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Evidence Review Group's Report
Strimvelis for treating severe combined immunodeficiency caused by adenosine deaminase deficiency

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Susan Griffin and Edward Cox undertook the critique of the cost-effectiveness submission and conducted the economic analyses, with Susan Griffin taking overall responsibility for the cost effectiveness sections. Nick Meader and Emily South undertook the critique of the clinical effectiveness submission, with Nick Meader taking overall responsibility for the clinical effectiveness sections of the report. Melissa Harden critiqued the literature searches in the submission. Nerys Woolacott provided advice and commented on drafts of the report.

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined

Copyright statement

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List of abbreviations

ADA	Adenosine deaminase
ADA-SCID	Adenosine deaminase deficiency severe combined immune deficiency
AE	Adverse event
aGvHD	Acute graft versus host disease
cGvHD	Chronic graft versus host disease
CNS	Central nervous system
CS	Company submission
CUP	Compassionate use programme
CVC	Central venous catheter
dATP	Deoxyadenosine triphosphate
dAXP	Deoxyadenosine nucleotides
EMBT	European Society for Blood and Marrow Transplantation
EQ-5D	EuroQol 5-dimension questionnaire
ERG	Evidence Review Group
ERT	Enzyme replacement therapy
ESID	European Society for Immunodeficiences
GCP	Good Clinical Practice
G-CSF	Granulocyte-colony stimulating factor
GSK	GlaxoSmithKline
GT	Gene therapy
GvHD	Graft versus host disease
HLA	Human leukocyte antigen
HRQoL	Health related quality of life
HSCT	Hematopoietic stem cell transplant
HST	Highly specialised technology
ICER	Incremental cost-effectiveness ratio
IQ	Intelligence quotient
IVIG	Intravenous immunoglobulin
LTFU	Long term follow up
LY	Life years
LYG	Life years gained
MeSH	Medical Subject Heading
MFD	Matched family donor
MRD	Matched related donor
MSD	Matched sibling donor

MUD	Matched unrelated donor
NHS	National Health Service
NK	Natural killer
NICE	National Institute for Health and Care Excellence
OS	Overall survival
OSR	Ospedale San Raffaele
PEG-ADA	Adenosine deaminase conjugated with polyethylene glycol
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
RBCs	Red blood cells
SCID	Severe combined immunodeficiency
SR-TIGET	San Raffaele Telethon Institute for Gene Therapy
TREC	T cell receptor excision circles
UCB	Umbilical cord blood
VCN	Vector copy number

1 Summary

1.1 Critique of the decision problem in the company's submission

The company's decision problem reflects the population specified in the NICE scope: people with ADA-SCID for whom no suitable HLA-matched related stem cell donor is available. The clinical evidence presented also reflects this population but the ERG identified some minor differences with the characteristics of the population that would be eligible for Strimvelis in England.

Based on the clinical pathway presented in the company submission (CS), the ERG would expect patients in England eligible for Strimvelis to be younger on average and have had a different treatment history, including much shorter average duration of PEG-ADA treatment. Additionally, information on race and country of origin of the patients in the clinical studies suggests they are unlikely to reflect the ethnicity of patients in England. Lastly, no patients had a confirmed active viral infection at screening. Given the potential for viral infection in ADA-SCID patients, and advice from the clinical advisor to the ERG that the presence of viral infection may be prognostic, it is unclear the extent to which the data can be generalised to patients presenting with viral infection. Despite these minor differences, the ERG acknowledges that due to the rarity of ADA-SCID and the small patient numbers, the population presented is appropriate for the decision problem in question.

The intervention in the submission is Strimvelis (retroviral-transduced autologous CD34+ cells), which matches the intervention described in the final NICE scope.

The company identifies the comparator as bone marrow transplant, specifically HSCT from an HLA-MUD or an HLA-haploidentical donor. This matches the NICE scope although the clinical advisor to the ERG advised that patients can be treated with HSCT using donated umbilical cord blood rather than bone marrow. The ERG notes that the study used as a historical comparator includes some cord blood transplants.

The decision problem in the CS includes all the outcomes described in the NICE scope, including overall survival, intervention-free survival, immune function, non-immunological aspects, need and duration of inpatient treatment and health-related quality of life for patients and carers. The outcomes are all addressed in the clinical evidence presented except for carer quality of life.

1.2 Summary of clinical effectiveness evidence submitted by the company

The company submission was focused on the Strimvelis Intergrated Population, although data on further patients receiving Strimvelis in the Named Patient Programme were also provided in

Appendix 6. Data on HSCT from a MUD (n=15) and HSCT from a haploidentical donor (n=7) were based primarily on a multi-centre study of reported outcomes in usual practice. In addition, data from smaller case reports and case series were also narratively synthesised.

Strimvelis

Evidence presented in the company submission for Strimvelis was based on the Strimvelis Integrated Population of 18 patients recruited from four studies (AD1117054 Pilot 1, AD1117056 Pilot 2, AD1115611 Pivotal, AD1117064 CUP) and AD1115611 LTFU a feeder study for longer term follow up data from these patients. Data were pooled and discussed as an integrated population. That is, the four studies were treated as if they were one study in contrast to a meta-analysis where data is analysed separately and weighted by study. A further [redacted] patients received Strimvelis in the Named Patient Programme but these were not included in the evidence synthesis.

Overall survival was 100% in the 18 patients that comprised the Strimvelis Integrated Population and the [redacted] patients from the Named Patient Programme. Follow up time in the Strimvelis Integrated Population ranged from 2.3 to 13.4 years (median =6.95 years); it was not reported for the Named Patient Programme.

Data on intervention free survival with Strimvelis was available for [redacted] patients: There was insufficient data on PEG-ADA use for Patient[redacted] to evaluate intervention-free survival for these patients. Of the evaluable patients [redacted] experienced intervention-free survival (i.e. did not require either ≥ 3 months of PEG-ADA treatment or HSCT): 14/17 (82.3%) in the Strimvelis Integrated Population, and [redacted] in the Named Patient Programme.

[redacted]

HSCT from a MUD or haploidentical donor

The key historical comparator data for HSCT is provided by Hassan et al which are the largest data source on outcomes for patients with ADA-SCID receiving HSCT currently available in the literature. Overall survival was 67% (10/15 patients) for those receiving HSCT from a MUD between 1995 and 2009. For HSCT from a haploidentical donor, overall survival was 71% (5/7 patients). This was based

only on data from 2000-2009 as this was considered a more applicable comparison with Strimvelis due to substantial improvements in effectiveness over time.

Intervention free survival data are very limited for HSCT from a MUD or haploidentical donor and it is not clear if the data reported on those receiving additional treatment is comparable with data on Strimvelis patients. Hassan et al reported one patient receiving a rescue transplant after HSCT from a MUD but no further information is provided about additional treatment. Following HSCT from a haploidentical donor (2000-2009 subgroup), 2/7 did not engraft, resulting in one patient receiving gene therapy and the other patient starting PEG-ADA followed by two rescue transplants before death.

Adverse events

Adverse events were largely similar for Strimvelis, HSCT from a MUD and HSCT from a haploidentical donor. Almost all (17/18) of the Strimvelis Integrated Population experienced a neurological, CNS or hearing event during treatment or follow up. Cognitive disorders were the most common event (n=5). Deafness was also a common problem with two patients reporting deafness and a further two patients reporting bilateral deafness. Three patients reported psychomotor hyperactivity. High incidence of non-immunological problems was also found for ADA-SCID patients following HSCT including behavioural problems and IQ scores substantially below general population means. The CS concluded that neither gene therapy nor HSCT appear to be effective in reducing non-immunological problems. The major difference between Strimvelis and HSCT in terms of adverse events was that some patients experienced Graft versus Host Disease (GvHD) after HSCT, whereas no patients experienced this adverse event following Strimvelis.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The clinical effectiveness evidence was based on a systematic review of Strimvelis, HSCT from a MUD and HSCT from a haploidentical donor. Although some limitations were identified with the search strategy the ERG did not identify any relevant studies that had been missed.

All data for the four studies and long term follow up feeder study that comprised the Strimvelis Integrated Population were pooled and treated as if comprising a single study. Although there were differences in methods between studies (particularly between the pilot studies and the pivotal study in terms of GCP) the ERG considered there was sufficient similarity between studies that this approach was unlikely to lead to substantial bias. However, the ERG did not consider it appropriate that data from the Named Patient Population were excluded from the narrative synthesis of clinical

effectiveness evidence. This is particularly important given the small sample size of the Strimvelis Integrated Population (n=18) and therefore the need to consider all available data when evaluating the effectiveness of this treatment.

