,780000)), based upon expert clinical judgement. Using these assumptions the expected UK incidence of SCID increases to approximately 1 in 40,000 (95% CI 1:58000, 1:35000). Figure 2 presents the SCID incidence rates reported in the international literature, including the unpublished UK study by Gaspar et al alongside the SCID incidence estimate used in the SCID cost effectiveness model.

A proportion of SCID patients are currently diagnosed before symptoms arise, principally via a family history. These patients have the benefit of being diagnosed early with improved outcomes compared to those patients diagnosed

with symptoms. Out of the 82 cases identified in the UK between 2008 and 2012, 25 of these (≐30%) were identified due to a family history (2).

Figure 2. Incidence of SCID, international evidence and the SCID model



Patients with ADA SCID have additional treatment options compared to patients with other forms of SCID. In order to model these it was necessary to estimate the proportion of SCID patients that have ADA SCID. As the distribution of types of SCID types differs in different countries we used the proportion of ADA SCID in the cohort of 82 SCID patients identified in the UK between 2008 and 2012. Of these 14 (17%) had ADA SCID. This is in line with estimates from the US with ADA SCID accounting for 10-15% of patients identified via screening (7, 8).

3.3 Epidemiology of non-SCID TCL conditions identified through screening for SCID.

The incidence of other conditions detected by the screening test following flow cytometry was estimated from the Californian screening programme data (2, 8). The Californian data is relevant to screening in the UK as it uses a relatively low TREC cut-off value of <40 copies/μL and a relatively low cut-off of <15000 T Cell/μL following flow cytometry. Other states in the US use both a higher TREC cut-off value and a higher cut-off value at flow cytometry. The use of higher cut-off values is associated with an increase in the number of patients labelled as having T-cell lymphopenia and may increase the incidence of the other conditions detected by TREC screening.

As there is uncertainty associated with generalising from the Californian data to incidence of these conditions in the UK, the denominator used in the sampling of the incidence in the model was taken to be 10% of the 3 year Californian birth rate. This will increase the uncertainty of the incidence within the model. As there is little evidence to indicate whether the mean incidence in the UK will be higher or lower than in the Californian population, this is assumed to represent an unbiased estimate of the mean.

3.4 Screening test

The TREC screening test has a two stage initial test process. In the first stage a punch from the DBS is tested in singlicate against the TREC cut-off value. For those samples that are below an initial TREC cut-off value a second and third punch are taken from the same DBS and these are tested in duplicate against both a beta-actin and a second TREC cut-off value (which may be the same or different from the initial cut-off value). Samples that are below the TREC cut-off values but within normal beta-actin in both stages are defined as presumptive positive results and are referred to flow cytometry (6). We have assumed that the cost of a screening test (basecase £3.50) covers both stages of the testing process (2).

The Adams et al study (6) is used in estimating the number of presumptive positive cases. The Adams et al study (6) tested UK DBS samples with the PerkinElmer test and calculated the number of presumptive positives results that would need to be referred to flow cytometry at different cut-off rates. At a cut-off of 20 copies/μL the presumptive positive referral rate to flow cytometry would be 0.04%. Which if multiplied by the UK birth rate would result in 312 referrals to flow cytometry per year. The presumptive positive rate is higher than the presumptive positive referral rate in California which is 0.02% (8). It is assumed that this will result in higher proportion of cases being referred to flow cytometry being classed as normal following flow cytometry than in California rather than a higher incidence of other non-SCID T-cell lymphopenia.

While studies have shown the TREC test to have a sensitivity of 1 a slightly lower sensitivity of 0.99 was used in the model to take into account the potential for false negatives in a population based screening programme. The overall specificity of the overall screening process including flow cytometry is estimated at 1 for non T-cell lymphopenia.

3.5 Survival of SCID patients

Five studies were identified that looked at the difference in survival in patients either diagnosed or transplanted by <3.5 months (5, 28, 29) or due to a family history (4, 30) and those that were diagnosed later. All the studies show an improvement in survival for those transplanted earlier. Out of the studies the Brown et al study (4) was selected for use in the model as it is a UK based study and it was the only study that explicitly considered mortality both pre and post HSCT. The other studies identified only provided survival estimates of those undergoing HSCT. It is important for the model to estimate both survival before and post HSCT in order to estimate the overall survival of patients in both the early and late diagnosed cohorts and also the different costs of treatment. One limitation of the Brown study (4) is that the study population were diagnosed between 1982 and 2010. Survival rate may have improved in both groups over this period due to better recognition of the disease and improvements in care. The post-transplant survival estimates slightly lower for Brown et al (4) in the late diagnosed group than for the other three studies that measured survival for those transplants pre and post 3.5 months (5, 28, 29). Brown et al (4) reported a survival rate of 61% in the proband/late diagnosed group compared to 70% in Dell Railey et al (5), 74% in Myers et al (29) and Pai et al (28) reports a range in the late diagnosed group from 50% survival in those who have an active infection at transplantation, to 82% in those who had a resolved infection at transplantation, to 90% survival in those who had never had an infection. It should be noted that both the Dell Railey et al (5) study and the Myers et al (29) study are both based on cohort of patients treated at Duke University Medical

Center. In the sibling/early diagnosed cohort the survival estimates are again slightly lower, 92% in Brown et al (4) compared to 94% in Pai et al (28) and 95-96% in the other two studies (5, 29).

The mortality following pre and post late HSCT is modelled as a proportion using the beta distribution, with the number of cases as reported in Brown (4). The model uses odds ratios to estimate pre and post-transplant mortality outcomes for early HSCT therapy. Odds ratio parameters are sampled from the lognormal distribution for the probabilistic analysis with mean and standard error estimated from the Brown study (4). The impact of pre and post mortality is further explored in threshold analyses described later.

Patients with ADA-SCID have two additional treatment options that are not available for other types of SCID. Firstly enzyme replacement therapy (ERT) can be used to stabilise patients before they undergo transplantation. It has previously been used long term in patients who did not have a well matched HSCT donor. However, with the introduction of gene therapy and with evidence of problems associated with long term ERT, it is now used in the UK to stabilise patients prior to them receiving definitive treatment of either HSCT or gene therapy. As those who are detected early already have a very low pre HSCT mortality rate we have assumed that ERT does not improve this. For those detected late we have assumed that ERT reduces the pre HSCT mortality rate. The UK clinical expert estimated that the mortality rate would be around 20% in this group. We adjusted the input parameters for the general late detected pre HSCT mortality to reduce it from 35% to 20%.

The second treatment option for ADA-SCID patients is gene therapy. While overall survival from HSCT is relatively high survival is influenced by the type of donor. Patients with a fully matched family donor have significantly better survival compared to those with a mismatched or haploidentical donor. For patients with ADA-SCID gene therapy can be used in patients without a fully matched family donor. A gene therapy product, Strimvelis, was licensed by the EMA in 2016 for use in those that do not have a fully matched family donor (31).

In addition patients in the UK have also been included in a trial for a separate gene therapy product.

In order to incorporate gene therapy for ADA SCID into the model a number of parameters needed to be estimated. Firstly, the clinical expert estimated that around 25% of ADA-SCID patients currently have a fully matched family donor (24). We modelled this proportion as a beta distribution based on the number of ADA-SCID patients in the UK 2008-2012 SCID cohort, 14, making this estimate highly uncertain.

Secondly the mortality rates of HSCT for both the early and late detected needed to be estimated. The Brown et al study (4) included mortality rates dependent on donor type for the proband and the sibling cohorts for all SCID types. We have assumed that the mortality rates for HSCT for ADA-SCID using a matched family donor in the proband/late detected and sibling/early detected is the same as for all SCID types in the Brown et al study (4). This gives an estimate of about 33% mortality in the late detected cohort, reduced from 39% in the all donor type cohort and 5.3% in the early detected cohort, reduced from 8.5% in the all donor type cohort. Odds ratios were then calculated based on the methods reported above.

Results from the gene therapy trials have so far shown a 100% survival rate. From the patient descriptions in the trials it is not clear how many were detected early compared to late but they did include those detected due to presenting with infections, suggesting a proportion of symptomatic late presentations in the population (32). Due to the 100% survival it appears the difference in survival found in HSCT between those identified early and late is reduced or eliminated. As these trials have all been relatively small we used the same mortality estimate for those detected early with a fully matched family donor of 5.3% for gene therapy in both those detected early and late. This assumption is explored with a scenario analysis described below.

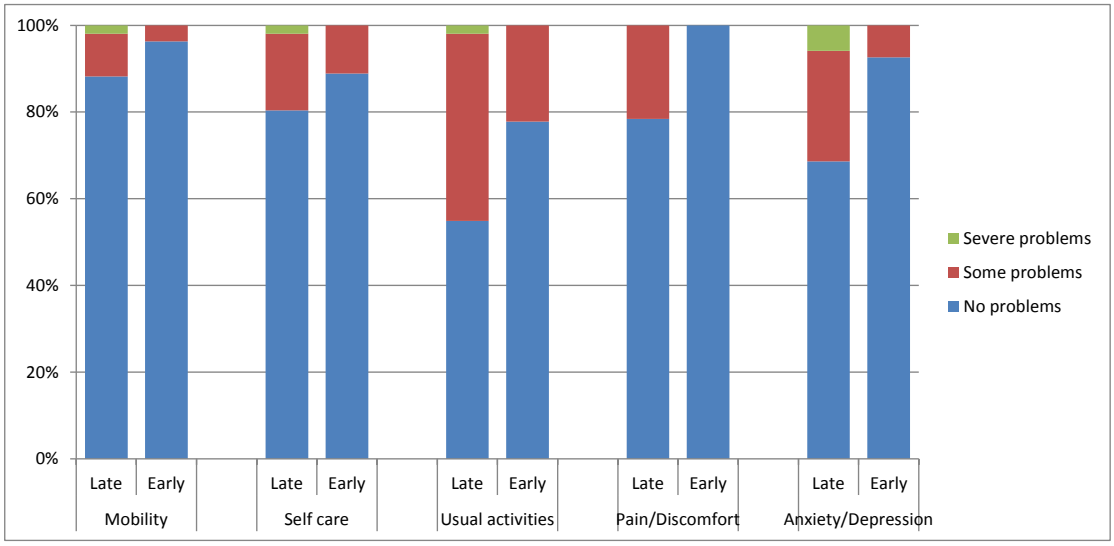
The model assumes that all deaths occur in the year in which HSCT takes place. This is a simplification as while the majority of patients die within the first year substantial proportion die between one and five years (5). However, the Brown et al (4) study did not give timings for the transplantation related mortality. The model also assumes that those patients that survive the year in which HSCT takes place have a normal life expectancy thereafter.

3.6 Quality of life of SCID patients

There are theoretical, methodological and practical difficulties in assessing the quality of life impacts of treatments in children and particularly in the very young populations typically involved in SCID transplantation. Whilst there exist a small number of HRQoL instruments specifically designed for use in children, including the PEDSQL (http://www.pedsql.org/) , the EQ5D-Youth (http://www.euroqol.org/eq-5d-products/eq-5d-y-youth.html) and Child Health Utility 9D (CHU9D) (https://www.shef.ac.uk/scharr/sections/heds/mvh/paediatric) , the only instrument with a utility valuation is the CHU9D. These methodological problems are exacerbated by practical difficulty in this setting that no HRQoL studies have been identified in the SCID transplant population. Whilst adjusting for quality of life may be methodologically controversial and open to perfectly valid criticism, not adjusting for quality of life would underestimate the potential benefits of early compared to late transplantation. For example if we do not attempt to adjust for quality of life, the assessment reduces to a life years gained model and potential benefits in long term morbidity associated with early transplantation compared to late transplantation will not be captured. In the face of these difficulties a pragmatic approach based around the EQ5D instrument is used, combining a probabilistic description of uncertainty in the baseline analysis, supported by a threshold analysis to explore the limiting impact of different HrQOL assumptions.

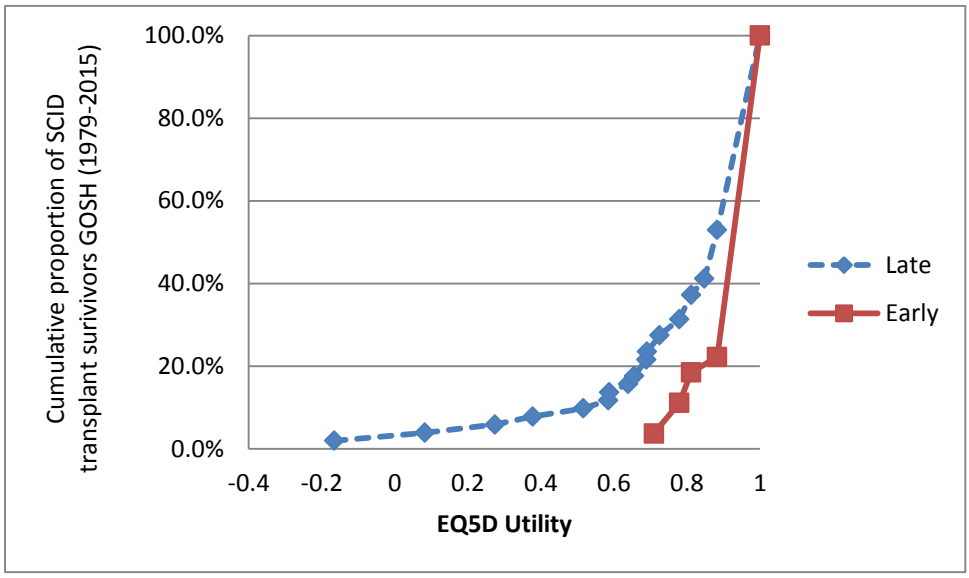
For the baseline analysis, the quality of life in SCID patients who receive HSCT was estimated by mapping information from a database of UK SCID patients onto the EQ-5D-3L health state descriptions (27). The quality of life assessments were based upon patients transplanted at GOSH between 2000-2015, including 27 patients diagnosed early and 51 patients with a late diagnosis. Specific assessments of mobility, self-care, usual activities, pain/discomfort and anxiety/depression were made by an immunologist for each patient on a three level scale approximating to no problems, some problems or severe problems. For 6 very young patients out of the 78, assessment of anxiety/depression were difficult, 5 out of these 6 patients were recorded as demonstrating no problems in any of the other four dimensions, no anxiety problems were also assumed. The EQ5D assessments for each dimension are presented in Figure 3 which demonstrates a consistent impact of early transplantation across all dimensions. The EQ-5D-3L time trade off valuations were applied to the health state profiles to derive health utility estimates.

Figure 3. EQ5D dimensions for early and late transplanted patients



The EQ-5D-3L time trade off valuations were applied to the health state profiles to derive health utility estimates. Figure 4 presents the distribution of EQ5D scores for early and late transplanted SCID patients. This shows that the outcomes following transplantation tend to be good for both early and late transplanted patients, though a small number of late transplanted patients tend to have more severe problems. The average health state utility for those diagnosed early was estimated at 0.96 (sd 0.09) compared to 0.82 (sd 0.25) for the later diagnosed patients. The model uses a beta distribution to represent uncertainty in QALY impacts based upon the average utilities. The model assumes that these health utility outcomes are maintained throughout life.

