

## Supplementary Material

Table S1: Detailed cost table

Cost description		Cost 2014/15	Reference
Screening	Band 5 worker (50% FTE)	£12,744	[1]
	Workstation	£2,700	[2]
	Screening test (per baby)	£3.50	[3]
Presumptive positives	Flow cytometry	£25	[3]
	1 x immunology appointment	£251	[4]
	<b>Total</b>	<b>£276</b>	
Follow up preterm & secondary to other conditions	2 x immunology appointments	£503	[4]
	2 x flow cytometry tests	£50	[3]
	<b>Total</b>	<b>£553</b>	
Syndromes 4 year follow up	2 x multispecialty appointments per year	£2,011	[4]
	2 x flow cytometry tests per year	£50	[3]
	<b>Total 4 years (undiscounted)</b>	<b>£5,107</b>	
	<b>Total 4 years (discounted)</b>	<b>£4,872</b>	
Idiopathic SCID 0-2 years old	3 x immunology appointments per year	£754	[4]
Idiopathic SCID 2-5 years	2 x immunology appointments per year	£503	[4]
Idiopathic SCID (IG and antibiotics)	Immunoglobulin 1 <sup>st</sup> year	£1,789	[5] [6] [7]
	Immunoglobulin 2 <sup>nd</sup> year	£2,716	[5] [6] [7]
	Immunoglobulin 3 <sup>rd</sup> year	£3,319	[5] [6] [7]
	Immunoglobulin 4 <sup>th</sup> year	£3,875	[5] [6] [7]
	Immunoglobulin 5 <sup>th</sup> year	£4,253	[5] [6] [7]

	Antibiotics 1 <sup>st</sup> year	£310	[5] [6]
	Antibiotics 2 <sup>nd</sup> year	£620	[5]
	Antibiotics 3 <sup>rd</sup> year	£620	[5]
	Antibiotics 4 <sup>th</sup> year	£620	[5]
	Antibiotics 5 <sup>th</sup> year	£620	[5]
	<b>Total 5 years (undiscounted)</b>	<b>£21,757</b>	
	<b>Total 5 years (discounted)</b>	<b>£20,142</b>	
Diagnosis SCID,	1 x immunology appointment	£251	[4]
	1 x genetic test	£567.5	[8]
	<b>Total</b>	<b>£711</b>	
Diagnosis idiopathic SCID	1 x immunology appointment	£251	[4]
	1 x genetic test (206 exome panel)	£1,300	[8]
	<b>Total</b>	<b>£1,551</b>	
Diagnosis syndromes	1 x immunology appointment	£251	[4]
	50% 1 x genetic test (206 exome panel)	£1,300	[8]
	<b>Total</b>	<b>£1,551</b>	
Enzyme Replacement Therapy (ERT) (Adagen)*	ERT 1 vial per week	£7,500	[9]
	Administration – 1 x non clinical immunology appointments per week	£180	[4]
	<b>Early diagnosed – 11 weeks</b>	<b>£84,475</b>	
	<b>Late diagnosed - 26 weeks</b>	<b>£199,668</b>	
Inpatient Care	Day cost inpatient paediatric disorder of the immunity (average)	£1,495	[4]
	Day cost inpatient paediatric critical care level 3	£1,967	[4]
HSCT	Cost of HSCT – 54 days	£80,556	[4]