Some concerns were noted regarding the representativeness of the Strimvelis Integrated Population to UK ADA-SCID patients. Firstly, there was lack of clarity regarding numbers screened or excluded for Pilot study 1, Pilot study 2, the Compassionate Use Programme and the [redacted]. Therefore, it is unclear if patients at greater risk were excluded from these studies or other selection biases occurred. Secondly, our clinical advisor noted that presence of viral infections at screening may be an important prognostic factor for treatment outcomes. In response to a request for clarification the company confirmed no patients had viral infections at screening. Therefore, this potentially raises issues regarding the generalisability of these patients to the UK and it is unclear the extent to which these findings are applicable to those with viral infections at baseline. Thirdly, it is likely that duration of PEG-ADA use was longer than would be expected in UK practice however since there is no evidence that this is an important prognostic factor it may not have impacted on outcomes. Whilst noting these concerns, the ERG concluded that as a whole data on Strimvelis is likely to be generalizable to the UK.

Although overall survival was 100% across all [redacted] patients that have received Strimvelis there are substantial limitations to these data. Firstly, this evidence is based on small open label single arm trials that are inherently at a high risk of bias and lack precision. A small number of deaths or treatment failures can lead to substantial changes in survival estimates making such estimates highly uncertain. Secondly, historical data on overall survival following HSCT from a MUD and HSCT from a haploidentical donor likely reflect an underestimate of the current effectiveness of these treatments. For example, there have been substantial improvements in matching of donors and provision of supportive care. Thirdly, the overall survival outcome overestimates the effectiveness of the intervention since those who experienced a Strimvelis treatment failure but did not die due to receiving an alternative treatment (such as PEG-ADA or HSCT) are still counted as a treatment success. Intervention-free survival was lower for Strimvelis ([redacted] and in the view of the ERG provides a better assessment of clinical effectiveness.

Although the CS demonstrated that some patients experienced GvHD following HSCT but not following Strimvelis there were limitations in estimating the rates of this adverse event. Estimates are based on very small case reports (ranging from n=1 to n=7) and by variations in definitions and reporting of these events. In addition, there were important limitations in how estimates of GvHD

were calculated in the company submission with data in case reports from different centres and different time periods pooled as if from a single study rather than using meta-analytic methods.

Although no events have occurred in Strimvelis-treated or other ADA-SCID patients, a potential risk of gene therapy identified in other SCID patients is the risk of leukaemia. Given the small sample size of patients who have received Strimvelis this cannot yet be ruled out as an important potential risk.

1.4 Summary of cost effectiveness submitted evidence by the company

The company submission included a review of published health-related quality of life data and a de novo economic evaluation. The economic evaluation compared Strimvelis to either HSCT from a MUD or HSCT from a haploidentical donor in a hypothetical cohort of patients aged one year old. The model consisted of a decision tree to establish the proportion of patients surviving initial transplant procedure and the proportion requiring rescue transplant in the first three years, combined with a Markov modelling approach to extrapolate costs and quality adjusted survival over a lifetime time horizon. The model assumed patients would be maintained on ERT with PEG-ADA while awaiting initial or rescue transplant procedures, and incorporated post-procedure IVIG use and risk of severe infection. Rescue transplant was assumed to occur two years after the initial procedure and to consist of HSCT from a MSD, with no risks of death or failure to engraft. It was assumed that the decision to utilise Strimvelis would be made before any search for a MUD was undertaken, and that HSCT from a haploidentical donor would only be used after a search for a MUD.

Patients who survived transplant procedures were assumed to return to the mortality and morbidity risk of the general population, and a discount rate of 1.5% was applied to costs and health outcomes to reflect this assumption of cure. The model characterised three main treatment benefits for Strimvelis: (i) reduced duration of ERT with PEG-ADA before the initial transplant procedure; (ii) reduced procedural mortality; and (iii) avoidance of GvHD. The model also assumed differences in the rates of rescue transplant between treatment arms.

The primary clinical effectiveness parameters in the model were informed by the Strimvelis Integrated Population long-term follow up study (n=17) and a retrospective, international survey of HSCT. The company model assumed overall survival of 100% with Strimvelis, 66.67% for HSCT from a MUD (based on 15 transplants performed between1995-2009) and 71.4% for HSCT from a haploidentical donor (based on seven transplants performed between 2000 and 2009). The rate of rescue transplant following failure to engraft was assumed to be 17.6% following Strimvelis, 6.7% following HSCT from a MUD and 28.6% following HSCT from a haploidentical donor. Rate of GvHD was informed

by the literature and assumed to occur in approximately of one third of patients undergoing HSCT, while Strimvelis was assumed to carry no risk of GvHD.

Health related quality of life was assumed equal to that of the general population, with decrements applied for six months in patients recovering from transplant procedures and to patients experiencing GvHD events.

The cost of Strimvelis was composed of two elements: (i) the cost of the retroviral mediated transduced cell product (£505,000); and (ii) related hospital procedures, including screening, blood tests, bone marrow sample, chemotherapy, infusion of Strimvelis, inpatient recovery and outpatient follow-up ([redacted]). These costs were informed by the clinical schedule and estimates provided by the HSR-TIGET and OSR hospital in Milan and converted to GBP using an exchange rate of €1=£0.85. The costs of HSCT from a MUD or haploidentical donor were based on NHS reference costs. Costs of screening for a MUD, long-term follow-up after any transplant procedure, cost of GvHD and cost of severe infection were informed by the literature and inflated to 2016 prices. The costs of PEG-ADA were informed by clinical expert opinion.

The company base case found Strimvelis to be more costly (cost difference £494,255 and £170,668) and more effective (QALY difference 13.6 and 11.7) compared to HSCT from a MUD and haploidentical donor, respectively. The deterministic ICERs were £36,360 for Strimvelis compared to HSCT from a MUD and £14,645 for Strimvelis compared to HSCT from a haploidentical donor. The ICERs remained lower than £100,000 per QALY gained across a range of one and two-way sensitivity analysis and scenario analyses.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG considered the company's economic submission to meet the requirements of the NICE reference case. The ERG was concerned that the model failed to characterise alternative points in the treatment pathway at which a decision to use Strimvelis may be taken. The company model applies only to younger patients in whom the decision is taken immediately following diagnosis and before any search for a MUD is undertaken.

The ERG thought it was unrealistic to assume that patients with ADA-SCID who survive an initial transplant procedure with either Strimvelis or HSCT are returned to the same level of health and life expectancy as the general population. The ERG felt that this would overestimate quality adjusted survival and underestimate health care costs due to the cognitive and neurological deficits of ADA-SCID and potential long-term adverse events associated with pre-transplant conditioning regimens.

Of similar concern was the assumption of 100% survival and 100% successful engraftment with rescue transplant, which overestimates quality-adjusted survival and underestimates the health care costs in patients that fail to engraft following the initial procedure. These factors cause the company model to overestimate the benefit of reductions in procedural mortality.

The ERG identified a number of costs associated with Strimvelis that were omitted from the company base case, including NHS supported travel costs to and from Milan, the cost of screening incurred for patients deemed unable to produce sufficient CD34+ cells to proceed to treatment with Strimvelis, additional hospitalisation costs for patients whose length of stay after Strimvelis exceeds 55 days and administration of back up bone marrow. The cost per HSCT from a MUD and per GvHD event in the company base case appear to have been overestimated.

The ERG consider that the available evidence does not support the assumption that Strimvelis will reduce the use of PEG-ADA prior to transplant. The ERG also consider that for some patients the decision to utilise Strimvelis will be taken only after a search for a MUD has been completed, and for these patients search costs will not be avoided.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The company submission included a systematic review which reflected the NICE scope and decision problem. Although there were some limitations to the search strategy, the ERG considered it unlikely that important studies had been missed when the addition of the Named Patient Programme data for all [redacted] patients were considered.

The ERG company economic submission met the requirements of the NICE reference case and utilised appropriate available evidence. The company submission included a range of sensitivity and scenario analyses to address uncertainties, and addressed additional uncertainties in response to ERG requests and clarifications.