Figure 4. Cumulative distribution of EQ5D utility scores for early and late transplanted SCID patients



3.7 Long term outcomes and follow up

A number of studies were identified that looked at the long term clinical outcomes of patients undergoing HSCT (5, 33-37). Of these five included detail on a range of long term clinical outcomes. One (35) focused on long-term immune reconstitution and therefore may not fully report all clinically relevant

long term outcomes. Differences in outcomes between those transplanted early vs late were presented and discussed in the main text of only one of the studies (5)in a further four studies (34-37) data was presented in tables and/or appendices that allowed a comparison to be made due to patient level information on outcomes and the time of transplantation.

Data was extracted from the studies with individual data (34, 36, 37) in order to explore the possibility of synthesising the data. All complications/conditions mentioned in the tables were extracted and then grouped into different types of clinical events and treatments; Autoimmune/inflammatory, severe or recurrent infection, chronic HPV, gastrointestinal, nutritional support, skin conditions, respiratory/lung issues, neurologic issues, sight issues, hearing issues, dentition, endocrine problems, other conditions. The long term outcomes data table is provided in APPENDIX C. After extracting the data it was decided not to try to synthesise the data. This decision was made for a number of reasons firstly the numbers of patients in the studies were small, eight patients transplanted early and 24 late in both the Patel et al studies (34, 37) and seven early and 33 late in Mazzorali et al (36). Therefore, even when the clinical events were grouped this still led to very small numbers in each group. Secondly it was not clear if all events had been recorded in all studies, for example only Mazzolari et al (36) reported hearing issues. The studies also differed in the population included and the length of follow-up. While we have not synthesised the data we have tried to report where differences in outcomes between those transplanted early and late are consistent across the studies. It is assumed that ADA-SCID patients undergoing either HSCT or gene therapy have the same long term outcomes as general SCID patients.

Instead of synthesising data the Dell Railey et al study (5) was used for the majority of the long term outcome parameter. It was chosen as it was the largest of all the studies and it was specifically designed to look for differences in outcomes in patients with early versus late HSCT. The Dell Railey et al study (5) followed up with all patients that had been transplanted at Duke University

Medical Center between 1982 and 2008 and who had survived. 111 out of 124 survivors were reached for clinical follow-up. Follow up ranged from 6 months to 26 years with a median of 8.7 years. The outcomes included in the model are listed in Table 4. The considered healthy parameter was those that were considered healthy by their family. There are limitations to using one single centre study to estimate the long term outcomes as some outcomes are related to the underlying molecular type of SCID and different areas have different incidences of the different molecular types of SCID. For example, developmental delay is more common in the *RAG*1 or *RAG*2 deficiency and ADHD is more common in the ADA deficiency. The cohort of patients in the Dell Railey et al (5) study do not represent the same molecular type of SCID as that found in the UK.

Compared to other studies the patient cohort in the Dell Railey et al study (5) also seem to have lower rates of autoimmune or inflammatory problems than other studies (33) it also does not report on sight or hearing problems that are included in other studies.

For the costing element of the model the focus was on identifying outcomes that would require treatments or supportive care in order to try to fully estimate the long term resources and cost impacts of screening. Treatments in the studies included immunoglobulin replacement therapy, booster transplants, enteral feeding, standing antibiotics, steroids and anti-seizure medication (33). Treatments received by less than 5% of the cohort have been excluded from the model. The length and type of treatment for each complication was discussed with our clinical expert.

One outcome that was consistent across all studies was that patients diagnosed earlier were more likely to be classified as healthy or as having no problems following HSCT (5, 35, 36). This is consistent with the quality of life data described above which is higher in the early diagnosed cohort compared to the later diagnosed cohort. Patients with no problems were estimated to have fewer follow-up appointments.

Table 4. Long term outcomes parameters

Parameter	Early Diagnosed		Late Diagnosed		Reference
	Value	Distribution	Value	Distribution	
Requires immunoglobin	0.25	Beta (9; 27)	0.25	Beta (9; 27)	(38)
Requires immunosuppressive drugs (steroids)	0.056	Beta (4; 67)	0.056	Beta (4; 67)	(33)
Considered healthy	0.88	Beta (36.08; 4.92)	0.85	Beta (59.5; 10.5)	(5)
No problems	0.49	Beta (20.09; 20.91)	0.29	Beta (20.3; 49.7)	(5)
Requires standing antibiotics	0.25	Beta (10.25; 30.75)	0.29	Beta (20.3; 49.7)	(5)
Persistent rashes	0.23	Beta (9.43; 31.57)	0.29	Beta (20.3; 49.7)	(5)
ADHD	0.16	Beta (6.56; 34.44)	0.17	Beta (11.9; 58.1)	(5)
Diarrhea	0.05	Beta (2.05; 38.95)	0.19	Beta (13.3; 56.7)	(5)

Height <3rd percentile	0.05	Beta (2.05; 38.95)	0.17	Beta (11.9; 58.1)	(5)
Weight <3rd percentile	0.02	Beta (0.82; 40.18)	0.17	Beta (11.9; 58.1)	(5)
Warts	0.11	Beta (4.51; 36.49)	0.16	Beta (11.2; 58.8)	(5)
Asthma	0.15	Beta (6.15; 34.85)	0.16	Beta (11.2; 58.8)	(5)
Developmental delay	0.05	Beta (2.05; 38.95)	0.18	Beta (12.6; 57.4)	(5)
GERD	0.05	Beta (2.05; 38.95)	0.04	Beta (2.8; 67.2)	(5)
Oral aversion	0.02	Beta (0.82; 40.18)	0.04	Beta (2.8; 67.2)	(5)
Hyperthyroidism	0.03	Beta (1.23; 39.77)	0.01	Beta (0.7; 69.3)	(5)
Seizure disorder	0.02	Beta (0.82; 40.18)	0.01	Beta (0.7; 69.3)	(5)
Skin GVHD	0.04	Beta (4.44; 106.56)	0.04	Beta (4.44; 106.56)	(5)
Cerebral palsy	0.02	Beta (2.22; 108.78)	0.02	Beta (2.22; 108.78)	(5)
Autoimmune disease	0.02	Beta (2.22; 108.78)	0.02	Beta (2.22; 108.78)	(5)

Two studies reported the reduction in the proportion of babies with low birth weight below 3rd percentile, in the early diagnosed cohort compared to the late diagnosed cohort (5, 36). This is likely to be due to infection prior to HSCT affecting the digestive system which would be more common in the later diagnosed group. The Dell Railey et al (5) estimates are used within the model and it is assumed that these patients require nutritional support. The model assumes that patients will have a gastrostomy and will receive 50% of their nutritional needs for 2 years (39) (25).

The Dell Railey et al study (5) also found a difference in the proportion of patients with developmental delay following early and late HSCT. This was consistent with the Mazzorali et al study (36). The study found that 5% of patients undergoing early HSCT had a developmental delay and 18% of those undergoing later HSCT went on to have a developmental delay. The model assumes that the costs related to this developmental delay are equivalent to those for a mild intellectual disability (18).

The Slatter et al (35) study was used to estimate the proportion of patients receiving immunoglobulin as it is likely to best represent UK practice. In this study a higher proportion of the late diagnosed cohort were on IG compared to the early diagnosed cohort. However, as this was not consistent with the other studies (5, 36, 37), the overall proportion of patients on IG, 25% is used for both cohorts. It is assumed that IG replacement therapy is lifetime (40) (39).

A number of patients have attention deficit disorder (ADHD). The cost of treating this is estimated by the cost of medication and the cost of two appointments with the child and adolescent mental health team per year which averages £890 per year (25) (39).

Other long term treatments for both arms of the model include antibiotics, 24% in the early diagnosed cohort and 29% in the late diagnosed cohort (5) and immunosuppressive drugs (5%) (33) . Prophylactic antibiotics are assumed to

be given for life. While immunosuppressive treatment with steroids is assumed to last 2 years (39).

Four studies (5, 34, 36, 37) reported a higher incidence of booster transplants in the late diagnosed cohort. Three studies (34, 36, 37) with a follow up of between one year and 26 years, gave the timings of the additional and booster transplants. Out of the 88 of patients in the three studies there were 19 patients that had a total of 26 additional or booster transplant. The timings of these ranged from 1 month to 22 months following the original transplantation with only three of these occurring more than six months following the original transplantation.

As the majority of additional transplantation occur in the immediate period following the original transplantation we have assumed that the costs of additional transplants are included in our costs of transplantation. As described below we have used data on the length of stay of SCID patients following transplantation to estimate total costs. The length of stay was up to 260 days in the early diagnosed patients and up to 400 plus days for late diagnosed patients and is therefore likely to include the costs for the inpatient stay of additional transplantations. The NHS reference cost of transplantation includes the procedure and the average length of stay. Including this cost on top of the length of stay estimate already included will overestimate the cost impact of the additional transplantation. Given this and as £1,492, the average cost per day given an average stay of 54 days for a HSCT, is very close to £1,495 the cost used per day for non-critical care. Including this cost on top of the length of stay estimate already included will overestimate the cost impact of the additional transplantation

3.8 Costs of screening and confirmatory testing

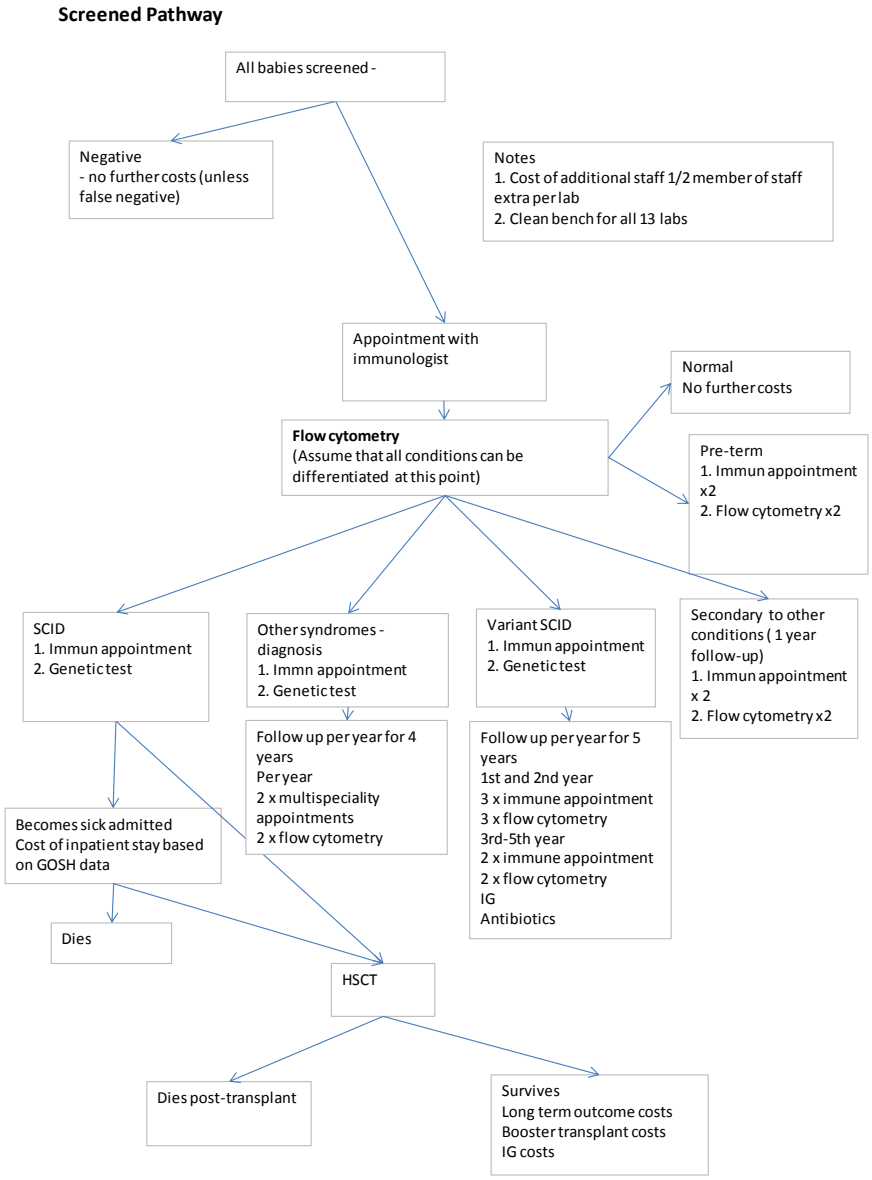
Perkin Elmer the makers of the SCID screening test proposed to be used in the UK have estimated the price of the test to be between £3 and £3.50 (2). In the

model we have used £.3.50 per test the upper end of the estimate. Multiplying this by the number of births per year gives a total cost of £2.7 million per year. As the TREC test is an additional test over and above the existing tests carried out on the newborn DBS it will require additional labour in the laboratories, based upon expert laboratory advice this was estimated to be 0.5 FTE of a grade 5 member of staff per laboratory. There are 13 laboratories conducting newborn screening and a full time grade 5 member of staff costs £25,500 per year (18). The estimated cost of the additional staff including on costs works out at an additional £166,000 per year. The laboratories may also need an area to prepare the samples. The cost of a UV cabinet and PCR workstation is £2,700, if all 13 laboratories need a UV/PCR cabinet this would total £35,000 but does not include installation costs (41).

Infants who have a positive TREC screen will go on to have a flow cytometry test. This has been estimated to cost £25 from the laboratory at Great Ormond Street Hospital (26). All patients will also have a consultation with an immunologist (25) to give a total cost of confirmation of £276.

A flow cytometry test is able to differentiate healthy false positive patients, SCID patients and some of the different conditions. Other markers such as physical features and the presence of other severe health problems in the other congenital syndromes and newborns with TCL secondary to other conditions can further differentiate patients. After this point the confirmatory tests and appointments are based on the condition/syndrome that the infant has and are shown in Figure 5 . The genetic test used differs depending on the conditions. For SCID patients a number of different genetic tests are available based on whether patients are for example B cell positive or negative. The average cost of these was £568. For patients with variant SCID and for 50% of those with other syndromes we have assumed that they have a fuller genetic work up using the primary immune deficiency syndromes 206 exome panel at a cost of £1,300 (REF find a test).

Figure 5: Screened Patient Pathways



3.9 Costs of HSCT and patients who die before HSCT.

Data from GOSH on the number of inpatient days for patients diagnosed early and late were used to calculate the total inpatient costs of HSCT. The data were split between critical care days and non-critical care days. On average those

diagnosed early had an inpatient stay of 83 days on a standard ward and 2.6 days on critical care compared to 144 days on a standard ward and 8 days on critical care for those diagnosed later (26). The average UK length of stay was higher than but not inconsistent with the US study (19) which estimated 63 days for those undergoing an early HSCT compared to 113 days for those undergoing a late HSCT. A French study (20) estimated the median length of stay for an early HSCT to be 94 days and the median length of stay for a late HSCT to be 138 days. The GOSH data include readmittances but do not include the length of stay at other hospitals before the patients were referred to GOSH. Given the length of stay is relatively long up to 260 days in the early diagnosed patients and up to 400 plus days for late diagnosed patients, as mentioned above, it is likely to include stays for complications following transplant such as additional transplants or graft versus host disease (GvHD) and therefore these were not costed out separately.