	<b>Early diagnosed HSCT – HSCT + 29 days non-critical care + 2.6 days critical care</b>	<b>£128,363</b>	[3, 4]
	<b>Late diagnosed HSCT – HSCT + 90 days non-critical care + 3.8 days critical care</b>	<b>£231,186</b>	[3, 4]
Gene therapy (GT)	Cost of Strimvelis	£509,027	[10]
	<b>Early diagnosed GT – GT + 12 days non-critical care + 0.25 days critical care</b>	<b>£527,829</b>	[3, 4]
	<b>Late diagnosed GT – GT + 45 days non-critical care + 3.3 days critical care</b>	<b>£585,994</b>	[3, 4]
<b>Death before transplant</b>	<b>12.5 days non-critical care + 12.5 days critical care*</b>	<b>£43,368</b>	[3, 4]
Follow up SCID well 1 <sup>st</sup> year	4 x immunology appointments per year	£1,005	[4]
Follow up SCID well 2 <sup>nd</sup> -3 <sup>rd</sup> year	2 x immunology appointments per year	£503	[4]
Follow up SCID well 4 <sup>th</sup> year +	1 x immunology appointments per year	£251	[4]
Follow up SCID not well 1 <sup>st</sup> year	6 x immunology appointments per year	£1,508	[4]
Follow up SCID not well 2 <sup>nd</sup> year	4 x immunology appointments per year	£1,005	[4]
Follow up SCID not well 3 <sup>rd</sup> -4 <sup>th</sup> year	2 x immunology appointments per year	£503	[4]
Follow up SCID not well 5 <sup>th</sup> year+	1 x immunology appointments per year	£251	[4]
SCID – enteral feeding	Gastrostomy surgery	£1,539	[4]
	6 x dietician appointments (per year)	£496	[4]
	Feeds 1 <sup>st</sup> year (50% calorific requirements)	£1,315	[5]

	Feeds 2 <sup>nd</sup> year (50% calorific requirements)	£1,996	[5]
SCID – Mild developmental delay	0-3 years	£1,404	[11] [5]
	4-11 years	£24,138	[11] [5]
	12-17 years	£24,138	[11] [5]
	18+ years	£9,347	[11] [5]
IG	For whole life (cost increases with age up to 18 years)	£1,789-£16,481	[5] [7] [6]
Antibiotics	1 <sup>st</sup> year per year (125 mg per day, oral solution)	£310	[5]
	2 <sup>nd</sup> -5 <sup>th</sup> year per year (250mg per day, oral solution)	£620	[5]
	6 <sup>th</sup> year+ per year (250mg per day, tablets)	£28	[5]
Steroids (2 years)	2 mg per kg per day	£772 - £943	[5] [7]
ADHD (5-18 years)	Medication per year	£295	[5]
	2 x CAHMs appointments per year	£599	[4]

FTE – Full time equivalent, SCID – Severe combined immunodeficiency, IG – Immunoglobulin, ERT – Enzyme replacement therapy, HSCT – Hematopoietic stem cell transplant, GT – Gene therapy, ADHD – Attention deficit hyperactivity disorder, CAHMS – Child and adolescent mental health service, \*Based on clinical advice patients with ADA-SCID were assumed to receive enzyme replacement therapy for 11 for those diagnosed early and 26 weeks for those diagnosed later and would receive gene therapy in the absence of a fully matched donor, + For patients that die before HSCT and those not diagnosed, we have assumed 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

**Table 2. Full parameters table and distributions.**

Parameter	Mean (95% Confidence Interval)	Distributions for use in the probabilistic sensitivity analysis	Reference
Number of births (UK)	780835	N/A	[12-14]
Incidence of SCID	1:49,000 (1:39,857, 1:61,527)	Beta (82; 4,012,522)	[15]
Incidence of undiagnosed SCID	1:521,000 (1:167,052, 1:7,236,800)	Beta (1.5; 780,833)	[15]
Incidence of syndromes	1:45,000 (1:24,390, 1:110,606)	Beta (7.2; 325,208)*	[16]
Incidence of secondary conditions	1:130,000 (1:50,686, 1:782,506)	Beta (2.5; 325,213)*	[16]
Incidence of idiopathic TCL	1:99,000 (1:42,255, 1:432,482)	Beta (3.3; 325,212)*	[16]
Incidence of preterms	1:99,000 (1:42,255, 1:432,482)	Beta (3.3; 325,212)*	[16]
Sensitivity for SCID	0.99 (0.985, 0.998)	Beta (1567.17; 15.83)	[17]
Presumptive positives (20 copies/ $\mu$ l)	0.041% (0.0035%, 0.1018%)	Beta (2.096; 5079)	[18]
Proportion of SCID patients with a family history	0.30 (0.21, 0.41)	Beta (25; 57)	[15]
Proportion of SCID ADA-SCID	0.17 (0.1, 0.26)	Beta (14; 82)	[15]
Proportion of SCID patients with a matched family donor available	0.25 (0.07, 0.5)	Beta (3.5,10.5)	[15]
Pre HSCT mortality (late diagnosed)	0.35	Beta (17; 31)	[19]