1.7 Weaknesses and areas of uncertainty

The ERG identified several limitations to the clinical effectiveness evidence. Firstly, the data is based on small open label single arm trials that are inherently at a high risk of bias and lack precision. Therefore all survival estimates are highly uncertain and future data could substantially change conclusions. Secondly, historical data on overall survival following HSCT from a MUD and HSCT from a haploidentical donor likely reflect an underestimate of the current effectiveness of these

treatments. For example, there have been substantial improvements in matching of donors, reduced conditioning, and better provision of supportive care. Thirdly, the overall survival outcome overestimates the effectiveness of the intervention since those who experienced a Strimvelis treatment failure but did not die due to receiving an alternative treatment (such as PEG-ADA or HSCT) are still counted as a treatment success. Intervention-free survival was lower for Strimvelis ([redacted] and in the view of the ERG provides a better assessment of clinical effectiveness.

The ERG identified a number of relevant costs and outcomes that were omitted from the company model, and that caused the benefits of reductions in procedural mortality to be overestimated. The simplified pathway in the company model does not characterise all the relevant routes by which patients may arrive to treatment with Strimvelis. Given the small sample sizes used to inform the key model parameters, each additional patient treated can have a large influence on estimates of overall survival, rates of successful engraftment and rates of rescue transplant.

While acknowledging that the company submission incorporates the best available evidence for survival in patients with ADA-SCID treated with HSCT from a MUD or haploidentical donor, the ERG understands that techniques for HSCT and overall survival continue to improve over time. In contrast, the use of overall survival rather than intervention-free survival to characterise the efficacy of Strimvelis at 100% means that survival for patients treated with Strimvelis is likely to reduce over time. The respective 33 and 29 percentage point reductions in procedural mortality with Strimvelis compared to HSCT from a MUD or from a haploidentical donor applied in the company submission may therefore represent the upper limit of additional benefit from Strimvelis.

1.8 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG made a number of changes to the company model that utilised a number of scenario analyses provided by the company:

- Disutility weight applied to patients receiving IVIG;
- Duration of chronic GvHD in line with timing of rescue transplant;
- Revised PEG-ADA dose determined by patient weight;
- Revised administration costs for PEG-ADA and IVIG;
- Inclusion of travel costs to and from Milan;

combined with further changes:

- Incorporate NPP to inform efficacy of Strimvelis

- Minor parameter corrections to company model;
- Assume equal duration of PEG-ADA pre-procedure across treatment arms;
- Assume rescue transplant has same cost and health outcomes as initial transplant from a MUD;
- Include ongoing healthcare costs and health related quality of life decrement for bilateral hearing impairment;
- Lower unit costs for HSCT from a MUD and per GvHD event;
- Incorporation of baseline screening costs incurred by patients deemed ineligible to proceed to Strimvelis.

The ERG use the revised base case to explore the sensitivity of the model to survival rates following Strimvelis and HSCT, the cost of Strimvelis, whether MUD search costs are avoided in patients treated with Strimvelis, and the rate of rescue transplant.

The ERG preferred base case predicts lower QALYs for all comparators compared to the company base case. This is attributable to the increased mortality and morbidity associated with rescue transplants and the application of HRQoL decrements for IVIG use and bilateral hearing impairment. The ERG's preferred base case predicts higher costs for Strimvelis, lower costs for HSCT from a MUD, and higher costs for HSCT from a haploidentical donor compared to the company base case. This is attributable to higher rates of rescue transplant for patients treated with Strimvelis and HSCT from a haploidentical donor, combined with the increased health care costs per rescue transplant to reflect risks of severe infection and GvHD, and the lower unit cost for HSCT from a MUD.

The ERG's base case ICERs are £86,815 for Strimvelis compared to HSCT from a MUD and £16,704 for Strimvelis compared to a haploidentical donor. These are higher than those estimated by the company, but remain below £100,000 per QALY. The ICER for Strimvelis compared to HSCT from a haploidentical donor is robust to a range of sensitivity analysis. However, the ICER for Strimvelis compared to HSCT from a MUD is very sensitive to the assumed difference in procedural mortality between the two procedures. If survival following HSCT from a MUD exceeds 75%, the ICER for Strimvelis compared to a MUD would no longer fall beneath the adjusted cost-effectiveness threshold determined by the extent of the undiscounted QALY gain with Strimvelis. Strimvelis must reduce procedural mortality by at least 30 percentage points compared to HSCT from a MUD in order for the ICER to remain below £100,000 per QALY gained. If survival with Strimvelis falls below 100%, the ICER for Strimvelis compared to HSCT from a MUD is also sensitive to variation in the additional cost of Strimvelis.

If search costs for a MUD are not avoided prior to treatment with Strimvelis the ICER increases to £91,644 compared to HSCT from a MUD and to £20,786 for HSCT from a haploidentical donor. The results were sensitive to alternative assumptions regarding the rate of rescue transplant. It is anticipated that the ICER for Strimvelis compared to HSCT may increase in patients that have a worse prognosis, in older patients and in those with active viral infection. Older patients are likely to incur greater drug acquisition costs for PEG-ADA and IVIG as dose is determined by patient weight. Older patients and or those with active viral infection are expected to experience worse procedural outcomes, which may diminish the potential reduction in procedural mortality and also the QALY gains from deaths avoided.

2 Background

2.1 Critique of company's description of underlying health problem.

2.1.1 Overview of the condition

The company submission (CS) provides a brief summary of disease morbidity, mainly focusing on the morbidity associated with current treatment options for adenosine deaminase-severe combined immunodeficiency (ADA-SCID).

The CS states that ADA-SCID is a fatal autosomal recessive monogenic inherited immune disorder. People with ADA-SCID have profound lymphopenia, impaired differentiation and function of T cells, B cells and natural killer cells, recurrent infections and failure to thrive. Unlike other forms of SCID, non-immunological abnormalities can also occur due to the systemic metabolic defect. Symptoms of ADA-SCID are developmental delay, chronic diarrhoea, failure to thrive and recurrent infections.[1]Patients can be hospitalised and kept in isolation due to frequent infections. ADA-SCID is usually diagnosed within the first year of life and without treatment patients are unlikely to survive beyond one to two years.[2] The CS claims that ADA-SCID is perceived in the clinical community as more difficult to treat than other types of SCID,[3] although the ERG notes that the cited paper says there is "no objective data to support this notion".[3]

This section of the CS provides details of the morbidity associated with current treatment options, particularly haematopoietic stem cell transplant (HSCT). HSCT involves the transplantation of haemopoietic progenitor cells from bone marrow or blood, which are able to differentiate into other cell types, including cells of the immune system.[4] For patients that receive HSCT from a human leukocyte antigen (HLA) matched related donor (MRD), the CS cites survival rates of 86% for matched sibling donors (MSD) and 83% for matched family donors (MFD).[3] According to the CS, only 20-25% of patients have an MRD available.[1, 5] The other main types of HSCT available for ADA-SCID are HSCT from a matched unrelated donor (MUD) or haploidentical donor. Based on external expert clinical advice, the CS states that HSCT from a MUD is preferred in the UK, with HSCT from a haploidentical donor not performed in an ADA-SCID patient in England in the last 15 years. The clinical advisor to the ERG confirmed that, based on European guidance, HSCT from a haploidentical donor is not carried out for ADA-SCID.

Survival rates provided in the CS for HSCT from a MUD are 67% in procedures since 1995.[3] For HSCT from a haploidentical donor the survival rate is 43% but this rises to 71% if just the more recent procedures performed in this cohort (from 2000-2009) are considered.[3] The ERG agrees that

these estimates reflect the best available published data on ADA-SCID patients. However, these data are based on small sample sizes (for HSCT from a MUD: n=15, HSCT from a haploidentical donor: n=30 and HSCT from a haploidentical donor 2000-2009: n=7) and therefore are inherently uncertain. In addition, the clinical advisor to the ERG advised that outcomes have continued to improve markedly in HSCT from MUD and haploidentical donors since 2009. Unfortunately the ERG has not been able to find any published data on more recent cohorts of ADA-SCID patients, although data on HSCT in other cohorts shows improvement over time.[6 4] The clinical advisor to the ERG estimated that, using new techniques, for HSCT from a haploidentical donor survival is now over 90% in other conditions. The clinical advisor also suggested that with current methods and techniques results achieved with MRDs are not necessarily better than those with MUD or haploidentical donors. However, these techniques are very recent and not yet reflected in published data. In addition, these improvements are not based exclusively on ADA-SCID patients. Therefore, there are important limitations in estimating overall survival after HSCT from a MUD or haploidentical donor based on published data and questions regarding the extent to which they reflect the effectiveness of currently provided treatment.