The average cost of HSCT was taken from the NHS reference costs (25) for transplants in those 18 years and under and estimated at £81,000. The average length of stay for elective and non-elective inpatients was calculated as 54 days from reference costs, which is lower than that recorded for HSCT in SCID patients. To adjust for this, the average number of days for an HSCT was subtracted from the total SCID HSCT non-critical care days to give the additional inpatient days for SCID HSCT compared to the reference cost HSCT. The non-critical care days were multiplied by the cost of a paediatric disorder of immunity day cost of £1,495 and the critical care days were multiplied by the cost of paediatric critical care advanced critical care 3 day cost of £1,967. This gives a total cost for an early diagnosed case of £128,000 compared to £231,000 for a late diagnosed case.

To account for patients that die before HSCT and for those not diagnosed we have assumed that they have an inpatient stay equivalent to half the pre-HSCT inpatient stay of a late diagnosed SCID case. To account for the seriousness of their condition we have estimated that the total inpatient stay of 25 days would

be split equally with 12.5 days on critical care and 12.5 days on a standard ward. This gives a total cost of £43,368.

For ADA-SCID patients the price of gene therapy was estimated at the European price of Stimvelis of 594,000 euros which was converted in British pounds (GBP) at an exchange rate of 0.857 (February 2017) euros to GBP to give a cost of £509,027 (42). This was assumed to include the inpatient stay following treatment. The average length or pre HSCT stay from GOSH was costed out as above and added to the cost of gene therapy to give the overall cost of £525,387 in the early diagnosed cohort and £587,799 in the later diagnosed cohort.

Following expert opinion we assumed that patients diagnosed early would be on ERT for 11 weeks and those diagnosed late would be on ERT for 26 weeks. The manufacturers Leadiant Biosciences provided us with a price of £30,000 for four vials (43). The dosage of patients differs with a higher dosage given to stabilise a patient with a lower dosage given following stabilisation. However, due to the size of the vials all infants would be given one vial per week at a cost of £7,500. We also included the cost of administration at a cost of a non-consultant led paediatric clinical immunology and allergy service outpatient appointment at £180 to give a total cost of ERT for early diagnosed patients of £84,475 and for later diagnosed patients a cost of £199,668.

3.10 Patients identified with non-SCID conditions

In order to reflect the full impact of TREC screening the impact on the other conditions with low T-cells needs to be included. We have estimated the additional appointments and treatments that patients have due to being identified with a TCL through TREC screening. The model is based on outcomes reported from the US screening programmes and consultation with two clinicians, Dr Andrew Gennery for DiGeorge and Dr Liz McDermott for Ataxia-Telangiectasia (see APPENDIX D).

During the first two years of screening in California eight babies with TCL associated with pre-term birth were identified. Of the six that were able to be followed up the TCL had resolved spontaneously. There were 14 patients that had TCL secondary to other conditions. Of these patients eight had died within four months of birth and in the other six babies their TCL had either resolved or was in the process of recovering at follow up. As both the pre-term infants and those with TCL secondary to other conditions do not seem to have long term TCL we have assumed that they have two further consultations with an immunologist and flow cytometry tests at a total costs of £553 (see Figure 5).

As shown in Figure 5 we have estimated additional appointments for all variant SCID patients for five years with the number of appointments decreasing each year. We have also included treatment with IG and antibiotics for these patients. The total undiscounted cost for five years is £22,000 (39) (25) (40). This may overestimate the incremental impact of identifying variant SCID patients through screening. In California there were six patients identified with variant SCID. Of these three babies were healthy at birth and one of these patients later developed pneumonia.

As shown in Figure 5, babies identified with other syndromes are assumed to incur an additional consultation with an immunologist and a genetic test for diagnosis. This is followed by four years of follow-up which includes two multi-speciality appointments per year and flow cytometry tests per year for a total of £2035 per year (25). In California there were 15 patients identified with congenital syndromes (8). Of these eight had partial DiGeorge, four had Trisomy 21, one had CHARGE syndrome, and two had Ataxia-Telangiectasia. Of the DiGeorge patients four were recognised before the screening results due to the congenital cardiac malformations. Only two of the DiGeorge patients were healthy at birth. It is likely that the majority of the DiGeorge, Trisomy, and CHARGE patients would have been identified without screening due to their characteristic facial and clinical features. The Ataxia-Telangiectasia patients were both healthy at birth and would have been unlikely to be identified until

they presented symptomatically, usually before the age of five, unless there was a family history of the syndrome. All patients with variant SCID, syndromes, and other conditions were assumed to incur additional monitoring and treatment costs due to screening. This may overestimate the incremental cost of screening in the model as some of these patients may have been identified symptomatically at birth.

No potential benefits of identifying patients earlier and offering treatment for the immunodeficiency, such as immunoglobulin therapy or antibiotics, have been included. There are also concerns about identifying patients before they become symptomatic as this may have a negative impact on their or their parents quality of life. Estimates of the number of newborns identified with the non SCID TCL by a UK screening programme are presented in Section 4.9.2, together with estimates of the number of children who might be identified by screening who would otherwise be health at birth. An unknown proportion of these children would be expected to arise symptomatically at a later age, and it is unclear whether these would benefit from earlier management or disbenefit from early medicalisation, a proportion of the newborns might remain undiagnosed without screening with subclinical symptoms and it is unknown whether any would remain entirely asymptomatic. An exploratory threshold analysis is conducted in Section 4.9.2 to identify the minimum QALY disbenefit that would be required for each healthy at birth non SCID TCL child to lift the cost-effectiveness of the entire screening programme over the £20,000 and £30,000 per QALY thresholds. A further qualitative exploration of these issues is presented in the discussion in Section 5.2.

3.11 Probabilistic sensitivity analysis

Uncertainty in model parameters was characterised with parametric distributions reported in Table 3. Model output uncertainty was generated from 10,000 runs of the model with samples of the model input parameters. Economic results are reported for a cost effectiveness threshold of £20,000 and £30,000 per QALY gained.

3.11.1 Scenario analysis –Discount rates

The standard discount used in economic analyses is 3.5% for both costs and benefits (16). However, for public health interventions NICE recommends a 1.5% discount rate for costs and benefits. This is because for many interventions in public health the intervention occurs over a relatively short period earlier in people's lives but the benefits accrue over a longer period (17). For technology appraisals NICE also recommends a 1.5% discount rate for health benefits and a 3.5% discount rate as a sensitivity analysis when "treatment effects are both substantial in restoring health and sustained over a long periods (normally at least 30 years) (16)". As screening for SCID could be classed as a public health intervention and as the impact of screening increases survival a 1.5% discount rate for both costs and benefits and a discount rate of 3.5% for costs and 1.5% for health benefits are presented.

3.11.2 Scenario analysis – The cost of the screening test

An estimate of £3-£3.50 was given as the cost of the test in the UK by the company producing the test. The base case analysis uses a cost of £3.50. A sensitivity analysis was run with the cost of the screening test increasing by £0.50 increments from £0.50 to £5 to explore the impact of the cost of the screening test cost on the results.

3.11.3 Scenario analysis – Mortality rates

To explore the uncertainty around the mortality estimates we ran two analyses that varied the odds ratio of the pre and post-transplant mortality rates. For these analyses different treatment options and different survival estimates were not included for ADA-SCID. The odds ratio for pre-transplant mortality rate increased from the basecase value of 0.03 to 1.03 in 0.1 increments. The odds ratio for the post-transplant mortality was 0.15 in the basecase and was varied from 0.05 to 1.05 in 0.1 increments.

3.11.4 Scenario analysis – QALY

In order to explore the impact of the QALY estimates and the differences in these between early and late on the results we ran an analysis that firstly assumed that the QALY would be the same for both early and late detected SCID. Secondly this was varied in 0.05 increments between 0.5 and 1.

3.11.5 Scenario analysis – Proportion detected by a family history

The proportion of SCID detected by a family history in an unscreened population is an important parameter as it sets the limit for the number of SCID patients that could benefit from screening. In order to explore the impact of this parameter we varied the proportion detected by a family history in 0.05 increments from 0 to 0.5.

3.11.6 Scenario analysis – ADA SCID

There are a number of uncertainties in including ADA-SCID in the model partly due to very low incidence of the condition and partly due to the recent licensing of gene therapy for this group. In the basecase we assumed that patients without a matched family donor would undergo gene therapy treatment. However, while gene therapy is only licensed in patients *without* a matched family donor, i.e. the trial populations, it is unclear if it would be restricted to this group in the future. The survival estimates in the model for those diagnosed late *with* a matched family donor are lower than for those undergoing gene therapy 66% survival vs 95% survival (suggesting that gene therapy may be a preferable treatment option for these patients. For a sensitivity analysis we have assumed that those diagnosed late would receive gene therapy regardless of whether they have a matched family donor available. In this case the mortality rate for all ADA-SCID patients is the same at 95% survival.

There is also uncertainty as to how ERT is used and how it will be used with the introduction of screening. To explore the impact of ERT on the results we ran the model assuming both those diagnosed early and late receive ERT for the same

period of time, firstly we assumed that all patients receive ERT for 11 weeks, and secondly that they received it for 26 weeks. This analysis removes any potential benefit for screening derived from reducing the uncertain cost of ERT.

3.11.7 Scenario analysis – Incidence

The incidence of SCID will affect the results of the cost-effectiveness analysis. To supplement the probabilistic uncertainty analysis included in the baseline we ran two analyses doubling and halving the incidence of SCID and undetected SCID.

3.11.8 Scenario analysis – TREC screening test cut-off

In the basecase we assumed that the SCID screening test would use a cut-off of 20 copies/μL. In two scenario analyses we used a cut-off of 30 copies/μL. From the Adams et al study (6) a higher cut-off rate will lead to more presumptive positive cases going for confirmatory testing. While the higher cut-off rate should not affect the number of SCID cases identified, as the sensitivity remains the same at 0.99, it is unclear if all additional cases would be false positive cases or you would see an increase in the non-SCID TCL cases. In the first analysis we assumed that all the additional cases identified would be found to be false positives at flow cytometry. In the second analysis we assumed that there would be a proportionate increase in all non-SCID TCL cases, with the remainder being additional false positives.

3.11.9 Threshold analyses - Quality of life impact of false positive results and for infants who would otherwise be identified as healthy at birth.

Infants with a positive TREC test are recalled in order to obtain a blood sample for flow cytometry that identifies patients requiring further investigation for SCID. Patients with a positive TREC test and negative flow cytometry result, that is (true) false positives, do not require further investigation. Whilst there is some

evidence to suggest that receiving a newborn screening recall notice can have some disbenefits the evidence is somewhat inconsistent and no impact on health related quality of life utilities has been demonstrated (44-48). A threshold analysis is used to determine the scale of quality of life impacts that would need to be associated with a false positive result in order to push the cost effectiveness of screening for SCID over a threshold of £20,000 or £30,000 per QALY.

A small number of newborns will also be identified by screening with non-SCID TCL who would otherwise be identified as healthy at birth. Of these newborns, a proportion would be expected to arise symptomatically at a later date. These may benefit or disbenefit from being screen detected at an early age. Data from the follow-up of screen detected cases in California suggest a proportion would be expected to see their TCL resolve naturally while others are still being followed up or have been lost to follow-up (8, 49). These have been classified as including variant-SCID and some congenital syndromes and they or their parents may potentially experience a disbenefit from screening. In order to explore the potential disbenefits for these infants who would otherwise be healthy at birth a threshold analysis is conducted that calculates the minimum per patient utility decrement that would bring the overall ICER to above £20,000 and £30,000 per QALY.

The model estimates the potential number of infants identified through screening that might not normally be diagnosed at birth. These estimates are generated from the Californian screening programme data, where 7 of the 21 infants diagnosed with variant SCID or congenital syndromes were healthy at birth (8). This proportion (33%) is applied to the number of variant SCID or congenital syndromes detected by screening in the model in order to estimate the number of patients that might incur this utility decrement. Note an update to these figures was provided in confidence to the authors and was including for consideration by the UK NSC.

A 2 dimensional threshold analysis is also presented that allows the joint impact of false positives and healthy at birth diagnoses to be examined.

3.11.10 Expected value of perfect information analysis

An expected value of perfect information (EVPI) analysis is reported using the Sheffield Accelerated Value of Information (SAVI) programme (50). EVPI calculates the value of having perfect information on all the uncertain parameters. The assessment reports overall EVPI, which calculates the value of eliminating all uncertainty in the model, and parameter EVPI, which identifies those parameters that cause decision uncertainty and what the potential value of reducing the uncertainty per parameter.

4 ECONOMIC MODELLING RESULTS

4.1 Baseline economic results

Table 5 presents estimates of the number of children with SCID and other TCL that will be detected annually in the UK with and without screening and the potential impact on SCID mortality. It estimates that screening will result in around 310 (72, 811) infants being referred to flow cytometry annually, leading to the early detection of 17 (14, 22) cases of SCID and a decrease in SCID mortality of 6.4 (4.0, 9.7) infants.

Table 5. Estimated number of SCID patients identified in the UK per year and associated mortality with and without screening

		Mean	95% credibility interval	
No screening	Children with SCID detected symptomatically	11.1	8.4	14.2
	Children with SCID detected via family history	4.9	3.2	7.0
	Children with SCID not diagnosed	1.5	0.1	4.6
	SCID mortality	8.1	5.3	12.0
Screening	Children with SCID screen detected	17.3	13.5	21.9
	Children with SCID detected symptomatically	0.2	0.1	0.3
	Subset with ADA SCID detected	2.9	1.6	4.7
	SCID mortality	1.7	0.6	4.1
	Non SCID TCL	25.6	9.3	50.0
	Number of pre-term children identified	6.8	0.5	21.2
	Total presumptive positives	309.8	72.0	811.4

It is estimated that screening will identify 260 (25, 764) true false positive cases who will undergo confirmatory testing followed by an all clear result in addition to 7 (1, 21) preterm newborns with T cell lymphopenia (TCL) annually. It is estimated that screening will also identify 26 (9, 50) children with TCL associated with causes other than SCID who may or may not benefit from being detected by screening. A further quantitative analysis of these impacts is presented in Section 4.9.2 and qualitative discussion in Section 5.2 .

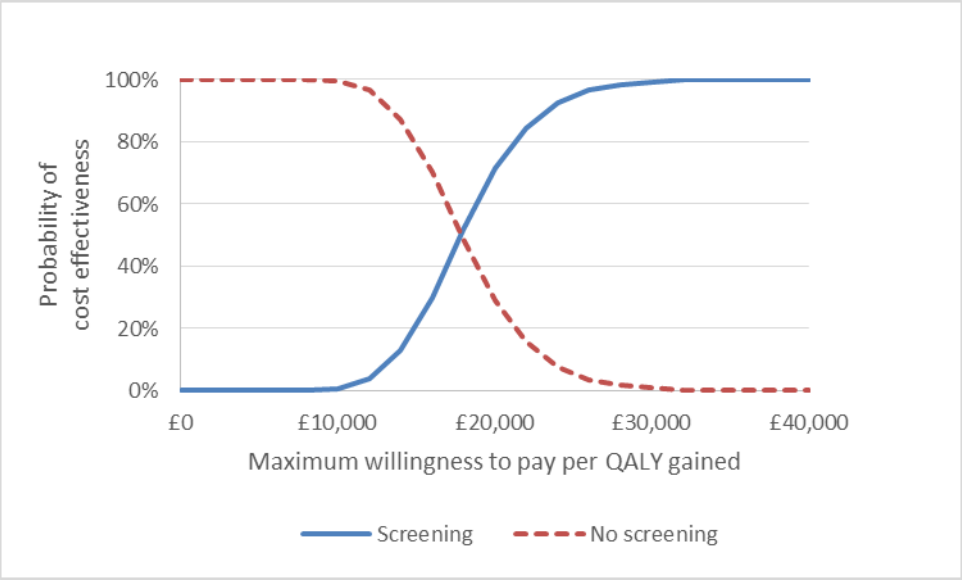
Table 6 presents the results of the probabilistic cost effectiveness analysis. The cost per QALY and cost per life year gained are relevant to each newborn baby

eligible for screening or the screening programme as a whole and are estimated at £17,600 (£11,500, £26,900) and £18,600 (£12,100, £28,900) respectively when both costs and benefits are discounted at 3.5%. The incremental net monetary benefit (INMB) is estimated for the screening programme as a whole for a 1 year period, and is estimated to be £433,600 (-£892,500, £2,075,000) at a willingness to pay (WTP) of £20,000 per QALY gained and £2,272,000 (£396,000, £4,665,000) at a WTP of £30,000. The negative INMB of screening at the lower range, indicates that the cost effectiveness of screening may be greater than the WTPs considered. The probability that screening is considered cost-effective at the £20,000 per QALY threshold is 71% and the probability is 99% at the £30,000 threshold. The cost-effectiveness acceptability curve (CEAC) shows the probability that a strategy is cost-effective at varying thresholds and is shown in Figure 6.