Pre HSCT mortality odds ratio (early diagnosed)	0.03	Lognormal (-4.03; 1.05)	[19]
HSCT mortality (late diagnosed)	0.39	Beta (12; 19)	[19]
HSCT mortality odds ratio (early diagnosed)	0.15	Lognormal (-2.1; 0.6)	[19]
ADA-SCID pre HSCT mortality (late diagnosed)	0.21	Beta (10, 38)	[3, 19]
ADA-SCID pre HSCT mortality odds ratio (early diagnosed)	0.06	Lognormal (-3.31; 1.07)	[19]
ADA-SCID HSCT mortality (matched family donor) (late diagnosed)	0.33	Beta (4; 8)	[19]
ADA-SCID HSCT mortality odds ratio (matched family donor) (early diagnosed)	0.11	Lognormal (-2.91; 1.2)	[19]
ADA-SCID Gene therapy mortality	0.05	Beta (1; 18)	[19]
Number of days HSCT	54.0	N/A	[3]
Early diagnosis - Total days non-critical care	82.6 (50.3, 122.8)	Gamma (19.73; 4.19)	[3]
Early diagnosis - Total days critical care	3.96 (0.15, 8.41)	Gamma (1.35; 1.92)	[3]
Late diagnosis - Total days non-critical care	144 (108.6, 184.3)	Gamma (55.39; 2.6)	[3]
Late diagnosis - Total days critical care	8.19 (3.72, 14.4)	Gamma (8.9; 0.92)	[3]
Early diagnosis - Gene therapy - Total non-critical care preGT	12.25 (7.8, 17.7)	Gamma (22.97; 0.53)	[3]

Early diagnosis - Gene therapy - Total critical care preGT	0.25 (0.03, 0.7)	Gamma (1.94; 0.13)	[3]
Late diagnosis - Gene therapy - Total non-critical care preGT	45.7 (35.6, 57.1)	Gamma (69.72; 0.66)	[3]
Late diagnosis - Gene therapy - Total critical care preGT	4.37 (1.59, 8.53)	Gamma (5.93; 0.74)	[3]
QALYs - early diagnosis	0.95	Beta (212.39; 6.62)	[20]
QALYs - late diagnosis	0.82	Beta (165.35; 21.89)	[20]