A complication associated with HSCT is graft versus host disease (GvHD), which the CS highlights can lead to significant morbidity and mortality.[3] The CS also mentions that, for ADA-SCID patients that survive bone marrow transplant, central nervous system (CNS) abnormalities represent a remaining unmet need for treatment.[7, 8]

The CS also addresses morbidity associated with supportive enzyme replacement therapy (ERT) with PEG-ADA. The CS cites a study by Chan et al that found with long-term PEG-ADA treatment lymphocyte counts, thymic function and mitogenic proliferative responses all started declining.[9] This was thought to be due to incomplete metabolic reconstitution in the thymus leading to gradual loss of immune function.

The CS identifies an unmet need for treatment options that provide long-term corrective therapy for those patients without an available MRD, with improved survival rates and without the complication of GvHD.

2.1.2 Incidence of ADA-SCID

There is a lack of data on ADA-SCID incidence in the UK, but the CS estimates an incidence of three to four patients with ADA-SCID per year in the UK, with three or fewer patients in England. As approximately 20% of these patients would have an MRD available,[1, 5] the CS claims that no more

than two patients per year in England would be eligible for Strimvelis. The CS notes that uptake of Strimvelis is not expected to be 100% due to the practicalities of treatment in Milan. The clinical advisor to the ERG confirmed that families may be reluctant to choose treatment in Milan if other options (e.g. a trial in the UK) are available.

There is difficulty estimating incidence of ADA-SCID in the UK based on the very limited data available. Additionally, given that ADA-SCID is concentrated within certain communities, it is not clear that the estimate used in the company submission takes into account demographic differences between the nations of the UK to calculate the England estimate. Results from newborn screening for SCID in the US have shown an incidence of SCID that was higher than previously reported[10, 11] so it is also possible that a screening programme for SCID in the UK would have an impact on the number of infants diagnosed with ADA-SCID. However, the ERG agrees incidence is likely to be very low and received a similar estimate from a clinical advisor based on their experience at one of the two treatment centres for ADA-SCID in the UK.

2.1.3 Life expectancy

The CS claims that with no treatment children with ADA-SCID rarely survive beyond two years,[2] but that there is currently no data available on life expectancy after HSCT. The clinical advisor to the ERG confirmed that there is very limited evidence on life expectancy, with a maximum of about 25-30 years of follow-up data on ADA-SCID patients after HSCT. The ERG notes that although the first bone marrow transplant for SCID took place in 1968, techniques to deplete T cells, making bone marrow transplantation possible in all forms of SCID, were only developed in the 1980s.[12] The clinical advisor predicted a normal life expectancy after a good quality transplant, although he noted that due to the metabolic nature of ADA-SCID there are heart and neurological impacts and a long term risk of cancer.

2.1.4 Quality of life

The CS describes how ADA-SCID impacts on the quality of life for both patients and carers. It highlights that without any treatment quality of life for patients and family members would decline as infections increased and patients would be expected to die at a young age.

[redacted]

[redacted]

The CS also suggests that choosing treatment with HSCT could have quality of life impacts for carers. The ERG identified two reviews of the literature on quality of life in children who survived HSCT (not specifically for SCID), which found a short-term decline in health-related quality of life following conditioning for HSCT and transplant.[13, 14]

The CS identifies one study of patients with SCID after HSCT (median 11 years post-transplant) which found a significantly lower quality of life in those with ADA-SCID than the UK normal on all components except emotional.[15] Patients with ADA-SCID were more at risk of poor quality of life than those with other types of SCID, which the CS suggests may be due to the impact of the non-immunological manifestations of ADA-SCID. The ERG notes that this study was in patients who had undergone treatment with HSCT and therefore indicates an ongoing impact on quality of life after curative treatment, rather than representing the impact on patients awaiting treatment.

The company expects quality of life for patients treated with Strimvelis, their carers and families to improve, with shorter waits for treatment than for HSCT from a MUD and reduced mortality risk. Overall, given the limited research and data available due to the rarity of ADA-SCID, the CS provides an appropriate and relevant summary of the disease area.

2.2 Critique of company's overview of current service provision

2.2.1 Current clinical pathway

The CS provides a summary of the current clinical pathway of care for ADA-SCID patients in England. Patients are usually diagnosed at one of the specialist SCID centres (Great Ormond Street Hospital or Great North Children's Hospital, Newcastle). The majority are diagnosed in the first year of life according to the CS,[2] although some have a delayed or late onset.[16] After diagnosis, the immediate clinical priorities are to reduce infection risk, conduct tests and assessments and provide supportive care. Patients are also screened for an MRD. The clinical advisor to the ERG specified that screening starts for an MRD while tests are ongoing to diagnose ADA-SCID. The clinical advisor also advised that patients are put on PEG-ADA as soon as they are diagnosed to help build immunity, to clear infections and reduce toxicities, improving the likelihood of treatment success.

The CS gives a figure of 20-25% of patients who have an MRD available,[1] although the ERG is not aware that there is currently any good quality epidemiological data available to inform this estimate. If patients do not have an MRD available, HSCT from a MUD is the current standard of care. The

clinical advisor to the ERG clarified that this could be from either umbilical cord blood (UCB) or a bone marrow donor, with the search for a cord blood match beginning at the same time as diagnostic tests and MRD screening. Clinicians decide whether to use cord blood or an adult donor, mainly based on availability and the level of infection. The CS explains that PEG-ADA is used as a supportive treatment, while the search for a MUD is ongoing. The CS specifies an average waiting time for a MUD of 19 weeks.[17] However the ERG notes that a presentation on the UK Stem Cell Strategic Forum Recommendations gives average times to transplant as 50 days for bone marrow and 13.5 days for cord blood.[18] Although this is not based on ADA-SCID patients specifically, it suggests some uncertainty over waiting times. HSCT from a haploidentical donor is currently not performed in ADA-SCID patients in England and long-term PEG-ADA is also not considered. The clinical advisor to the ERG confirmed that this is the basic pathway, and also advised that if a good match from an unrelated donor is not available then gene therapy may be considered. Kohn & Gaspar's overview of the management of ADA-SCID,[19] though not exclusively UK based, also confirms that HSCT from an MRD is the current standard of care where possible, with ERT, HSCT from a MUD or haploidentical donor, or gene therapy as options for those without an MRD.

2.2.2 Issues relating to clinical practice

The CS highlights some of the clinical issues relating to the current treatment options. While HSCT from an MRD usually doesn't need preconditioning, other types of HSCT may require chemotherapeutic preconditioning. They also have increased risk of mortality and morbidity from inadequate immune reconstitution and GvHD. While the CS claims that there is significantly decreased survival from MUD or haploidentical donors compared with MRD, the clinical advisor to the ERG advised that using current methods survival from HSCT from a MUD or haploidentical donor would be expected to be much higher than the most recent published data, which is based on transplants only up to 2009. The CS also mentions that MUD donor availability can depend on ethnicity, with non-White patients facing a longer wait.[20-22]

In terms of ERT with PEG-ADA, the CS mentions that it is a non-curative and expensive treatment that requires weekly or bi-weekly injections and regular monitoring. Long-term efficacy can be limited due to incomplete immune reconstitution and the development of antibodies.[23-25] Although it is available through expanded access and compassionate use programmes, it is not approved in the EU and is used to stabilise patients before HSCT or gene therapy rather than as a long term treatment (although the ERG notes that this may depend on the waiting time until curative treatment). The clinical advisor to the ERG confirmed that although patients are put on PEG-ADA initially, it is used as a bridge to curative treatment in the UK.

Overall, the CS provides an accurate and appropriate overview of the current treatment pathway for ADA-SCID and some of the associated issues.

2.2.3 Description of technology under assessment

Strimvelis is a gene therapy treatment in which autologous bone marrow-derived cells are transduced to express adenosine deaminase (ADA). After infusion, CD34+ cells engraft in the bone marrow, where they repopulate the haematopoietic system with a proportion of cells that express pharmacologically active levels of the ADA enzyme. If engraftment is successful, the effects of a single dose are expected to be life-long. Strimvelis was given EU marketing authorisation on 26 May 2016. It is given as an intravenous infusion, which must be administered in a specialist transplant centre by a physician with previous experience in the treatment and management of ADA-SCID and the use of autologous CD34+ ex vivo gene therapy products. It is currently only available at the Hospital San Raffaele Telethon Institute for Gene Therapy (HSR-TIGET) in Milan, Italy. For successful manufacture of Strimvelis, the patient needs to be able to donate adequate CD34+ cells and a CD34+ stem cell back up is also required. This is harvested at least 3 weeks before treatment with Strimvelis and is required as a rescue treatment if there is failure during product manufacture or transplant or prolonged bone marrow aplasia after treatment.