Table 6. Cost effectiveness of screening compared to no screening

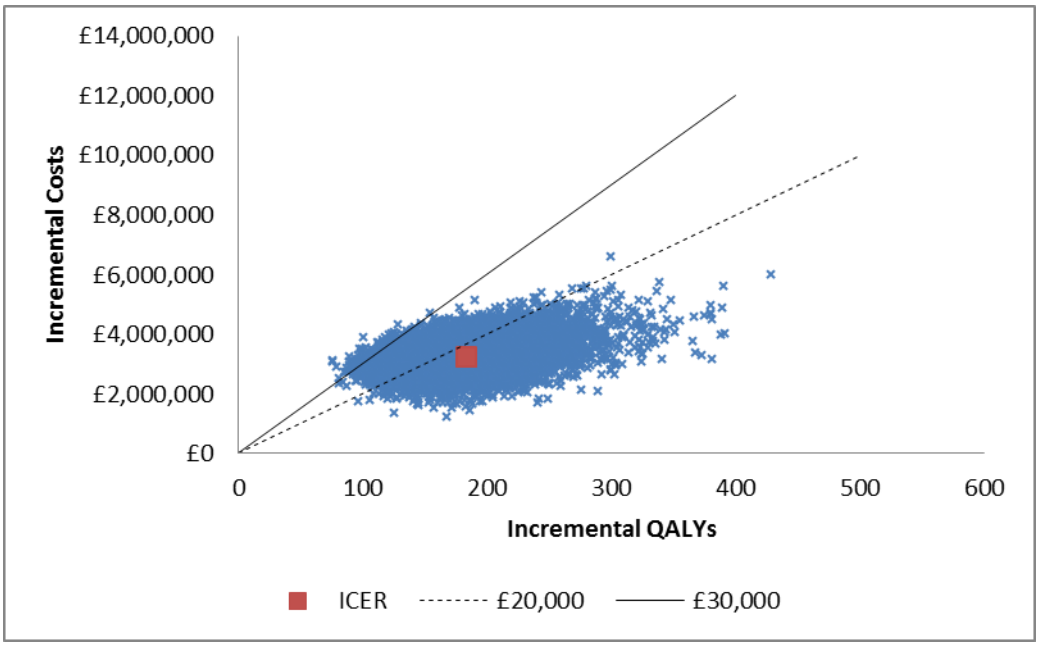
	Mean	95% credibility interval	
Cost per QALY gained	£8,652	£5,629	£12,477
discounted	£17,642	£11,496	£26,863
Cost per life year gained	£9,118	£5,992	£13,272
discounted	£18,591	£12,052	£28,856
INMB @ £20k per QALY	£433,570	-£892,490	£2,074,664
INMB @ £30k per QALY	£2,271,996	£395,848	£4,664,709
Probability:			
Cost saving	0%		
Cost per QALY <£20k	71%		
Cost per QALY <£30k	99%		

Figure 6. Cost-effectiveness acceptability curve



The impact of screening on costs, QALYs and life years gained are presented in Table 7 and Table 8 respectively and the associated cost-effectiveness plane is shown in Figure 7. The diagonal dotted line shows the £20,000 per QALY gained threshold and the solid line the £30,000 threshold. The crosses represent costs and effects estimated in each of the 10,000 runs of the model in the PSA. The square dot is the mean ICER.

Figure 7. Cost-effectiveness plane for screening compared to no screening



The direct cost of screening for a 1 year cohort is estimated at £3,036,000 (£2,970,000, £3,175,000), with a total discounted incremental cost of £3,243,000 (£2,257,000, £4,385,000) over the lifetime of that same cohort. The different cost categories shown in Table 7 demonstrate that screening leads to an increase in all associated costs apart from pre-treatment and HSCT costs. In particular the long term follow up and management costs are higher with screening compared to the no screening arm. On a per patient basis the costs for an early diagnosed SCID patient are lower than those in children diagnosed symptomatically later. However, as survival improves with earlier diagnosis more SCID patients are surviving and incurring long term costs which results in a higher total cost for follow-up and treatment costs for the screened arm compared to the no screen arm.

Table 7. Cost impact of screening

		Mean	95% credibility interval	
Screening costs		£3,036,097	£2,970,380	£3,174,701
Follow up pre-terms	Screening	£3,731	£263	£11,708
Follow up secondary to other conditions	Screening	£3,250	£159	£10,869
Diagnosis and follow up syndromes	Screening	£87,246	£20,520	£199,451
Diagnosis and follow up variant SCID	Screening	£97,895	£2,145	£358,390
Diagnostic costs SCID	Screening	£14,281	£11,181	£18,054
	No Screening	£13,070	£13,070	£16,041
	Incremental	£1,211		
Pre & HSCT costs	Screening	£3,348,195	£2,194,629	£4,783,393
	No Screening	£3,640,832	£2,664,381	£4,845,071
	Incremental	-£292,636		
Long term costs	Screening	£6,025,695	£3,279,851	£9,686,142
	No Screening	£4,087,335	£2,356,731	£6,405,216
	Incremental	£1,938,360		
Long term costs discounted	Screening	£1,951,985	£1,122,170	£3,046,012
	No Screening	£1,304,969	£781,722	£2,002,497
	Incremental	£647,017		
Total costs	Screening	£12,451,953	£9,206,457	£16,778,030
	No Screening	£7,741,236	£5,404,082	£10,712,627
	Incremental	£4,710,717	£2,915,841	£7,140,123
Total discounted costs	Screening	£7,221,277	£5,878,719	£8,974,846
	No Screening	£3,977,996	£2,913,430	£5,259,911
	Incremental	£3,243,281	£2,257,100	£4,385,141

The discounted and undiscounted life years and QALYs for screening and no screening are shown in Table 8. Screening results in a substantially higher number of both life years and QALYs than no screening. The model estimates 174 (108, 267) discounted incremental life years and 184 (118, 274) QALYs for each annual screened cohort. The incremental QALYs are greater than the incremental life years gained since in addition to mortality gains, screening results in improved morbidity associated with early rather than late transplantation.

Table 8. QALYs and life years

	Mean	95% credibility interval	
Total QALYs screening	1219	916	1573
Total QALYs no screening	675	493	884
Incremental	544	351	812
Total discounted QALYs screening	412	309	531
Total discounted QALYs no screening	228	167	298
Incremental	184	118	274
Total life years screening	1277	966	1644
Total life years no screening	761	557	992
Incremental	517	321	791
Total discounted life years screening	431	326	555
Total discounted life years no screening	257	188	335
Incremental	174	108	267

Table 9 presents the estimated health outcomes for a one year cohort of newborns with SCID under screening and no screening policies. These estimates are based upon the outcomes reported by Dell Railey et al (5) in their single centre cohort study applied to the UK population. This study reported outcomes experienced in the cohort with a median follow-up of 8.7 years, there is no information however on either the duration or time of onset of the different

outcomes. There are some known issues in generalising between these populations, for instance there is some evidence to suggest a slightly different distribution of underlying molecular types. For instance, if the UK screening population has a higher proportion of newborns with RAG1 or RAG2 deficiency, this may mean that the incidence of developmental delay may be under estimated.

The proportion of newborns experiencing most health outcomes is similar between screening and no screening, indicating that the actual number of cases is likely to increase with the increased survival consequent on screening. The primary impact of screening in improving outcomes is through reducing those symptoms associated with early insults to the system in symptomatically detected patients, for example developmental delay.

Table 9. Health outcomes for an annual cohort of newborns with SCID under screening and no screening

Outcomes	Proportion of survived		Screening			No screening		
	Screening	No screening	Mean	95% credibility interval		Mean	95% credibility interval	
Survived HSCT			13.6	10.1	17.8	7.7	5.5	10.4
Survived Gene therapy			2.1	1.0	3.6	1.6	0.8	2.8
Considered healthy by parents	88%	86%	13.8	10.2	18.1	8.1	5.8	10.7
No problems	49%	38%	7.7	4.9	11.1	3.6	2.4	5.1
Requires standing antibiotics	25%	27%	3.9	2.0	6.5	2.5	1.6	3.8
Persistent rashes	23%	26%	3.6	1.7	6.1	2.5	1.5	3.6
ADHD	16%	16%	2.5	1.0	4.7	1.5	0.9	2.4
Diarrhea	5%	12%	0.8	0.1	2.2	1.2	0.6	1.9
Ht <3%	15%	16%	2.3	1.2	3.9	1.5	0.8	2.5
Wt <3%	2%	10%	0.3	0.0	1.2	0.9	0.5	1.6
Warts	11%	14%	1.7	0.5	3.6	1.3	0.7	2.1
Asthma	15%	15%	2.3	0.9	4.5	1.4	0.8	2.3
Developmental delay	5%	12%	0.8	0.1	2.2	1.1	0.6	1.9
GERD	5%	5%	0.8	0.1	2.1	0.4	0.1	0.9
Oral aversion	2%	3%	0.3	0.0	1.3	0.3	0.1	0.7
Hyperthyroidism	3%	2%	0.5	0.0	1.6	0.2	0.0	0.5
Seizure disorder	2%	1%	0.3	0.0	1.2	0.1	0.0	0.4
Skin GVHD	4%	4%	0.6	0.2	1.4	0.4	0.1	0.8
Cerebral palsy	2%	2%	0.3	0.0	0.9	0.2	0.0	0.5
Autoimmune disease	2%	2%	0.3	0.0	0.9	0.2	0.0	0.5
Requires IG	25%	25%	3.9	1.8	6.7	2.3	1.1	4.0

4.2 Scenario analysis – Impact of discount rate

This scenario analysis explores the impact of different discount rates on the cost effectiveness of screening for SCID. The baseline analysis discounts both costs and benefits at 3.5% in line with NICE guidance on technology appraisals, this analysis explores rates of 1.5% for both costs and benefits, in line with NICE public health economics guidance and the impact of discounting benefits at 1.5% and costs at 3.5% in line with treasury guidelines. Table 10 presents the impact of discounting on incremental costs and QALYS and the cost per QALY and cost per life year gained. Note that the results in Table 10 are presented as total programme costs and QALYs and not as the incremental per person. The use of a 1.5% discount rate improves the cost-effectiveness of screening, reducing the ICER from £17,600 to £11,700 per QALY gained and the use of mixed discounting improves the cost effectiveness further to £10,300. The cost-effectiveness plane and the cost effectiveness acceptability curves (CEACs) are shown in

		Mean	95% credibility interval	
Incremental QALYs	Undiscounted	544	351	812
	Discounted 1.5%	316	202	468
	Discounted 3.5%	184	118	274
Incremental costs	Undiscounted	£4,710,717	£2,915,841	£7,140,123
	Discounted 1.5%	£3,709,773	£2,466,487	£5,205,175
	Discounted 3.5%	£3,243,281	£2,257,100	£4,385,141
Cost per QALY gained	Undiscounted	£8,652	£5,629	£12,477
	Benefits 3.5%, costs 3.5%	£17,642	£11,496	£26,863
	Benefits 1.5%, costs 1.5%	£11,741	£7,617	£17,354
	Benefits 1.5%, costs 3.5%	£10,265	£6,773	£15,772
Cost per life year gaine	Undiscounted	£9,118	£5,992	£13,272
	Benefits 3.5%, costs 3.5%	£18,591	£12,052	£28,856
	Benefits 1.5%, costs 1.5%	£12,369	£8,142	£18,420
	Benefits 1.5%, costs 3.5%	£10,813	£7,175	£16,778

Figure 8 and Figure 9 respectively. Whilst the probability that screening is cost-effective at a threshold of £20,000 in the baseline analysis is approximately 71% this increases to over 99% for both alternative discounting scenarios, similarly these figures are even better at a threshold of £30,000 per QALY gained The lower discount rate increases the total number of QALYs gained from 184 to 316 and increases total costs from £3.2 million to £3.7 million. This differential impact of discounting occurs because the QALYs gained are accumulated over the life of the child and are therefore subject to significant discounting, whereas the major part of the costs of screening occur early in lifetime and are therefore discounted less heavily.