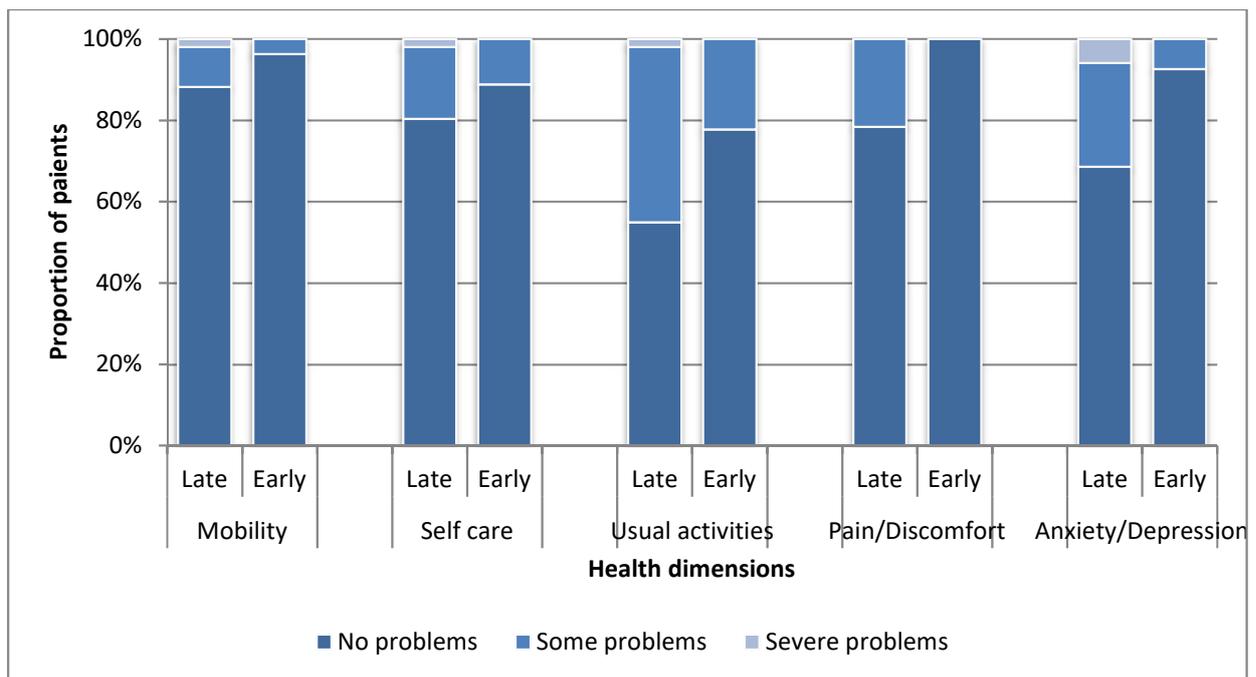
UK - United Kingdom, SCID - severe combined immunodeficiency disorder, TCL - T Cell lymphopenia, TREC - T cell receptor excision circle, ADA - adenosine deaminase deficiency, HSCT - hematopoietic stem cell transplantation, QALYs - quality adjusted life years. \* The denominator used in the sampling was taken to be 10% of the Californian birth rate in order to take into account the uncertainty with using non UK data.

**Table S3: Long-term outcomes**

Parameter	Early Diagnosed				Late Diagnosed				Reference
	Proportion	Distribution	Cases	95% CI	Proportion	Distribution	Cases	95% CI	
Requires Immunoglobulin	0.25	Beta (9; 27)	3.926	(1.9,6.7)	0.25	Beta (9; 27)	2.337488	(1.1,4.0)	[21]
Requires immunosuppressive drugs (steroids)	0.056	Beta (4; 67)			0.056	Beta (4; 67)			[22]
Considered healthy	0.88	Beta (36.08; 4.92)	13.85	(10.2,18.1)	0.85	Beta (59.5; 10.5)	8.10096	(5.9,10.6)	[23]
No problems	0.49	Beta (20.09; 20.91)	7.684	(4.9,11.0)	0.29	Beta (20.3; 49.7)	3.597459	(2.4,5.1)	[23]
Requires standing antibiotics	0.25	Beta (10.25; 30.75)	3.932	(2.0,6.5)	0.29	Beta (20.3; 49.7)	2.535932	(1.6,3.7)	[23]
Persistent rashes	0.23	Beta (9.43; 31.57)	3.624	(1.7,6.2)	0.29	Beta (20.3; 49.7)	2.451313	(1.5,3.6)	[23]
ADHD	0.16	Beta (6.56; 34.44)	2.505	(1.0,4.6)	0.17	Beta (11.9; 58.1)	1.547135	(0.9,2.4)	[23]
Diarrhea	0.05	Beta (2.05; 38.95)	0.799	(0.1,2.1)	0.19	Beta (13.3; 56.7)	1.160669	(0.6,1.9)	[23]
Height <3rd percentile	0.05	Beta (2.05; 38.95)	2.343	(1.2,3.9)	0.17	Beta (11.9; 58.1)	1.498138	(0.8,2.5)	[23]
Weight <3rd percentile	0.02	Beta (0.82; 40.18)	0.328	(0.0,1.3)	0.17	Beta (11.9; 58.1)	0.928681	(0.5,1.6)	[23]
Warts	0.11	Beta (4.51; 36.49)	1.724	(0.5,3.6)	0.16	Beta (11.2; 58.8)	1.276165	(0.7,2.1)	[23]
Asthma	0.15	Beta (6.15; 34.85)	2.363	(0.9,4.5)	0.16	Beta (11.2; 58.8)	1.456902	(0.8,2.3)	[23]
Developmental delay	0.05	Beta (2.05; 38.95)	0.793	(0.1,2.2)	0.18	Beta (12.6; 57.4)	1.111199	(0.6,1.9)	[23]
GERD	0.05	Beta (2.05; 38.95)	0.782	(0.1,2.1)	0.04	Beta (2.8; 67.2)	0.41712	(0.1,0.9)	[23]
Oral aversion	0.02	Beta (0.82; 40.18)	0.313	(0.0,1.2)	0.04	Beta (2.8; 67.2)	0.28656	(0.1,0.7)	[23]
Hyperthyroidism	0.03	Beta (1.23; 39.77)	0.471	(0.0,1.6)	0.01	Beta (0.7; 69.3)	0.18217	(0.0,0.5)	[23]
Seizure disorder	0.02	Beta (0.82; 40.18)	0.313	(0.0,1.2)	0.01	Beta (0.7; 69.3)	0.138039	(0.0,0.4)	[23]
Skin GvHD	0.04	Beta (4.44; 106.56)	0.63	(0.2,1.4)	0.04	Beta (4.44; 106.56)	0.375435	(0.1,0.8)	[23]
Cerebral palsy	0.02	Beta (2.22; 108.78)	0.318	(0.0,0.9)	0.02	Beta (2.22; 108.78)	0.189226	(0.0,0.5)	[23]
Autoimmune disease	0.02	Beta (2.22; 108.78)	0.313	(0.0,0.8)	0.02	Beta (2.22; 108.78)	0.186521	(0.0,0.5)	[23]