Similarities and differences between Strimvelis and HSCT from a MUD or haploidentical donor

Gene therapy with Strimvelis is a type of autologous transplant, which includes any treatment where stem cells are collected from the patient themselves and then re-infused. [4] HSCT from a MUD or haploidentical donor is allogeneic, which means the stem cells are from a donor.[4]

The CS states that low dose busulfan conditioning is used for Strimvelis. While the clinical advisor to the ERG explained that there is no consensus on conditioning regimes, he advised that more conditioning is required for HSCT from an unmatched donor than for gene therapy. According to the CS, Strimvelis does not carry the risk of graft versus host disease that has a significant effect on morbidity and mortality in allogeneic HSCT. Strimvelis also differs in that it does not require the search for a donor before treatment. In terms of similarities, the clinical advisor to the ERG advised that both gene therapy and HSCT require the insertion of a central venous catheter (CVC), with the same risk of infection in both cases. The clinical advisor also does not expect much difference in the frequency of follow up between the two procedures, although there may be small differences in the testing required. According to the CS the hospital stay required after treatment would also be very similar.

2.2.4 New pathway of care

The CS describes the new pathway of care incorporating Strimvelis that would exist following national commissioning by NHS England. According to the CS, patients without an MRD should be offered Strimvelis. Screening would be conducted at specialist centres in England once established that an MRD is not available. HSR-TIGET would liaise with the clinical team in England to confirm that treatment with Strimvelis is appropriate for the patient. Before the Strimvelis treatment, patients would be seen at HSR-TIGET for just over a month for necessary procedures, including obtaining a bone marrow backup. Hospitalisation during Strimvelis treatment is for approximately 50 days before being seen as an outpatient for 2-3 months. After this the patient would return to the UK and follow-up care will be given by the referring physician, with specific guidance and recommendations from HSR-TIGET.

Although this pathway reflects the EMBT/ESID guidance,[26] the ERG questions whether all patients without an MRD would choose to receive Strimvelis as their first choice treatment. Based on expert clinical advice, the ERG understands that the need to travel to Milan may act as a barrier to some families and a decision may be taken to initially explore HSCT from a MUD as a treatment option. Therefore in practice, the ERG considers that Strimvelis may be a first line treatment for some patients in England but also a second line treatment for others either after the search for a MUD is unsuccessful or following a failed HSCT from a MUD.

3 Critique of company's definition of decision problem

3.1 Population

In the statement of the decision problem, the company identifies the population as people with ADA-SCID for whom no suitable HLA-matched related stem cell donor is available. This reflects the population specified in the NICE scope and the population in the clinical evidence presented. However, the ERG notes some minor differences between the population in the clinical evidence and the characteristics of the patient population that would be eligible for Strimvelis in England.

Firstly 16 of the 18 patients in the integrated population (the combined population of patients that received Strimvelis in the four trials and one LTFU study presented in the clinical evidence) had previously received either HSCT from a haploidentical donor and/or PEG-ADA treatment for over six months (median 12 months; range: one to 71 months). Neither long-term PEG-ADA nor HSCT from a haploidentical donor are currently used as treatments for ADA-SCID patients in the UK. According to the clinical pathway presented in the CS, most patients eligible for Strimvelis in England would be

referred for treatment soon after diagnosis of ADA-SCID and therefore will have had a much shorter duration of PEG-ADA than the average in the clinical evidence. However, the clinical advisor to the ERG advised that PEG-ADA use is not prognostic for HSCT outcomes so it is possible that it would not have an effect on the efficacy of Strimvelis. Additionally, due to uncertainties around the clinical pathway discussed in section 2.2.4, the ERG believes some patients in England may have prior treatment before referral for Strimvelis.

The median age of the integrated population was 1.37 years and seven of 18 patients were over two years old. The CS states that the majority of ADA-SCID patients are diagnosed in the first year of life[2] and the time to Strimvelis treatment provided in the company's model is nine weeks. Based on the clinical pathway presented, the ERG would therefore expect eligible patients in England to be younger on average than the patients in the clinical studies. The clinical advisor to the ERG advised that younger patients tend to respond better to HSCT, as they are less likely to have an active infection, which is prognostic for HSCT outcomes.[27, 28] The ERG therefore acknowledges that younger age may also have a positive effect on treatment outcomes with Strimvelis, if less infections are present in the population. However, as above, the ERG believes there may be uncertainties around the clinical pathway presented so it is not possible to draw firm conclusions on how the average age of the eligible population would differ.

According to the CS and the clinical advisor to the ERG, ADA-SCID is concentrated in several ethnic minority groups within the UK, including those of Somalian ethnicity.[29] None of the patients included in the CS came from the UK and information on their race and country of origin suggests they are unlikely to reflect the population in England in this respect. However the clinical advisor to the ERG confirmed that he would not expect differences in the efficacy of treatment due to patient ethnicity.

Additionally, the ERG requested further clarification regarding the proportion of patients with viral infection at baseline. The company responded that there was no data on this but that no patients had a confirmed active viral infection at screening. Given the potential for viral infection in ADA-SCID patients, and advice from the clinical advisor that the presence of viral infection may be prognostic,[27, 28] it is unclear the extent to which the data on the integrated population can be generalised to ADA-SCID patients presenting with viral infections.

Overall, while the population presented in the clinical evidence matches the NICE scope, the ERG considers there to be small differences compared with the population that would be eligible for Strimvelis treatment in England. However the ERG acknowledges that, due to the rarity of ADA-

SCID and the small patient numbers, the population presented is appropriate for the decision problem in question.

3.2 Intervention

The intervention in the CS is Strimvelis (retroviral-transduced autologous CD34+ cells), which matches the intervention described in the final NICE scope. Strimvelis is a gene therapy treatment in which autologous bone marrow-derived cells are transduced to express ADA and is intended to be administered once per lifetime as an intravenous infusion. However the ERG notes that one patient in the clinical evidence presented in the CS received a second dose of Strimvelis after an unsuccessful response to the first treatment.

3.3 Comparators

The comparator in the decision problem described in the CS is bone marrow transplant, specifically HSCT from an HLA-MUD or an HLA-haploidentical donor, which matches the NICE scope. However the clinical advisor to the ERG advised that UK patients will often be treated with HSCT using donated UCB rather than bone marrow. The decision to use cord blood often depends on how much infection the patient has. The ERG notes that the Hassan et al. study[3] (used as a comparator in the CS) includes a small number of transplants which used UCB (n=9). Hassan et al. do not report which transplants UCB was used in, so it is not possible to ascertain whether cord blood was used in the MUD or haploidentical HSCT procedures that the comparison is based on.

Long term enzyme replacement therapy (ERT) can act as an efficacious alternative to transplantation.[30] However, it is not licensed for such use in the UK, and in line with the NICE scope, this comparator was omitted from the cost-effectiveness analysis. Alternative treatment options for ADA-SCID are continuing to develop. An ongoing Phase III clinical trial is exploring a recombinant preparation of ADA ERT, which has the potential to reduce manufacturing costs compared to bovine derived PEG-ADA (NCT01420627 expected to report March 2019). There is an ongoing trial in the UK for an alternative gene therapy delivered via a lentiviral vector (NCT01380990). While this is not yet available as a comparator, patients in the UK may enter into the trial and it has the potential to be a relevant comparator in the future. These initial trials of lentiviral vector gene therapy have used concomitant ERT until 1 month after transplant, and so immediate survival may be confounded by use of PEG-ADA. However, initial reports are promising, showing 100% overall survival in 32 patients treated with lentiviral vector mediated gene therapy.[19]

3.4 Outcomes

The decision problem set out in the CS includes all the outcomes described in the final scope: overall survival; intervention-free survival; immune function (rate of severe infections, lymphocyte counts, thymopoiesis, use of IVIG, vaccination response); non-immunological aspects; need and duration of in-patient treatment; and health-related quality of life for patients and carers. All of these outcomes are included as part of the clinical evidence presented, except for carer quality of life which is not addressed. The ERG considers outcomes to be appropriately measured. However, quality of life was measured only as part of the long-term follow up (LTFU) study and some of the measures used were non-standardised assessments, which were not pre-specified and for which no baseline assessments were collected.