Table 10. Impact of discounting on cost effectiveness of screening for SCID

		Mean	95% credibility interval	
Incremental QALYs	Undiscounted	544	351	812
	Discounted 1.5%	316	202	468
	Discounted 3.5%	184	118	274
Incremental costs	Undiscounted	£4,710,717	£2,915,841	£7,140,123
	Discounted 1.5%	£3,709,773	£2,466,487	£5,205,175
	Discounted 3.5%	£3,243,281	£2,257,100	£4,385,141
Cost per QALY gained	Undiscounted	£8,652	£5,629	£12,477
	Benefits 3.5%, costs 3.5%	£17,642	£11,496	£26,863
	Benefits 1.5%, costs 1.5%	£11,741	£7,617	£17,354
	Benefits 1.5%, costs 3.5%	£10,265	£6,773	£15,772
Cost per life year gaine	Undiscounted	£9,118	£5,992	£13,272
	Benefits 3.5%, costs 3.5%	£18,591	£12,052	£28,856
	Benefits 1.5%, costs 1.5%	£12,369	£8,142	£18,420
	Benefits 1.5%, costs 3.5%	£10,813	£7,175	£16,778

Figure 8. Cost-effectiveness plane for different discount rates

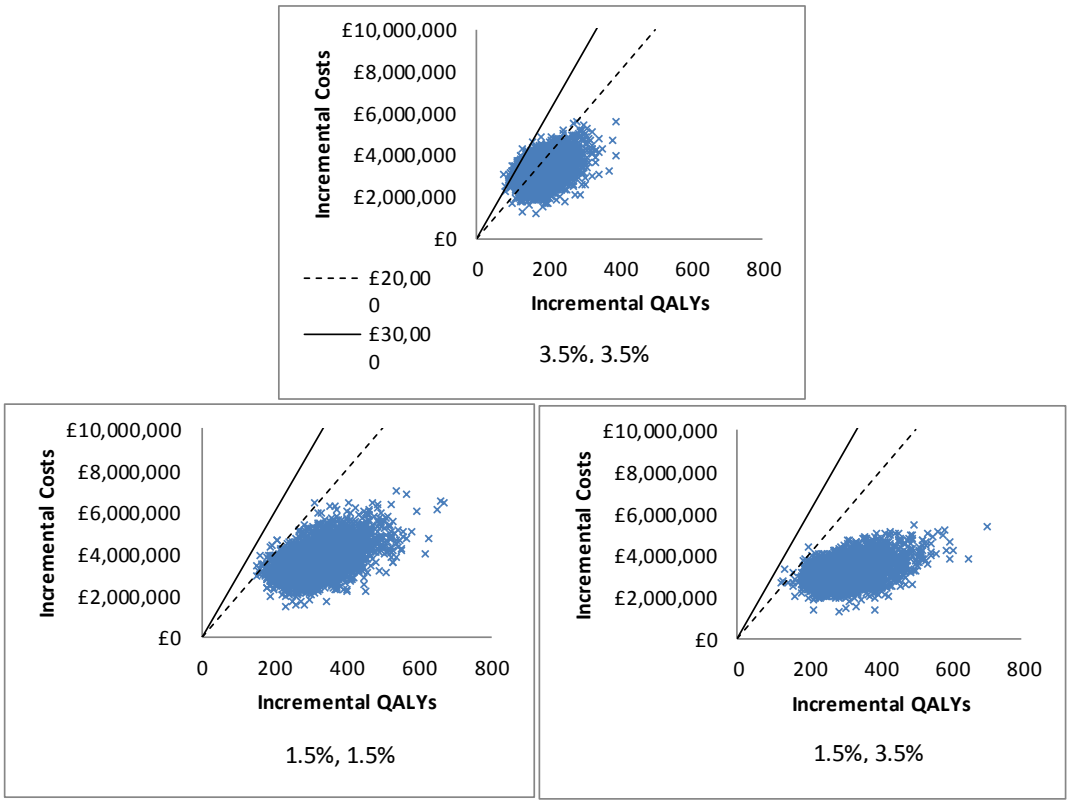
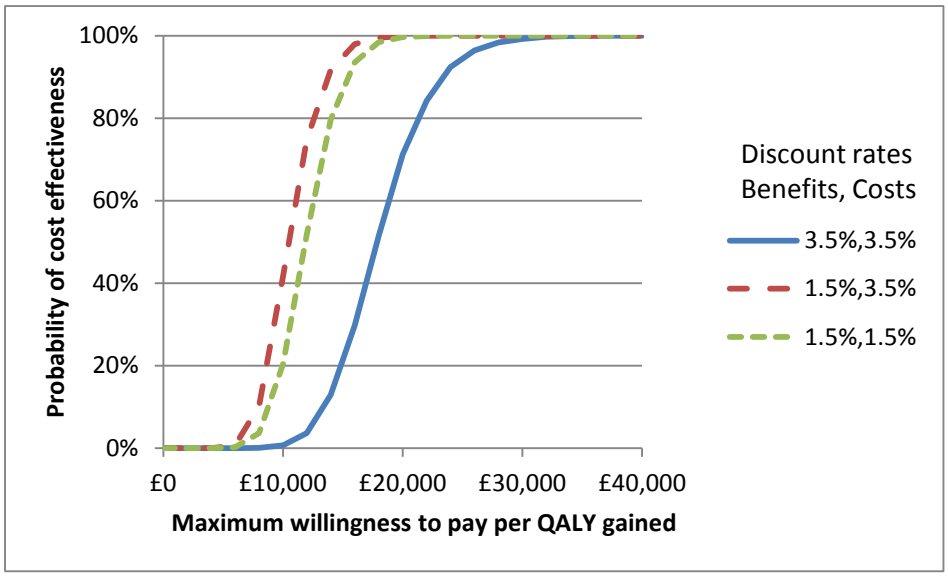


Figure 9. CEACs for different discount rates



4.3 Expected value of information analysis

The overall expected value of information (EVPI) results are presented in Table 11, the overall EVPI per person affected by the decision is estimated at £ 0.15 per person. Assuming an annual number of people affected by the decision of 780,835 the overall EVPI per year is estimated at £119,200 for UK.

When thinking about the overall expected value of removing decision uncertainty, one needs to consider how long the current decision will remain relevant, for instance if new treatments options or diagnostic technologies are anticipated to become available for SCID treatment. For a decision horizon of 5 years the overall expected value of removing decision uncertainty for the UK is estimated at £595,900.

Research or data collection exercises costing more than this amount would not be considered a cost-effective use of resources. This is because the return on investment from the research, as measured by the health gain and cost savings of improved decision making, is expected to be no higher than £595,900.

Table 11. Overall expected value of perfect information (EVPI) results

	Overall EVPI	
	£	QALY
Per person affected by the decision	£0.15	8E-06
Per year in UK assuming 780834 births	£119,200	6.0
Over 5 years	£595,900	29.8
Over 10 years	£1,192,000	59.6
Over 15 years	£1,788,000	89.4
Over 20 years	£2,384,000	119.2

The total EVPI for varying willingness to pay thresholds is illustrated in Figure 10. Since the baseline cost effectiveness threshold is close to £20,000 per QALY the overall decision uncertainty at this threshold and hence EVPI is near its

maximum. At a threshold of £30,000 per QALY, the decision uncertainty and hence the estimated EVPI is much lower.

Figure 10. Overall population EVPI for a 5 year horizon by willingness to pay threshold

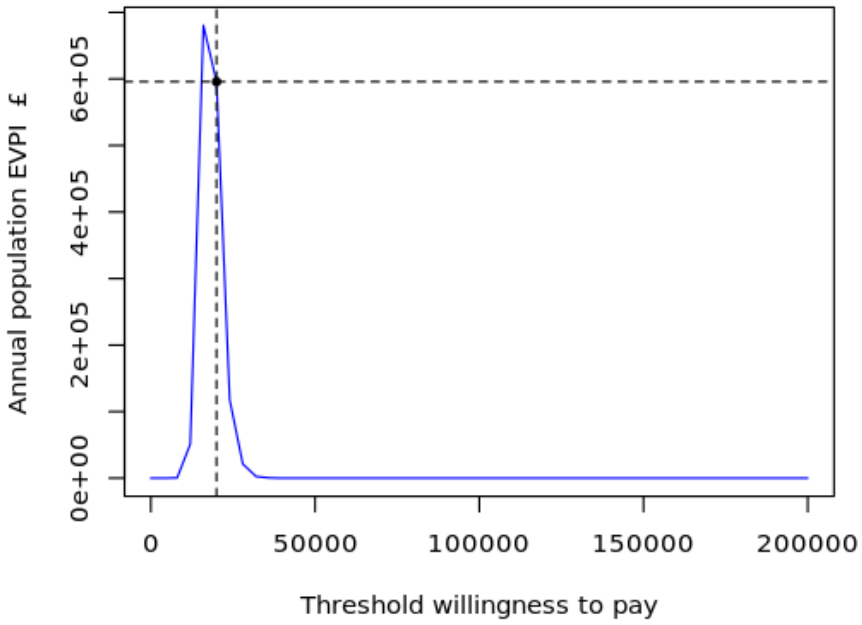
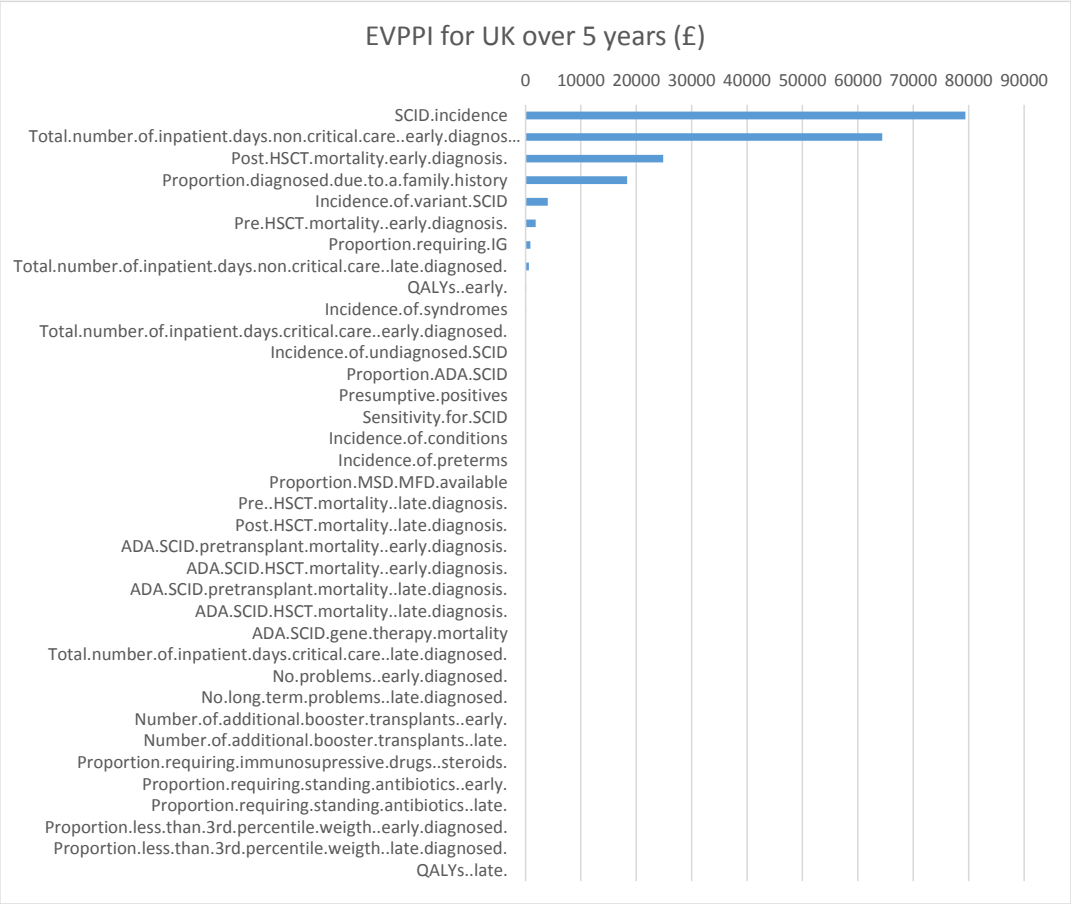


Figure 11 presents the single parameter EVPI (EVPPI) for parameters in the model. The primary uncertainties in the model relate to the underlying incidence of SCID in the population and the cost of early transplantation, specifically the length of stay in non-critical care. The second biggest group relate to the relative survival benefit from early versus late transplantation, followed by the proportion of cases that could be identified by family history in the absence of screening and the incidence of variant SCID. These uncertainties together with related assumptions in the model are explored in the subsequent scenario and threshold analyses.

Figure 11. Single parameter EVPI Overall population EVPI for a 5 year horizon by willingness to pay threshold



4.4 Scenario analysis – The cost of the screening test

Table 12 shows the ICER, the probability of screening being cost-effective at a threshold of £20,000 and £30,000 per QALY gained and the total costs of screening. The reduction in the cost of the screening test leads to a reduction in the total costs of screening, reduces the ICER, and increases the probability that screening is cost-effective at the two thresholds.

Table 12. Results at different screening test costs

	Cost of the screening test									
Outcome	£0.50	£1.00	£1.50	£2.00	£2.50	£3.00	£3.50	£4.00	£4.50	£5.00
ICER	£4,922	£7,020	£9,154	£11,290	£13,459	£15,494	£17,701	£19,791	£21,867	£24,052
Cost-effective @£20,000	100%	100%	100%	99%	96%	87%	71%	49%	30%	15%
Cost-effective @£30,000	100%	100%	100%	100%	100%	100%	99%	98%	93%	85%
Total Screening costs	£693,493	£1,085,087	£1,474,209	£1,866,684	£2,256,016	£2,646,026	£3,036,639	£3,427,996	£3,817,664	£4,207,232

4.5 Scenario analysis – Effectiveness of early versus late HSCT

Table 13 shows the ICER and the probability of screening being cost-effective at thresholds of £20,000 and £30,000 per QALY gained for different assumptions regarding pre transplant mortality. The odds ratio for pre-transplant mortality in those diagnosed early compared to those diagnosed late used in the basecase is 0.03. The mortality in late diagnosed does not change as the analysis changes the odds ratio between the late and early mortality. As the odds ratio increases the mortality in the early diagnosed increases. Survival falls in both the screened and the non-screened arms of the model as some SCID patients are detected early by a family history in the non-screened arm of the model. The survival numbers refer to the number of SCID patients that will survive transplantation per year.

Table 13. Results at different odds ratios of pre-transplantation mortality

	Odds Ratio										
Outcome	0.03	0.13	0.23	0.33	0.43	0.53	0.63	0.73	0.83	0.93	1.03
ICER	£18,030	£18,955	£19,766	£20,816	£21,823	£22,760	£23,909	£25,173	£26,445	£27,964	£29,392
Pre HSCT mortality (early diagnosed)	1.7%	6.9%	11.4%	15.5%	19.3%	22.7%	25.8%	28.7%	31.4%	33.9%	36.1%
Pre HSCT mortality (late diagnosis)	35.4%	35.6%	35.3%	35.4%	35.4%	35.4%	35.4%	35.4%	35.5%	35.5%	35.5%
Survival screened	15.64	14.78	14.10	13.39	12.80	12.31	11.81	11.33	10.91	10.51	10.15
Survival non-screened	8.78	8.52	8.35	8.14	7.96	7.85	7.70	7.56	7.43	7.33	7.21
Probability cost-effective £20,000	68%	58%	49%	40%	33%	27%	22%	17%	14%	11%	8%
Probability cost-effective £30,000	99%	98%	97%	94%	91%	86%	79%	73%	65%	56%	49%

Table 14 shows the ICER and the probability of screening being cost-effective at a threshold of £20,000 and £30,000 per QALY gained for different assumtions regarding post HSCT mortality. The odds ratio in the basecase is 0.15. As above an increase in the odds ratio results in an increase in the mortality rate in those diagnosed early and reduces survival in both the screened and non-screened arms of the model.

Table 14. Results at different odds ratios of post-transplantation mortality

	Odds Ratio										
Outcome	0.05	0.15	0.25	0.35	0.45	0.55	0.65	0.75	0.85	0.95	1.05
ICER	£16,949	£18,159	£19,386	£20,768	£22,120	£23,648	£25,273	£26,735	£28,590	£30,538	£32,588
Post HSCT mortality (early diagnosed)	3.2%	9.0%	14.1%	18.5%	22.6%	26.1%	29.5%	32.3%	35.1%	37.6%	39.8%
Post HSCT mortality (late diagnosis)	38.7%	38.6%	38.8%	38.6%	38.8%	38.7%	38.9%	38.6%	38.8%	38.8%	38.6%
Survival screened	16.52	15.56	14.68	13.93	13.20	12.63	12.03	11.60	11.09	10.69	10.32
Survival non-screened	9.02	8.77	8.50	8.30	8.07	7.93	7.73	7.65	7.49	7.38	7.29
Probability cost-effective £20,000	79%	67%	54%	41%	30%	21%	15%	11%	7%	5%	4%
Probability cost-effective £30,000	100%	100%	99%	96%	92%	85%	74%	66%	54%	44%	35%

4.6 Scenario analysis – QALYs

Table 15 shows the ICER and the probability of screening being cost-effective at a threshold of £20,000 and £30,000 per QALY gained for different QALY values if we assume the same QALY value for both early and late diagnosed HSCT survivors. The ICER falls as the QALY goes up. However, without the benefit from additional QALYs from those diagnosed early the ICER does not drop below £20,000 until a QALY of 0.95 and at this point there is still only a 50% probability that it is cost-effective at £20,000. From the GOSH cohort the average QALY value across both the early and late diagnosed cohort was 0.8. At this value there is a 22% probability that screening is cost-effective at the £20,000 threshold and an 87% probability that it is cost-effective at the £30,000 threshold.