CI – Confidence Interval, ADHD –Attention deficit hyperactivity disorder, GERD – Gastroesophageal reflux disease, GVHD – Graft versus host disease

**Figure S1: QALY dimensions**



The EQ5D assessments for each dimension are presented in Figure E1 for the diagnosed at birth cohort (early) and the diagnosed later cohort (late). They demonstrate a consistent impact of early diagnosis across all dimensions.

**Table S4: QALY decrement threshold analysis for false positive cases and those with non-SCID TCL who are healthy at birth**

	Cost per TRECT test £3.50					
	Discounting 3.5% (costs and QALYs)			Discounting 1.5% (costs and QALYs)		
	Mean	95% confidence interval		Mean	95% confidence interval	
Baseline cost effectiveness	£18,588	£12,220	£28,661	£12,090	£7,945	£17,935
Baseline incremental cost	£3,337,979	£2,356,494	£4,480,687	£3,797,777	£2,564,260	£5,324,277
Baseline QALYs gained	180	114	271	314	202	464
Excess QALYs before £20,000 threshold is crossed	13	-4	47	124	74	197
Excess QALYs before £30,000 threshold is crossed	68	35	122	188	117	286
Non-SCID TCL health at birth analysis						
Number of newborns with non-SCID TCL healthy at birth	8	3	17	8	3	17
Minimum QALY decrement for those healthy at birth to increase the screening programme cost effectiveness to be:						
greater than £20,000 threshold	1.5	-1.3	2.7	14.8	25.2	11.4
greater than £30,000 threshold	8.1	12.1	7.0	22.4	39.8	16.5
False positive analysis						
False positives	266	24	796	266	24	796
Minimum QALY decrement for those healthy at birth to increase the screening programme cost effectiveness to be:						
greater than £20,000 threshold	0.05	-0.16	0.06	0.47	3.05	0.25
greater than £30,000 threshold	0.26	1.46	0.15	0.71	4.81	0.36

TREC – T-cell receptor excision circles, QALYs – quality adjusted life years, TCL – T-cell lymphopenia

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