3.5 Other relevant factors

The CS includes a section on equity considerations. It identifies no ways in which the evaluation could impact adversely on people protected by equality legislation. It does highlight that MUD donor availability can vary by ethnicity, with finding a donor more difficult for non-White patients[20, 21] and suggests that using gene therapy treatments such as Strimvelis will avoid the longer wait for these patients. The CS also mentions that no sub-analysis by race was carried out due to the small number of patients.

4 Clinical Effectiveness

This section contains a critique of the methods of the review of clinical effectiveness data, followed by a description and critique of the trials included in the review, including a summary of their quality and results and the results of any synthesis of studies.

4.1 Critique of the methods of review(s)

4.1.1 Searches

The company submission (CS) contained the search strategies used to identify relevant clinical data on the treatment of ADA-SCID with HSCT or gene therapy. The search strategies were briefly described in the main body of the submission in Section 9.1.1 (published studies) and Section 9.1.1 (unpublished studies). Full details were provided in Appendix 1, Section 17.1.

The electronic database EMBASE was searched on 20th May 2016 via the Elsevier host. The search combined terms for ADA-SCID with terms for the following treatments: gene therapy, stem cell transplantation, or bone marrow transplantation. The EMBASE search was limited by date from 2000 onwards, and restricted to English language studies.

The company supplemented the search of EMBASE with unpublished data of completed and ongoing GSK studies of Strimvelis. In addition, unpublished studies on any treatments for ADA-SCID were sought from searches of ClinicalTrials.gov, the Cochrane Central Register of Controlled Trials (CENTRAL), the UK Clinical Trials Gateway, the EU Clinical Trials Register and the World Health Organisation International Clinical Trials Registry Platform. The trial register searches were carried out on 20th May 2016.

The reporting of the searches was clear with sufficient detail to allow the searches to be reproduced. The databases searched, the service providers used, the date of the searches, limits, and complete strategies were all clearly reported. However, some limitations are noted below which may have reduced the comprehensiveness of the searches.

The CS noted that EMBASE hosted by Elsevier includes the PubMed database. However, the information provided by Elsevier on their website (https://www.elsevier.com/solutions/embase-biomedical-research/learn-and-support) indicates that records from MEDLINE are added to EMBASE. PubMed includes extra records that are not included in MEDLINE. Therefore a search of PubMed in addition to EMBASE would have been a better option to identify relevant records from PubMed that are not contained in MEDLINE.

The sources used to search for unpublished data were comprehensive, including data from the company on Strimvelis and a wider search of several national and international trial registers to capture ongoing studies of any treatments for ADA-SCID.

The EMBASE search strategy could not be fully appraised by the ERG due to a lack of access to the Elsevier hosted version of EMBASE. However, it was possible to note some general limitations of the EMBASE search strategy presented in the CS. Firstly, truncation was not used throughout the strategy. For example, the strategy contained text word searches for bone marrow transplantation, which may miss studies that used the terms bone marrow transplant or bone marrow transplants. It is good practice when producing search strategies for systematic reviews to make use of truncation to ensure that the search strategy is sensitive enough to capture all relevant studies. Although the use of truncation will increase the numbers of records identified it is essential to ensure the comprehensiveness of the search. Secondly, the term gene therapy was included in the search strategy, but the term Strimvelis was missing. Although the company clarified that that they were aware of all Strimvelis publications, it is usual to include all possible alternative terms and synonyms for the interventions under consideration within the search strategy for a systematic review. Finally, the main subject heading (EMTREE term) for the population, adenosine deaminase deficiency/, was not included in the EMBASE strategy which may have further limited the comprehensiveness of the search.

For the search of CENTRAL, the company did not include the Medical Subject Heading (MeSH) Severe Combined Immunodeficiency/ or Adenosine Deaminase/. Unlike the other trial registers searched, CENTRAL has an advanced search interface which allows MeSH searching as well as searching in the title and abstracts of records. Inclusion of these MeSH terms would have improved the comprehensiveness of the search strategy to ensure that all potentially relevant studies about ADA-SCID were retrieved from CENTRAL.

Although the company were aware of all publications about Strimvelis, studies of other comparator treatments for ADA-SCID may not have been identified by the searches presented in the CS, due to the limitations described above.

4.1.2 Inclusion criteria

In the systematic review in the CS, the following inclusion criteria were stated for both published and unpublished studies (see Table 1)**.**

Table 1 Inclusion criteria for systematic review included in CS

Inclusion criteria	Description
Population	Patients with ADA-SCID
Interventions	HSCT from an HLA-matched unrelated donor or HLA haploidentical donor, gene therapy
Outcomes	overall survival, intervention-free survival, rate of severe infections, in-patient hospital stay, lymphocyte counts, AEs, quality of life, and neurological/neurodevelopment events (including deafness).
Study design	No restrictions applied
Other restrictions	English language only

The inclusion criteria are largely appropriate and reflect the decision problem. However the submission lacks transparency and consistency in its treatment of gene therapy in the systematic review. It is unclear whether the systematic review included all studies of gene therapy in ADA-SCID populations as is implied by the inclusion criteria. The main clinical effectiveness section (section 9) discusses only gene therapy data on Strimvelis, which appropriately reflects the decision problem but is a narrower focus than suggested by the inclusion criteria. However Appendix 17.7.2 includes adverse events in other gene therapy trials, which suggests these trials were included in the systematic review.

4.1.3 Critique of data extraction

Limited information is provided on the study selection and data extraction processes used in the systematic review. For example, it was not reported whether study selection or data extraction was completed by one reviewer or whether appropriate methods for minimizing error and bias were used (e.g. a second reviewer either checking the first reviewer's responses, or conducting the same process independently and in duplicate). Therefore, potential errors in study selection and data extraction cannot be ruled out.

4.1.4 Quality assessment

The critical appraisal questions were based on an adaptation of the CASP tool for cohort studies. The criteria were appropriate and included items on recruitment, measurement of exposure, measurement of outcome, identification and adjustment for important confounding factors, completeness of follow up and precision of results.

There were limitations in the reporting of the quality assessment. Firstly, quality assessments were only reported for studies on the effectiveness of Strimvelis and not for all studies included in the systematic review. Secondly, it was not reported whether quality assessment was completed by one reviewer or whether appropriate methods for minimizing error and bias were used (e.g. a second reviewer either checking the first reviewer's responses or conducting the same process independently and in duplicate). Therefore, potential errors in quality assessment cannot be ruled out.

4.1.5 Evidence synthesis

The company did not undertake a meta-analysis of all included studies due to substantial heterogeneity between included studies (e.g. patient characteristics, inclusion criteria, treatment duration and follow up time). The ERG agrees that narrative syntheses were appropriate given the nature of these data.

However, data from 4 studies (AD1117054 Pilot 1, AD1117056 Pilot 2, AD1115611 Pivotal, AD1117064 CUP) and the feeder study which included longer term follow up data from patients in these studies (AD1115611 LTFU) in the Strimvelis clinical programme were pooled and discussed as an integrated population which is equivalent to conducting an unweighted meta-analysis. Although there are some differences in methods between studies (particularly between the pilot studies and the pivotal study in terms of GCP) the ERG considered there was sufficient similarity in populations and study conduct for this approach to be appropriate.

Data from the Named Patient Programme (patients [redacted]) were not included in the pooling of the Strimvelis Integrated Population nor were they included in the narrative syntheses. However some data from this population is provided in Appendix 6. Although GSK does not sponsor the programme and has limited ongoing access to the data, it would appear these data meet the inclusion criteria of the systematic review and should have been included in the narrative syntheses.

There was a lack of transparency regarding how the survival data from HSCT was narratively synthesised. The narrative synthesis on survival focused on studies of HSCT with five or more patients, but it is unclear whether the decision to use a threshold of five patients was made *a priori* or

driven by the data, and no justification is provided for this judgement. However, data from all included studies were provided in Table C22 of the CS.

4.1.6 Summary statement

The reporting of the searches was clear with sufficient detail to allow the searches to be reproduced. However, limitations in the search strategy reduced comprehensiveness of the searches. Therefore some studies of comparator treatments for ADA-SCID may not have been identified by the searches presented in the CS. Appropriate criteria were used to critically appraise Strimvelis treatment however no critical appraisal was conducted on studies of comparator treatments.