Table 15. Results at different QALY values

	QALY										
Outcome	0.5	0.55	0.6	0.65	0.7	0.75	0.8	0.85	0.9	0.95	1
ICER	£37,200	£33,853	£31,019	£28,682	£26,542	£24,865	£23,274	£21,882	£20,715	£19,685	£18,604
Probability cost-effective £20,000	0%	1%	2%	5%	9%	15%	22%	31%	41%	50%	61%
Probability cost-effective £30,000	15%	26%	40%	56%	70%	79%	87%	92%	95%	97%	99%

4.7 Scenario analysis – Proportion detected through SCID family history

Table 16 shows the ICER and the probability of screening being cost-effective at a threshold of £20,000 and £30,000 per QALY gained by proportion of patients diagnosed with SCID due to a family history. In the basecase it is estimated that about 30% of patients are diagnosed due to a family history. A lower proportion

detected by a family history in the absence of screening results in a better screening cost effectiveness as the number of SCID patients that will benefit from screening increases.

Table 16. Results for different proportions detected by a family history

	Proportion detected by a family history										
Outcome	0	0.05	0.1	0.15	0.2	0.25	0.3	0.35	0.4	0.45	0.5
ICER	£12,512	£13,183	£13,908	£14,665	£15,513	£16,555	£17,536	£18,774	£20,216	£21,704	£23,537
Probability cost-effective £20,000	98%	98%	96%	93%	89%	82%	73%	60%	45%	30%	18%
Probability cost-effective £30,000	100%	100%	100%	100%	100%	100%	100%	99%	97%	94%	87%

4.8 Scenario analyses – SCID incidence, treatments for ADA-SCID and the TREC cut-off.

The result of the scenario analyses on SCID incidence, treatments for ADA-SCID and the TREC cut-off are shown in Table 17.

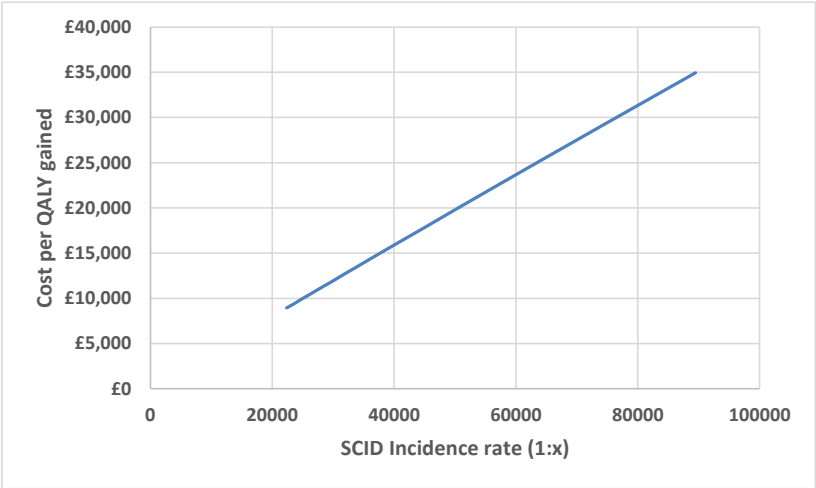
The incidence of SCID has a large impact on the cost effectiveness of screening, this is further investigated in Figure 12. The lower the incidence of SCID, the worse the cost effectiveness of screening, thus if the incidence is less than 1:50,000 or 1:75,000 newborns then the costs effectiveness rises above the £20,000 and £30,000 per QALY gained threshold respectively. Conversely if the SCID incidence is higher than the baseline estimate of 1:44,000 births then the cost effectiveness improves over and above the £17,600 estimate.

Table 17. Results for scenarios analyses

	Cost per QALY gained (discounted)	95% credibility interval		Probability cost per QALY <£20k	Probability cost per QALY <£30k
Basecase	£17,642	£11,496	£26,863	71%	99%
SCID Incidence					
Doubled	£8,942	£3,904	£14,914	100%	100%
Halved	£35,166	£24,634	£53,406	0%	18%
ADA SCID					
Late detected patients without a MFD receive gene therapy	£17,812	£11,669	£27,244	69%	99%
All patients receive ERT for 26 weeks	£18,969	£12,666	£28,447	58%	99%
All patients receive ERT for 11 weeks	£18,843	£12,573	£28,121	59%	99%
TREC test cut-off 30 copies/µl					
All additional presmptive positives are false positives	£18,591	£12,194	£28,132	61%	99%
Non-SCID TCLs increase proportionately with presumptive positive rate	£20,740	£13,785	£31,779	40%	96%

For the ADA SCID patients, assuming no difference between the duration of ERT in early or late detected patients increases the cost per QALY gained to just under £19,000, as it reduces cost saving benefits of screening. Increasing the proportion of patients undergoing gene therapy in the no screen arm raises the cost per QALY gained by around £200. This analysis reduces the benefit of screening in the ADA SCID cohort by assuming late detected patients would receive gene therapy whether or not they had a MFD thus improving survival in the no screen arm of the model. However, increasing the number of patients undergoing gene therapy would also increase the costs in the no screen arm of the model as gene therapy is more expensive than HSCT.

Figure 12. Impact of SCID incidence on cost effectiveness



Using a higher TREC test cut-off would increase the cost per QALY gained. If it is assumed that all additional presumptive positives results were found to be false positives at flow cytometry, the cost effectiveness is increased by about £1,000. If it is assumed that the number of non-SCID TCLs increases proportionately with the presumptive positive rate of about x3, the cost effectiveness is increased by about £3,000 to just above £20,000 per QALY gained. In contrast, it is understood that the feasibility of a lower TREC test cut-off is being investigated in order to reduce the false positive rate, whilst retaining the high SCID sensitivity. If this is achieved this would improve the cost effectiveness.

4.9 Threshold analyses - Quality of life impact of false positive results and for infants who would otherwise be identified as healthy at birth.

4.9.1 False positives threshold analysis

The model estimates that 260 (25, 264) infants will receive a false positive TREC test result, will be called in for flow cytometry and will receive a negative result with parents being told that no further immunological follow-up is required.

Table 18 presents a threshold analysis that explores the magnitude of potential disbenefits from a false positive TREC test that would be necessary in order for the cost effectiveness of screening to increase over £20,000 and £30,000 per QALY respectively for the whole screening programme. The analyses are presented for different discounting scenarios and for two different costs of the TREC test, that is £2.50 and £3.50 per test.

The numbers in yellow are highlighted to aid interpretation rather than suggesting these are preferred estimates. For instance, at a cost per test of £3.50 and with discounting at 3.5%, if 260 children are identified with a false positive result, we would have to assume that each child suffered a disbenefit of 0.08 QALYs (30 days) in order for the cost effectiveness of screening to go over a £20,000 threshold. The equivalent figure with discounting at 1.5% is 0.5 QALYs (183 days).

If the cost of the TREC test is reduced to £2.50 per test then we would have to assume that each child suffered a disbenefit of 0.23 QALYs (85 days) in order for the cost effectiveness of screening to go over a £20,000 threshold with discounting at 3.5% and 0.65 QALYs (236 days) with discounting at 1.5% .

Table 18. Threshold analysis – Quality of life disbenefit to children & families associated with a false positive result.

	Cost per TREC Test £3.50						Cost per TREC Test £2.50					
	Discounting @ 3.5%			Discounting @ 1.5%			Discounting @ 3.5%			Discounting @ 1.5%		
	Mean	95% credibility interval		Mean	95% credibility interval		Mean	95% credibility interval		Mean	95% credibility interval	
Baseline cost effectiveness	£17,642	£11,496	£26,863	£11,741	£7,617	£17,354	£13,446	£8,033	£20,776	£9,335	£5,579	£14,121
Baseline incremental cost	£3,243,281	£2,257,100	£4,385,141	£3,709,773	£2,466,487	£5,205,175	£2,472,602	£1,495,973	£3,597,203	£2,940,600	£1,712,766	£4,508,886
Baseline QALYs gained	184	118	274	316	202	468	184	120	274	315	204	468
Excess QALYs before £20,000 threshold is crossed	22	6	55	130	78	208	60	45	94	168	118	243
Excess QALYs before £30,000 threshold is crossed	76	43	128	192	119	295	101	70	154	217	147	318
False positives	260	25	764	260	25	764	260	25	764	260	25	764
Minimum QALY decrement for a false positive result to increase the screening programme cost effectiveness to be:												
greater than £20,000 threshold	0.08	0.22	0.07	0.50	3.19	0.27	0.23	1.84	0.12	0.65	4.82	0.32
greater than £30,000 threshold	0.29	1.76	0.17	0.74	4.87	0.39	0.39	2.86	0.20	0.83	5.99	0.42

4.9.2 Newborns with non-SCID TCL and the potential impact on infants who would be otherwise healthy at birth.

In addition to identifying newborns with SCID the TREC screening test identifies a group of infants with non-SCID TCL including a range of congenital syndromes, TCL secondary to other congenital conditions, newborns with variant SCID an and preterm births. The number of preterms that screening might be expected to identify have been discussed above. Table 19 presents estimates of the number of children with other non SCID TCL conditions identified.

Table 19. Newborns with non-SCID TCL

	Mean	95% credibility interval	
Children with TCL defined as variant SCID	4.5	0.1	16.5
Children with TCL due to congential syndromes	15.2	3.6	34.7
Children with TCL secondary to other conditions	5.9	0.3	19.7
Children with non SCID TCL who might be identified at birth without screening	19.0	6.7	38.4
Children with variant SCID or congenital syndromes who might be healthy at birth	6.5	1.5	16.0

The model estimates that there will be on average 26 (9, 50) babies identified each year with non-SCID TCL conditions other than preterms. It is estimated that of these newborns 19 (7, 38) would be symptomatic at birth and might be expected to be identified without screening at or shortly after birth, with some associated mortality. There is no evidence to suggest screening would benefit or conversely disbenefit these patients. It is estimated that screening would identify 7 (2, 16) newborns that may otherwise have been identified as healthy at birth. A proportion of these children might be expected to present to the health and social care system with symptoms at a later age without screening and these children would potentially stand to benefit from early diagnosis, but this proportion is currently unkown. This group is likely to include patients with ataxia telangiectasia and variant SCID. A recently published paper reporting the Californian experience (51) suggests in the order of 2 children with ataxia

telangiectasia and 5 with variant SCID. The paper, which refers to variant SCID as idiopathic TCL, reports that of 5 patients, one has resolved, two are continuing in follow-up and two have been lost to follow-up (Note that the follow-up of all patients within the paper ranges between 1 and 5 years) (51).

The quality of life decrement that would need to be applied to each healthy at birth non-SCID TCL patient identified through screening in order to bring the ICER to the threshold of £20,000 or £30,000 per QALY at a costs of £3.50 and £2.50 per test are shown in Table 20.

For the base case analysis, with a cost of £3.50 per test and discounting at 3.5%, a maximum of 22 QALYs could be lost before the ICER becomes £20,000. This would imply that if on average more than 3.3 QALYs were lost per healthy at birth non-SCID TCL child over their lifetime then the SCID screening programme cost effectiveness would increase over £20,000 per QALY. With discounting at 1.5% the equivalent figure is 20 QALYs.

If the cost of the TREC test is reduced to £2.50 per test then on average more than 9.1 QALYs need to be lost per healthy at birth non-SCID TCL child for the SCID screening programme cost effectiveness to increase over £20,000 per QALY. This threshold increases to 25.6 QALYs per healthy at birth child for discounting at 1.5 %.

Table 20. QALY decrement threshold analysis for newborns with non-SCID TCL who are healthy at birth

	Cost per TREC Test £3.50						Cost per TREC Test £2.50					
	Discounting @ 3.5%			Discounting @ 1.5%			Discounting @ 3.5%			Discounting @ 1.5%		
	Mean	95% credibility interval		Mean	95% credibility interval		Mean	95% credibility interval		Mean	95% credibility interval	
Baseline cost effectiveness	£17,642	£11,496	£26,863	£11,741	£7,617	£17,354	£13,446	£8,033	£20,776	£9,335	£5,579	£14,121
Baseline incremental cost	£3,243,281	£2,257,100	£4,385,141	£3,709,773	£2,466,487	£5,205,175	£2,472,602	£1,495,973	£3,597,203	£2,940,600	£1,712,766	£4,508,886
Baseline QALYs gained	184	118	274	316	202	468	184	120	274	315	204	468
Excess QALYs before £20,000 threshold is crossed	22	6	55	130	78	208	60	45	94	168	118	243
Excess QALYs before £30,000 threshold is crossed	76	43	128	192	119	295	101	70	154	217	147	318
Number of newborns with non-SCID TCL healthy at birth	7	2	16	7	2	16	7	2	16	7	1	16
Minimum QALY decrement for those healthy at birth to increase the screening programme cost effectiveness to be:												
greater than £20,000 threshold	3.3	3.6	3.4	20.0	51.4	13.0	9.1	29.9	5.8	25.6	79.5	15.3
greater than £30,000 threshold	11.6	28.3	8.0	29.5	78.4	18.4	15.3	46.4	9.5	33.1	98.7	20.0

4.9.3 Joint threshold analyses for the quality of life impacts of false positives and for infants who would otherwise be identified as healthy at birth.

Table 21 present a 2 dimensional threshold analysis that allows an exploration of the potential impact of QALY disbenefits from the identification of infants with false positive results and for infants who might be classified as idiopathic SCID who would be otherwise identified as healthy at birth.

Table 21. Joint threshold analysis for quality of life impacts of false positives and for infants who would otherwise be identified as healthy at birth

		Cost per TREC Test £3.50						Cost per TREC Test £2.50					
		False positive disbenefit threshold (quality adjusted days)						False positive disbenefit threshold (quality adjusted days)					
		Discounting @ 3.5%			Discounting @ 1.5%			Discounting @ 3.5%			Discounting @ 1.5%		
		Mean	95% credibility interval		Mean	95% credibility interval		Mean	95% credibility interval		Mean	95% credibility interval	
Healthy at birth disbenefit (QALY)	0	30	82	26	183	1166	99	82	656	44	230	1717	113
	1	21	59	19	174	1143	92	73	634	36	221	1696	106
	2	12	37	11	165	1121	84	64	612	29	212	1674	98
	3	3	14	3	156	1098	76	55	590	21	203	1652	91
	4	0	0	0	146	1075	69	46	568	13	194	1631	84
	10	0	0	0	91	939	23	0	437	0	140	1501	39
	20	0	0	0	0	712	0	0	217	0	50	1285	0

As an example to aid interpretation, with a cost per TREC test of £3.50, if 7 healthy at birth children had on average a disbenefit of 2 QALYs lost as a result of being identified with variant SCID (or other congenital condition) through screening, we would have to assume that each of the 260 false positive infants also suffered a disbenefit of over 12 quality adjusted days in order for the cost effectiveness of screening to go over a £20,000 threshold with discounting at 3.5%. The equivalent figure with discounting at 1.5% is 165 days disbenefit.