Narrative synthesis was an appropriate method of synthesis for the nature of the evidence included in the CS. Although limited data were available from the Named Patient Programme the ERG did not judge it appropriate to exclude these data from the narrative syntheses. Since the Strimvelis Integrated Population comprised only 18 patients, the ERG considered it important to take into account data on the further [redacted] patients of the Named Patient Programme when drawing conclusions about the effectiveness of Strimvelis.

4.2 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

4.2.1 Studies on the clinical efficacy and safety of Strimvelis

Table 2 provides a summary of the Strimvelis Integrated Population and the Named Patient Programme.

The company narrative synthesis includes only data from the Strimvelis Integrated Population. This is the combined total of 18 patients treated in four trials: AD1117054 (Pilot study 1 (N=1)); AD1117056 (Pilot study 2 (N=2)); AD1115611 (Pivotal study (N=12)); and AD1117064 (Compassionate Use Programme (N=3). In addition, patients from these four studies who completed three years of follow up (N=17) were enrolled in a long term follow up study (AD1115611 LTFU); these data were also included in the Integrated population. However long term follow up study data from only 14 patients were available as one patient withdrew (to receive HSCT from a sibling matched donor) and follow up data at year 4 were not available for two patients in the compassionate use programme.

Table 2 Summary of the Strimvelis Integrated Population and the Named Patient Programme (adapted from Tables C5-C9 and Appendix 6).

Study Population	Study Design	Intervention and Comparator (where applicable)	Survival	Immune function	Health related quality of life
Strimvelis Integrated Treatment Population	Combined population of 4 open label, single arm trials and a long term follow up study (includes data from AD1117054, AD1117056, ,AD1117064 , AD1115611, AD115611 LTFU) with historical comparator	Strimvelis (n=18) versus HSCT for haploidentical donor (n=7) versus HSCT for a MUD (n=15)	Survival at longest follow up period Intervention-free survival at longest follow up period	Key secondary outcomes: Severe infection rate, Lymphocyte subset counts, T cell receptor excisions circle analysis, T cell proliferative capacity Post-hoc analyses: Transduced cell engraftment in CD15+ and CD34+ cells, antibody response to vaccination, duration of IVIG administration	Lansky performance index Paediatric Quality of Life Inventory
Named Patient Programme 200893	Investigator sponsored study initiated in 2014 after the enrolment in AD1117064 compassionate use programme had ended	Strimvelis ([redacted])	Survival at longest follow up period Intervention-free survival at longest follow up period	Not reported	Not reported

Outcome data from a long term follow up of ADA-SCID patients receiving HSCT from a matched unrelated donor or HSCT from a haploidentical donor [3] were included as historical comparators to studies AD1115611 and AD1115611 LTFU. Overall survival was the primary outcome in the pivotal (AD1115611) and long term follow up studies (AD1115611 LTFU). Key secondary outcomes

focused on factors related to immune reconstitution such as rate of severe infections, T-cell counts and modification of systemic metabolic defects. Physical growth was also listed as a key secondary outcome in the long term follow up study. Primary and secondary outcomes were not available for Pilot study 1 (AD1117054), and while outcomes were predefined for Pilot study 2 (AD1117056), no distinction was made between primary and secondary. For the Compassionate Use Programme (AD1117064), the primary outcome was the safety of Strimvelis.

Data from [redacted] patients in the Named Patient Programme (recruited from 2014 after the data cut from AD1115611 LTFU) were not included in the company submission evidence synthesis. The reasons given for this were, firstly that the company did not have direct access to the data in the same way as for the other studies of Strimvelis as the study was not sponsored by GSK. Secondly, formal data analysis is planned after 3 years of follow up has been completed. However, some data from the Named Patient Programme was provided in Appendix 6 and the company also provided additional patient characteristics in response to a request for clarification made by the ERG (where applicable these data will be discussed below).

Although there are limitations in terms of reporting study design, methods and results for the Named Patient Programme, the ERG judged it important to consider all available data on patients receiving Strimvelis. This is particularly important given the small sample size (N=18) of the Strimvelis Integrated Population included in the narrative synthesis of the company submission. Including the Named Patient Programme increases the total Strimvelis-treated population to [redacted].

4.2.2 Inclusion Criteria for Strimvelis Integrated Population and the Named Patient Programme

The main inclusion criteria across studies in the Strimvelis Integrated Population were:

- ADA-SCID patients
- No available HLA-identical sibling donor
- ≥ 6 months of PEG-ADA treatment with demonstrated inefficacy or intolerance; or where PEG-ADA treatment was not a long term option

The inclusion criteria appear appropriate and reflect the NICE scope. The criterion of ≥ 6 months of PEG-ADA treatment with demonstrated inefficacy or intolerance is likely to differ from current UK practice. However, this may not be important as there is no evidence that duration of PEG-ADA use is prognostic for treatment outcomes.

No inclusion criteria were reported for the Named Patient Programme.

4.2.3 Patient Characteristics

Strimvelis Integrated Population

Summary characteristics for the 18 patients included in the Strimvelis Integrated Population are provided in Table C21 of the company submission. Four patients had received a prior HSCT from a haploidentical donor. Only three patients did not receive any prior PEG-ADA treatment, the other 15 patients received PEG-ADA for a mean of 20.4 months (range 1 to 71 months).

The median age was 1.37 years (mean= 2.09 years, range 0.5 to 6.1 years); 40% were female; 55.6% were White, 27.8% White/Arabic, 11.1% African heritage, and 5.6% Asian. 44.4% travelled from a European country to receive treatment, 27.8% from the Middle East, 16.7% from South America, 11.1% from North America.

The ADA-SCID treatment population in the UK is very small and epidemiological data for this population is limited. Therefore it is difficult to draw firm conclusions on the representativeness of the data to the UK. Although no patients from the UK have yet received Strimvelis, in consultation with a clinical advisor (Dr Andrew Gennery, who treats ADA-SCID patients at one of the two specialist centres in UK), the ERG judged that there did not appear to be substantial concerns regarding the representativeness of the Strimvelis Integrated Population to ADA-SCID patients in England.

In terms of important prognostic indicators, the clinical advisor suggested viral infection at baseline would be an important factor to consider when evaluating the generalisablity of this population. He suggested that viral infection is likely to be high in ADA-SCID patients (except for very young patients). We requested clarification from the company on presence of viral infection at baseline. The company response stated that no patients were identified with viral infections at screening. Therefore, this potentially raises issues regarding the generalisability of these patients to the UK and it is unclear the extent to which these findings are applicable to those with viral infections at baseline.

A further ERG request for clarification was on number of patients screened for eligibility and the number of patients excluded. The company responded that 12 patients were screened for the Pivotal Study and no patients were excluded. However, no information was available on numbers screened or excluded for Pilot Study 1, Pilot Study 2 and the Compassionate Use Programme (comprising a third of the Strimvelis Integrated Population). Therefore, there is uncertainty regarding recruitment of these 6 patients and whether patients at greater risk were excluded from these studies.

The historical comparator population[3] of patients receiving HSCT from a MUD had a similar but slightly lower median age of 0.58 years (range was narrower than for Strimvelis: 0.08 to 2 years). The

median age for patients receiving HSCT from a haploidentical donor was lower (0.42 years, range 0.17-1.33 years) but these data were not available for the subgroup (receiving treatment from 2000-2009) used for historical comparison in the company submission.

Prior PEG-ADA treatment was much lower in the historical comparator population (22% compared with 83% for the Strimvelis Integrated Population)[3]but was not broken down by type of transplant so this is the average for all included transplants, not just MUD and haploidentical.

Named Patient Programme

The ERG requested comparable patient characteristics for those included in the Named Patient Population (see Table 3).

[redacted]

Table 3 Patient characteristics included studies of the evaluation of clinical efficacy and safety (provided by company in response to ERG request A3 for clarification)

Subject	Sex	Race	Country of origin at diagnosis	Prior SCT or PEG-ADA treatment	Age at gene therapy, years	GSK2696273 treatment date	GSK2696273 dose, CD34+ cells x 106/kg	VCN of product

4.2.4 Quality assessment of studies of Strimvelis Patients

The ERG's critical appraisal of data from the Strimvelis Integrated Population is given in Table 4.