5 DISCUSSION

5.1 Summary of results

For the UK as a whole and with complete uptake of screening, it is estimated that screening for SCID would identify 17 (14, 22) newborns with SCID annually with the prevention of 6.4 (4.0, 9.7) SCID related deaths and a total gain of 184 (118, 274) discounted QALYs. It is estimated that screening for SCID would cost approximately £3.0 million per year, with discounted lifetime health and social care costs increasing by an estimated total of £3.2 (£2.3, £4.4) million for each annual cohort (inclusive of the above immediate screening cost). The baseline estimate of cost effectiveness of screening for SCID is £17,600 per QALY gained, with a 71% probability of this being better than a cost effectiveness threshold of £20,000.

It is estimated that screening will identify 260 (25, 764) true false positive cases who will undergo confirmatory testing followed by an all clear result. The evidence concerning impact of false positives on quality of life and parental preferences is mixed, therefore the baseline cost effectiveness estimates make no quality of life adjustment for this group.

The programme would also be expected to identify approximately 7 (1, 21) preterm newborns with TCL and 26 (9, 50) newborns with non-SCID TCL of other causes. Many of these newborns may be expected to show symptoms or be otherwise diagnosed in the absence of screening. However it is estimated that 7 (2, 16) newborns might be identified by screening that would otherwise be healthy at birth. There is currently no evidence to suggest that early diagnosis can benefit these children and no relevant UK evidence on incidence. In the Californian SCID screening programme, around half had resolved within the one to 5 year follow up period and half were either still being followed up or had been lost to follow up.

The results of the analysis are highly sensitive to the discount rate used. The use of a 1.5% discount rate for both benefits and costs results in a lower ICER of £11,700 per QALY, whilst the probability that cost effectiveness is better than £20,000 rises to over 99%. This is due to the majority of costs for screening and transplantation occurring in the first year and not being subjected to discounting. Whereas the QALY benefits of the intervention are spread over the patient's life and are discounted less with a reduced discount rate. NICE recommends that public health interventions use 1.5% for both costs and benefits for this reason. NICE also recommends that appraisal committees can consider a sensitivity analysis with a discount rate of 1.5% for benefits and 3.5% for costs when the intervention has a substantial and sustained impact on health.

The results are also sensitive to the per person cost of the screening test as this forms the largest single cost in the screening model, this may be particularly important when the potential impact on non-SCID cases is taken into account as discussed further below.

EVPI analysis suggests that the key uncertainties are SCID incidence, post HSCT mortality rates in the early diagnosed population, the length of stay in hospital of the early diagnosed SCID patients and the proportion detected by family history in the absence of screening. To a lesser extent there is also some uncertainty in the pre HSCT mortality rate in early diagnosed patients, the incidence of variant SCID, the QoL adjustment in SCID patients and the proportion of patients who receive IG.

The baseline estimates of SCID incidence in the UK have been obtained from 5 years historical experience without screening including some allowance for ascertainment bias. The UK estimate, in so far as it is based on non-screening experience is likely to represent a minimum but is in line with the incidence found in the US screening programmes. Further scenario analyses have explored a doubling and halving of the SCID incidence, increasing incidence improves cost

effectiveness of screening, whilst reducing the incidence worsens cost effectiveness the threshold incidence for a cost effectiveness of £20,000 and £30,000 per QALY is approximately 1:50,000 and 1:75,000 respectively.

The post HSCT mortality, baseline 9%, is a key parameter, the threshold analysis suggests that this could be as high as 15-16% and still be cost effective at the £20,000 threshold and 35% compared to 39% in the late diagnosed HSCT population, suggesting that the gain in pre-transplant mortality alone is sufficient to make screening cost effective at the higher threshold.

The proportion of SCID cases determined through family history without screening is also a key uncertainty. The model uses an estimate of 30% in the baseline, the threshold analysis suggests that this can rise to around 40% before the cost effectiveness of screening goes higher than £20,000.

5.2 Infants with non-SCID TCL

As discussed above, in addition to identifying newborns with SCID the TREC screening test identifies a group of infants with non-SCID TCL including a range of congenital syndromes, TCL secondary to other congenital conditions, preterm births and newborns with variant SCID.

The congenital syndromes identified such as DiGeorge, Trisomy 21, and Ataxia-Telangiectasia are life-limiting and non-treatable. Whilst many of these babies may present symptomatically without screening, screening for untreatable conditions is generally not recommended. The identification of these babies through screening has potential benefits and disbenefits for the patients and families. The diagnosis process for rare disorders can be long with often multiple visits to GP's or specialists before a diagnosis is made. Many Ataxia-Telangiectasia patients are also wrongly diagnosed with cerebral palsy. There is evidence that this delay can adversely affect the quality of life of the parents and can prevent suitable specialised support being offered (52-54). Identifying these

conditions through NBS would simplify the diagnosis process and prevent the 'diagnostic odyssey'. Earlier diagnosis may also allow supportive treatments to be offered earlier and allow families to prepare both practically and emotionally for the future.

For hereditary genetic disorders an early diagnosis can provide information that may have a bearing on parents' future reproductive plans. Families are likely to have additional children, who will also have a risk of being affected, when the diagnosis is not made until early childhood. A diagnosis through NBS would allow families to make an informed choice about their future reproductive plans - this may be to not have any more children, to undergo preimplantation genetic testing, or to undergo prenatal testing. This issue was raised at multiple points in the consultations with clinicians.

However, identifying these conditions may cause parents stress and anxiety and they may feel that 'ignorance would have been better' in terms of spending and enjoying time with their child before they were symptomatic. Both the clinician we spoke to were in favour of NBS for SCID and in general felt it would be positive for those identified with DiGeorge and Ataxia-Telangiectasia.

There are a number of studies in the literature that research parents' views on identifying untreatable conditions through NBS (55-62). However, none of these studies address the issue of identifying these conditions as a secondary finding. The studies identified addressed attitudes to NBS for specific conditions including fragile X syndrome (FXS) (59, 61), Duchenne, Becker, or Spinal muscular dystrophy (56-58), or Lysomol storage disorders such as mucopolysaccharidoses (MPS) (62) as well as studies on general attitudes to untreatable conditions (55, 60). Some studies asked expectant or postnatal parents whereas others questioned parents and patients of untreatable conditions that were identified by NBS or through symptomatic presentation. The studies were conducted in the US, Australia, New Zealand, Wales and the Netherlands. In general the majority of respondents in all the studies were in favour of screening for untreatable conditions. In those studies where

expectant/postnatal parents were consulted, the main benefit of screening given was that screening would give them time to prepare and that screening could prevent a long diagnosis process. There were two pilots for screening for Fragile X syndrome (59, 61) and in both there was evidence of parental anxiety. In one pilot 10% of respondents said they felt anxious about the test results (59) and in the other pilot the 21% of those that declined the test did so as they did not want to worry. Another 21% said the main reason was logistics and only 5% identifying no treatment or cure as a reason for declining the screening test (61). The importance of reproductive choice differed between the studies with 64% of those in the Australian pilot agreeing that they would use the information when planning more children (59). In the US pilot (61) only 8% identified future reproductive choice as a reason for agreeing to screening.

With regards to the studies that looked at the attitudes of parents and patients with life-limiting conditions there was broad support for NBS for the conditions with between 80% and 100% supporting NBS for the relevant condition. There was a concern in the non-screened groups that NBS may lead to anxiety (56-58) however, this was not found to be the case in the screened group. The screened groups were also more likely to say that screening gave them a chance to 'make good memories' (56, 57). However, in one study 3 of the 10 families felt that screening had impacted detrimentally on the non-symptomatic period (57). Whereas there was some concern in one of the screened and one of the non-screened groups that NBS would remove the period of good health before symptoms occur, a period they greatly treasured (57, 62). Overall the screened groups were more positive in their views of screening compared to the non-screened groups and also identified reproductive choice as an important issue. Over 50% of affected screened parents in the Chung et al study and 80% of affected screened parents in the Parsons et al study said that screening and the subsequent diagnosis had affected their reproductive plans (57, 63).

5.3 Limitations of the analysis

In addition to the limitation discussed above the TREC test is assumed to have a very high sensitivity. This is in line with the available evidence, however the proposed UK TREC threshold for screening is lower than has been used throughout the US. This lower threshold has the benefit of reducing the false positive rate and whilst the sensitivity is well supported by evidence from the UK population (6), this is still a relatively small study and the test characteristics achieved in practice should be monitored and cut-offs adjusted accordingly. Scenario analyses have examined the potential impact of increasing the TREC threshold to 30 copies/μL which triples the false positive rate and cost effectiveness remains better than £25,000 per QALY gained.

The model assumes that the survival effectiveness of transplantation following an early SCID diagnosis from screening is the same as in infants identified asymptomatically by family history. This is a proxy subgroup and outcomes in screen identified patients may differ somewhat. Furthermore there is evidence that transplantation outcomes have improved with developments in practice. Recent evidence from the follow up of patients identified by screening in California has reported survival rates of 94% (51), this is higher than the 90% estimate used in the model for the early diagnosed cohort, though follow up in more recent cohorts is necessarily limited. In line with available evidence, the model has assumed that, if patients survive the immediate transplant period then subsequent mortality follows a normal population. Long term follow-up is required to confirm this assumption.

There is currently no quality of life utility evidence available in the SCID population. This methodological weakness is not specific to the SCID population, but rather arises primarily from deeper foundational, if not philosophical controversies associated with undertaking economic evaluation in child health (64). With regard to preference based measures of child health, the CHU9D (developed at ScHARR) is currently the only measure that can provide validated utility valuations for children (65). Further whilst there has been development

and testing of a paediatric EQ-5D-Y across many languages (66) there are currently no paediatric value sets available. In the absence of such measures, this study has used an adult EQ-5D valuation applied to health state descriptions generated with reference to medical records of affected children. Whilst there undoubted methodological weaknesses in this approach, there is no evidence to suggest a structural bias in the estimates obtained.

There are further methodological issues for screening associated with treatments for very rare conditions. Such treatments are now assessed by NICE's highly specialised technologies committee (67) which does not use the threshold of £20,000-£30,000 per QALY to make decisions, rather no threshold value is used and decisions are made based on an assessment of the overall value of the new technology. The knock on impact on screening programmes that have the potential to initiate such therapies for example gene therapy, which would not normally be considered cost-effective at the standard threshold of £20,000-£30,000 per QALY needs to be assessed.

Lastly there is a high degree of variation in the incidence of SCID found in different population subgroups. The economic model assumes an average UK population level of risk, for both SCID and the other non-SCID TCL conditions in assessing the essential trade-off between costs and health benefits. It should be noted that the economic effectiveness may be expected to vary greatly in the different population subgroups. Furthermore, since the incidence of the non-SCID TCL conditions may also vary and not necessarily in line with SCID, giving rise to an inequitable distribution of benefits and disbenefits.

6 REFERENCES

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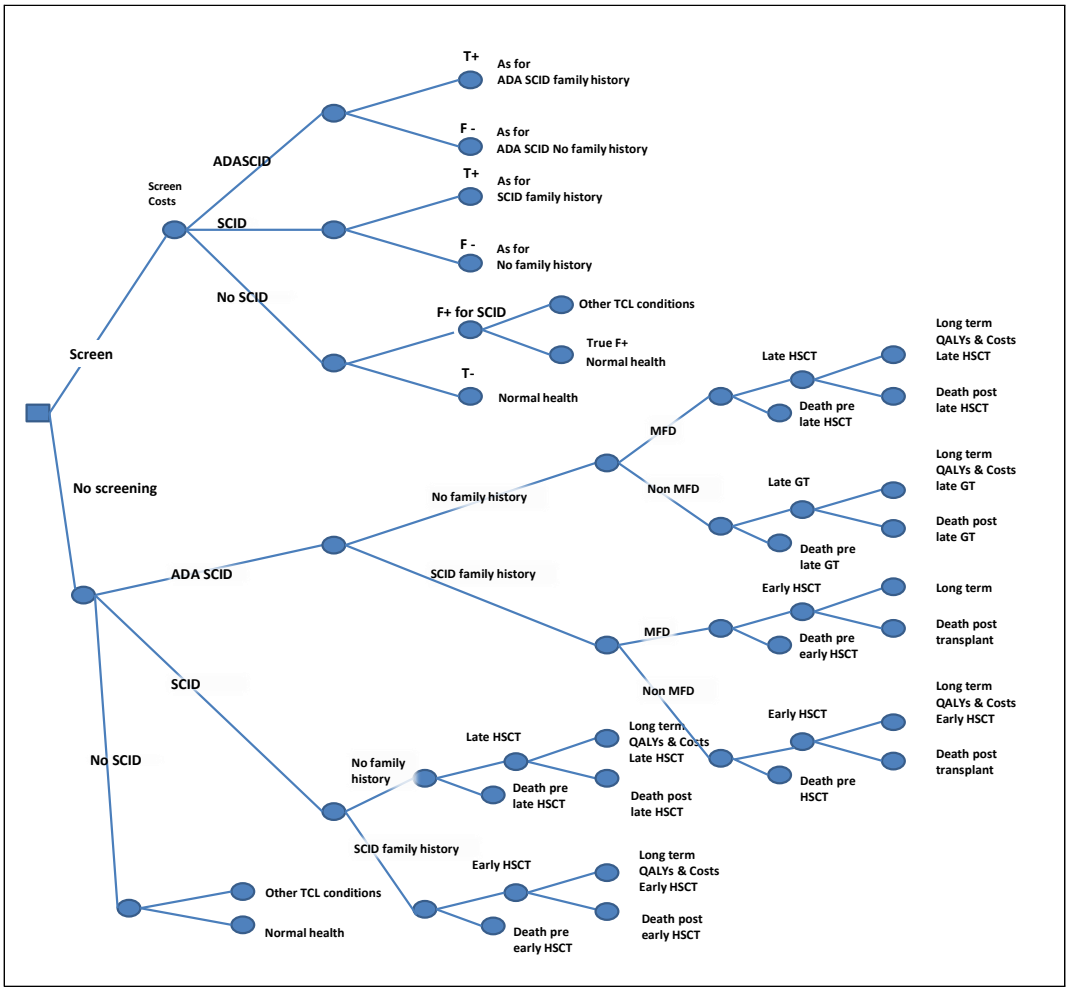
APPENDIX A: Full Decision Tree Diagram



APPENDIX B: Detailed cost table

Cost description		Cost 2014/15	Reference
Screening	Band 5 worker (50% FTE)	£12,744	(18)
	Workstation	£2,700	(41)
	Screening test	£3.50	(2)
Presumptive positives	Flow cytometry	£25	(26)
	1 x immunology app	£251	(25)
	Total	**£276**	
Follow up preterm & secondary to other conditions	2 x immunology app	£503	(25)
	2 x flow cytometry	£50	(26)
	Total	**£553**	
Syndromes 4 year follow up	2 x multispecialty app per year	£2,011	(25)
	2 x flow cytometry per year	£50	(26)
	Total 4 years (undiscounted)	**£5,107**	
	Total 4 years (discounted)	**£4,872**	
Variant SCID 0-2 years old	3 x immunology app per year	£754	(25)
Variant SCID 2-5 years	2 x immunology app per year	£503	(25)
Variant SCID (IG and antibiotics)	IG 1st year	£1,789	(39) (40) (68)
	IG 2nd year	£2,716	(39) (40) (68)
	IG 3rd year	£3,319	(39) (40) (68)
	IG 4th year	£3,875	(39) (40) (68)
	IG 5th year	£4,253	(39) (40) (68)
	Antibiotics 1st year	£310	(39) (40)
	Antibiotics 2nd year	£620	(39)
	Antibiotics 3rd year	£620	(39)
	Antibiotics 4th year	£620	(39)
	Antibiotics 5th year	£620	(39)
	Total 5 years (undiscounted)	**£21,757**	
	Total 5 years (discounted)	**£20,142**	
Diagnosis SCID,	1 x immunology app	£251	(25)
	1 x genetic test	£567.5	(69)
	Total	**£711**	
Diagnosis variant SCID	1 x immunology app	£251	(25)
	1 x genetic test (206 exome panel)	£1,300	(69)
	Total	**£1,551**	
Diagnosis syndromes	1 x immunology app	£251	(25)
	50% 1 x genetic test (206 exome panel)	£1,300	(69)

	Total	**£1,551**	
ERT	ERT 1 vial per week	£7,500	(43)
	Administration – 1 x non clinical immunology app per week	£180	(25)
	Early diagnosed – 11 weeks	**£84,475**	
	Late diagnosed - 26 weeks	**£199,668**	
Inpatient Care	Day cost inpatient paediatric disorder of the immunity (average)	£1,495	(25)
	Day cost inpatient paediatric critical care level 3	£1,967	(25)
HSCT	Cost of HSCT – 54 days	£80,556	(25)
	Early diagnosed HSCT – HSCT + 29 days non-critical care + 2.6 days critical care	**£128,363**	(26)
	Late diagnosed HSCT – HSCT + 90 days non-critical care + 3.8 days critical care	**£231,186**	(26)
Gene therapy (GT)	Cost of Strimvelis	£509,027	(42)
	Early diagnosed GT – GT + 12 days non-critical care + 0.25 days critical care	**£527,829**	(26)
	Late diagnosed GT – GT + 45 days non-critical care + 3.3 days critical care	**£585,994**	(26)
Death before transplant	**12.5 days non-critical care + 12.5 days critical care**	**£43,368**	(26)
Follow up SCID well 1st year	4 x immunology app per year	£1,005	(25)
Follow up SCID well 2nd-3rd year	2 x immunology app per year	£503	(25)
Follow up SCID well 4th year +	1 x immunology app per year	£251	(25)
Follow up SCID not well 1st year	6 x immunology app per year	£1,508	(25)
Follow up SCID not well 2nd year	4 x immunology app per year	£1,005	(25)
Follow up SCID not well 3rd-4th year	2 x immunology app per year	£503	(25)
Follow up SCID not well 5th year+	1 x immunology app per year	£251	(25)
SCID – enteral feeding	Gastrostomy surgery	£1,539	(25)
	6 x dietician appointments (per year)	£496	(25)
	Feeds 1st year (50% calorific requirements)	£1,315	(39)
	Feeds 2nd year (50% calorific requirements)	£1,996	(39)
SCID – Mild developmental delay	0-3 years	£1,404	(70) (39)

	4-11 years	£24,138	(70) (39)
	12-17 years	£24,138	(70) (39)
	18+ years	£9,347	(70) (39)
IG	For whole life (cost increases with age up to 18 years)	£1,789-£16,481	(39) (68) (40)
Antibiotics	1st year per year (125 mg per day, oral solution)	£310	(39)
	2nd-5th year per year (250mg per day, oral solution)	£620	(39)
	6th year+ per year (250mg per day, tablets)	£28	(39)
Steroids (2 years)	2 mg per kg per day	£772 - £943	(39) (68)
ADHD (5-18 years)	Medication per year	£295	(39)
	2 x CAHMs appointments per year	£599	(25)

APPENDIX C: Long Term Outcomes Extraction Table

Study	Patel et al 2008 & Patel et al 2009 (individual data)	Patel et al 2009 E (Tx)	Patel et al 2009 L (Tx)	Patel et al 2008 E (Tx)	Patel et al 2008 L (Tx)	Patel et al 2009&2008 9	Patel et al 2009&2008 24	Dell Railey et al 2009	Early Tx 41	Late Tx 70	Mazzolari et al 2007 (individual data)	Early Tx 7	Late Tx 33	Early Tx 7	Late Tx 33
Overall															
Considered Healthy								Y	88.00%	85.00%					
Alive and Well															
No complications								Y (no problems)	49.00%	29.00%	Y (no problems/complications)	3	12	42.86%	36.36%
Treatments															
No treatment															
Infection prophylaxi via immunoglobulin substitution, antibiotic treatment or both															
Requires standing antibiotics								Y	25.00%	29.00%	Y	1	2	14.29%	6.06%
Enteral feeding for anorexia															
Immunosuppressive drugs for cGVHD and/or autoimmunity/inflammation															
Thyroid hormone replacement therapy											Y	0	4	0.00%	12.12%
Pancreatic enzymes and neuroleptic and antiepileptic drugs											Y (antiepileptic)	0	3	0.00%	9.09%
Combined medical and surgical treatmetns for severe HPV infections															
Testosterone											Y	0	1	0.00%	3.03%
Growth hormone											Y	0	1	0.00%	3.03%
Ursodiol (to dissolve gall stones)											Y	1	0	14.29%	0.00%
Omeprazole (to treat GERD)											Y	1	0	14.29%	0.00%
Methymazole - to treat hyperthyroidism											Y	0	1	0.00%	3.03%
Steroids											Y	0	1	0.00%	3.03%
Retransplant	Y							Y	10.00%	34.00%					
Requires IG	Y	1	2	0	0	11.11%	8.33%	Y	58.00%	56.00%	Y	3	2	42.86%	6.06%
GvHD or cGVHD complications															
Persistent cGVHD	Y (area and grade)							Y (skin)	4.00%	in both	Y (aGVHD)	0	4	0.00%	12.12%
veno-occlusive disease															
Autoimmune/inflammatory															
AIHA	Y	0	1	0	0	0.00%	4.17%				Y	0	3	0.00%	9.09%
Myositis						0.00%	0.00%								
Psoriasis, vitiligo, alopecia	Y (vitiligo, alopecia)	0	0	1	1	11.11%	4.17%				Y (vitiligo)	0	1	0.00%	3.03%
Ill-defined inflammatory disease						0.00%	0.00%								
Disseminated granulomatous disease						0.00%	0.00%								
Autoimmune fasciitis (eosinophilic fasciitis)	Y	0	0	0	1	0.00%	4.17%								
Bronchiolitis obliterans (obstruction of the smallest airways of the lungs due to inflammation)	Y	0	0	1	2	11.11%	8.33%								
Hypothyroidism											Y	0	4	0.00%	12.12%
Hyperthyrodidism								Y	3.00%	1.00%	Y	0	1	0.00%	3.03%
Myasthenia (Autoimmunity) - affects the nerves and muscles											Y	0	1	0.00%	3.03%
Encephalitis (could be immune or infection)											Y	0	1	0.00%	3.03%
Guillain-Barre like															
Allergic rhinitis (inflammation of the inside of the nose)	Y	0	1	0	0	0.00%	4.17%								
Spongiotic dermatitis	Y	0	0	0	1	0.00%	4.17%								
Immune thrombocytopenia															
Total autoimmune/inflammatory		**0**	**2**	**2**	**5**	**22.22%**	**29.17%**					**0**	**11**	**0.00%**	**33.33%**

Severe or recurrent infection															
Opportunistic infection															
Recurrent LRTI											Y (RTI)	2	1	28.57%	3.03%
Chronic sinusitis and/or chronic bronchopneumopathy															
Viral encephalitis															
Chronic HHV6 infection	Y	1	1	0	0	11.11%	4.17%								
Chronic hepatitis B infection	Y	0	0	0	1	0.00%	4.17%								
EBV infection															
Pharyngeal abscess															
Osteomyelitis (bone infection)															
Atypical mycobacteria infection															
Pneumonia								Y (in past 2 years)	11.00%	5.00%					
Otitis media (ear infection) in past 2 years								Y	5.00%	for both					
CMV retinitis											Y	0	1	0.00%	3.03%
B-lymphoproliferative disease															
Sinustis in past 2 years								Y	21.00%	22.00%					
Total infection		**1**	**1**	**0**	**1**	**11.11%**	**8.33%**					**2**	**2**	**28.57%**	**6.06%**
Chronic HPV															
Severe HPV infection															
Mild HPV infection															
Gastro															
Protein-losing enteropathy (damage to gut wall that results in a net loss of protein from the body)	Y	1	0	0	0										
Eosinophilic gastroenteritis	Y	0	1	0	0										
Chronic colitis	Y	0	0	0	1										
Diarrhea								Y	5.00%	17.00%					
GERD								Y	5.00%	4.00%					
Total		**1**	**1**	**0**	**1**	**11.11%**	**8.33%**								
Nutritional Support															
Enteral feeding															
Parenteral nutrition															
Boost															
Growth insufficiency (weight and/or height less than the third percentile)	Y (poor growth, short stature)	0	1	0	0			Y (height & weight <3rd)	2.00%	17.00%	Y (height & weight percentile)	0	7	0.00%	21.21%
Obesity	Y	1	1	0	1										
Oral aversion (food aversion)	Y	0	0	0	1			Y	2.00%	4.00%					
Skin conditions															
Eczema	Y	0	2	0	0										
Cutaneous candidiasis (skin infection)	Y	0	0	1	0										
Warts (same as HPV infection above)	Y	1	1	1	3			Y	11.00%	16.00%					
Perstient rashes								Y	23.00%	29.00%					
Genodermatosis (inherited single-gene disorders with skin manifestations)											Y	0	1	0.00%	3.03%
Precanerous skin lesions	Y	0	0	0	1										
Total		**1**	**3**	**2**	**4**	**33.33%**	**29.17%**								

Respiratory/lung issues															
Asthma	Y	3	3	0	1			Y	15.00%	16.00%					
reactive airway disease (could refer to asthma or upper respiratory infections	Y	0	2	0	0										
chronic lung disease	Y	0	0	1	0										
bronchiectasis	Y	0	0	1	0						Y	1	1	14.29%	3.03%
Mild obstructive insufficiency											Y	1	0	14.29%	0.00%
Pneumothoraces															
Total respiratory issues		**3**	**5**	**2**	**1**	**55.56%**	**25.00%**					**2**	**1**	**28.57%**	**3.03%**
Neurologic issues															
Neurogenic bladder (caused by neurologic damage)	Y	0	0	1	0										
Paraplegia											Y	0	1	0.00%	3.03%
Tetraparesis											Y	0	1	0.00%	3.03%
Seizure disorder inc epilepsy	Y	0	0	2	0			Y	2.00%	1.00%	Y	0	3	0.00%	9.09%
Ataxia - affects co-ordination, balance, and speech											Y	0	1	0.00%	3.03%
Cerebral palsy								Y	2.00%	for both	Y (Diplegia)	0	1	0.00%	3.03%
CNS asphyxia											Y	0	1	0.00%	3.03%
ADHD								Y	16.00%	17.00%	Y	0	1	0.00%	3.03%
Speech delay	Y	0	1	0											
Developmental delay	Y (mental retardation)							Y	5.00%	18.00%	Y (cognitive impairment)	0	2	0.00%	6.06%
Special needs at school								Y	3.00%	4.00%					
Behavioural disorder															
Hypotonia (decreased muscle tone)											Y	0	2	0.00%	6.06%
Migraines	Y	1	0	0	0										
Total neurolgoical issues		**1**	**1**	**3**	**0**	**44.44%**	**4.17%**					**0**	**13**	**0.00%**	**39.39%**
Sight															
Cataracts	Y	0	1	0	0						Y	0	2	0.00%	6.06%
Blindness	Y	0	0	1	0										
myopia	Y	0	0	1	0						Y	0	1	0.00%	3.03%
Hypermetropia (long sight)											Y	0	1	0.00%	3.03%
Left eye isotropism											Y	0	1	0.00%	3.03%
Astigmatism											Y	0	1	0.00%	3.03%
Lenses											Y	0	1	0.00%	3.03%
Keratopathy (corneal disease)											Y	0	1	0.00%	3.03%
Total sight issues		**0**	**1**	**2**	**0**	**22.22%**	**4.17%**					**0**	**8**	**0.00%**	**24.24%**
Hearing															
Hearing loss											Y	1	1	14.29%	3.03%
Dentition	Y (Dental caries)	1	1	1	0						Y (molars agenesia, enamel hypoplasia)	0	3	0.00%	9.09%
Endocrine problems															
Hypogonadotropic hypogonadism											Y	0	2	0.00%	6.06%
Amenorrhea (absence of menstruation)	Y	0	0	1	0										
Adrenal insufficiency	Y	0	0	1	0										
Pituitary micoadenoma	Y	0	0	1	0										
Other conditions															
Fire ant hypersensitivity	Y	1	0	0	0										
Anemia	Y	1	1	0	0										
Cavernoma - a cluster of abnormal blood vessels, usually found in the brain and spinal cord											Y	1	0	14.29%	0.00%
Congenital lymphedema - swelling of certain parts of the body											Y	0	1	0.00%	3.03%
Splenectomy															
Renal impairment															
Hypertension	Y	0	0	0	1										
BCGosis															
Sleep apnea	Y	0	0	1	0										
Ganglion cysts	Y	0	0	0	1										

APPENDIX D: Record of expert consultations: Non-SCID congenital syndromes.

Ataxia-Telangiectasia - Telephone call with Dr Elizabeth McDermott. Consultant Immunologist, Nottingham University Hospitals NHS Trust. 30th March 2016

Patients are usually diagnosed at around 4 to 5 years old. However, they may have been symptomatic since they were toddlers and would probably have been to see the GP multiple times before a diagnosis is made. A number of patients are also mis-diagnosed as having cerebral palsy.

Patients may present with infections before other symptoms of AT are noticeable. Children can develop lung disease due to persistent infections. Some patients will need immunoglobulin or antibiotics.

TREC numbers are generally low in patients with AT. Immunology blood tests aren't always a good measure of which patients will go on to develop infections.

Patients diagnosed through screening will be seen every other year at the National AT clinic or yearly if there is an issue.

Babies are already tested if there is a family history of AT.

Screening is a good idea and the benefits for AT patients of being diagnosed through screening are likely to be a quicker diagnosis, a possible reduction in infections or damage done by infections, and it will allow families to make future reproductive choices. However, it is likely to lead to an increase in immunology referrals.

DiGeorge - Telephone call with Dr Andrew Gennery Honorary Consultant in Paediatric Immunology and Haematopoietic Stem Cell Transplantation, Newcastle Hospitals NHS Trust. 1st March 2016

The prevalence of DiGeorge is estimated at 1:4,000. A US paper estimated that 30% of DiGeorge cases are picked up with TREC screening

The diagnosis process is variable with patients presenting with number of different symptoms. Patients can present from any time from a few days/weeks after birth to a few years later. Those with heart defects present within the first few weeks following birth and those without a heart defect present at at a few months to a few years old.

Those with milder immune problems are likely to get picked up later and those with severe immune problems are likely to get picked up earlyish.

Patients are likely to be symptomatic from an early age but this may not be recognised as DiGeorge immediately.

There are possible improved outcomes for severe patients if they are diagnosed earlier and receive a transplant. There are also potential benefits for milder patients in that they will receive support earlier will may lead to better outcomes both for the patient and their family.

Patients with DiGeorge can be diagnosed by a physical examination but all patients will have a genetic test to confirm the diagnosis.