Table 4 ERG's critical appraisal of data from the Strimvelis Integrated Population

Study question	Response	How is the question addressed in the study?
Was the cohort recruited in an acceptable way?	Not clear	There were limitations in reporting of recruitment methods particularly for Pilot Study 1, Pilot Study 2, and the Compassionate Use Programme. Particularly in terms of numbers screened and excluded.
Was the exposure accurately measured to minimise bias?	Yes	No evidence of bias was identified regarding measurement of exposure
Was the outcome accurately measured to minimise bias?	Not clear	Only results for the pivotal study are reported as being collected according to GCP.
Have the authors identified all important confounding factors?	No	Although some discussion of confounding was included it was judged that the impact of potential confounding was not sufficiently considered in the description of the results in the company submission.
Have the authors taken account of the confounding factors in the design and/or analysis?	N/A	As indicated in the company submission it was not possible to adjust for confounding in the analyses.
Was the follow up of patients complete?	Yes	All patients are described and withdrawals from the study are accounted for.
How precise (for example, in terms of confidence interval and p values) are the results?	N/A	As reported in the company submission all comparisons are descriptive.

Critical appraisals were conducted separately for studies AD1115611: Pivotal, AD1115611 LTFU, AD1117056: Pilot 2, AD1117054: Pilot 1, AD1117064 CUP (see tables C11-C15 in the company submission) which comprised the Strimvelis Integrated Population. No critical appraisal was conducted for the study of the Named Patient Programme. All included studies were open label, single armed trials, with small sample sizes ranging from 1-14 patients providing data on a total of [redacted] patients receiving Strimvelis. Small single arm trials compared to historical comparators are often at

strong risk of bias and lack precision in estimation of effects. However, given the low incidence of ADA-SCID the study design used to evaluate clinical effectiveness was considered appropriate.

The ERG conducted their own critical appraisal for each study using the same questions provided in the company submission. Given the similarity of methods and critical appraisal ratings across studies these will be discussed as a whole for the Strimvelis Integrated Population. There was insufficient information reported to conduct critical appraisal for data from the Named Patient Programme.

The ERG critical appraisal largely agreed with that conducted by the company (see Table 4). The main difference in judgement was whether all important confounding had been identified. The ERG considered that the potential impact of confounding between Strimvelis and the historical comparator was substantial and judged that this was not sufficiently communicated in the company submission.

4.2.5 Summary of data on overall survival and intervention-free survival

The data on overall survival and intervention-free survival are summarised in Table 5.

Table 5 Survival outcomes and reported additional treatment for Strimvelis patients

Patient number	Clinical study	Repeat dose or second bone marrow harvest	Overall survival	Intervention-free survival	Additional treatment required	Length of follow up, years
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Overall survival

Strimvelis

Overall survival was 100% in the [redacted] patients that comprised the Strimvelis Integrated Population and the Named Patient Programme (see Table 5). Follow up time in the Strimvelis Integrated Population ranged from 2.3 to 13.4 years (median =6.95 years); it was not reported for the Named Patient Programme.

A limitation of the overall survival data is that it overestimates the benefits of Strimvelis as those who survived but required alternative treatments (such as HSCT or long-term PEG-ADA treatment) due to the lack of efficacy of Strimvelis are counted as treatment successes. As noted by the European Medicines Agency,[31] intervention-free survival (see below) is more likely to provide a better reflection of the effectiveness of Strimvelis.

HSCT from a MUD or a haploidentical donor

The key historical comparator data for HSCT is provided by Hassan et al[3] which is the largest data source on outcomes for patients with ADA-SCID receiving HSCT currently available in the literature. Overall survival was 67% (10/15 patients) for those receiving HSCT from a MUD between 1995 and 2009. For HSCT from a haploidentical donor, overall survival was 71% (5/7 patients). This was based only on data from 2000-2009 as this was considered a more applicable comparison with Strimvelis due to substantial improvements in effectiveness overtime.

Although the ERG acknowledges these are the best available published estimates for HSCT in ADA-SCID patients, there are substantial limitations of these data as a historical control for Strimvelis. As noted by our clinical advisor, overall survival has increased substantially over time following HSCT after data was collected in this historical comparison. This reflects several innovations such as genomic tissue typing which improves matching of unrelated donors, more frequent use of reduced-intensity conditioning to reduce mortality, improved surveillance and treatment of infections, and advances in supportive care. [6]

For HSCT from a haploidentical donor overall survival improved from 43% for patients receiving for all treatment periods to 71% for patients receiving treatment between 2000 and 2009.[3] A similar subgroup analyses by year for HSCT from a MUD was not available from that dataset which particularly limits the comparison between this treatment and Strimvelis. Therefore the data used in the company submission suggests HSCT from a haploidentical donor is more effective than HSCT from a MUD for overall survival. This lacks face validity since currently HSCT from a haploidentical donor is considered a second line option in UK practice after HSCT from a MUD.

Although data for improvements in HSCT from a MUD are not currently available specifically for ADA-SCID patients, a study[6]assessing outcomes in children with non-malignant diseases observed an increase in 5 year overall survival from 72% (in 1992-2002) to 93% (in 2003-2013).

The CS also provided a narrative synthesis of case reports and case-series of overall survival in patients receiving HSCT from a MUD or a haploidentical donor. Their narrative synthesis reported ranges of overall survival for studies with a minimum of 5 patients (and Table C22 summarises all included studies). Reported ranges in the narrative synthesis of 60-71% for HSCT from a MUD and 23-68% for HSCT from a haploidentical donor potentially overestimate the precision of overall survival for these treatments. Small changes in the threshold of minimum included patients impacts substantially on the range of overall survival estimates. For example, for HSCT from a MUD if the threshold changes to four or more patients the range for overall survival is 60-100%. Similarly for

HSCT from a haploidentical donor, reducing the threshold to at least 4 patients (range: 0-68%) or at least 3 patients (range 0-100%) changes the range substantially. When considering all studies included in CS Table C22 overall survival estimates ranged from 0-100% for both HSCT from a MUD and HSCT from a haploidentical donor. Therefore, the ERG judged the data reported as a whole in Table C22 provided a better reflection of the uncertainty regarding overall survival from HSCT from a MUD or haploidentical donor than the reported ranges provided in the text of the narrative synthesis.

Intervention free survival

Strimvelis

Data on intervention free survival with Strimvelis was available for [redacted] patients: There was insufficient data on PEG-ADA use for Patient[redacted] to evaluate intervention-free survival for these patients. Of the evaluable patients [redacted] experienced intervention-free survival (i.e. did not require either ≥ 3 months of PEG-ADA treatment or HSCT): 14/17 (82.3%) in the Strimvelis Integrated Population, and [redacted] in the Named Patient Programme.

[redacted]

Of the [redacted] patients requiring additional interventions, two received a sibling donor transplant (Patient[redacted] and Patient [redacted]) [redacted] One patient (Patient[redacted]) received a second dose of Strimvelis and 8.7 years of PEG-ADA treatment at the time of last follow-up. [redacted]

In response to an ERG request for clarification, the company stated that [redacted] Strimvelis patients (four from the Strimvelis Integrated Population [redacted]) received back up bone marrow cells. The company reported that one patient received a contaminated product, three patients received back up bone marrow cells due to events after Strimvelis. However, in an additional request for clarification the company stated that two patients had a contaminated drug product so the data provided appeared inconsistent.

[redacted]

HSCT from a MUD or a haploidentical donor

Intervention free survival data is very limited for HSCT from a MUD or haploidentical donor and it is not clear if the data reported on those receiving additional treatment is comparable with data on Strimvelis patients. Hassan et al[3]reported one patient receiving a rescue transplant after HSCT from a MUD but no further information is provided about additional treatment. Following HSCT from a haploidentical donor (2000-2009 subgroup), 2/7 did not engraft, resulting in one patient receiving gene therapy and the other patient starting PEG-ADA followed by two rescue transplants before death.

4.2.6 Immune function

Key secondary endpoint data relating to immune reconstitution are summarised in Table 6 below. Comparisons between Strimvelis, HSCT from a MUD and HSCT from a haploidentical donor were limited by a lack of comparable data. The proportion of Strimvelis patients experiencing a severe infection (requiring hospitalisation or prolonging hospitalisation after first 3-months of treatment) reduced from 14/17 (pre-gene therapy) to 10/17 (post-gene therapy) as did the severe infection rate. Although infection rates were described for HSCT from a MUD or haploidentical donor, differences in reporting prevented the ability to draw comparisons across treatments.

Rates of metabolic detoxification (based on dAXP and dATP levels) were high for Strimvelis, HSCT from a MUD, and HSCT from a haploidentical donor. The European Medicines Agency assessment[31] also reported responder rates for lymphocyte ADA activity in Strimvelis patients. Data were more variable with 56% responding at year 2 of follow up which dropped to 20% at year 4 and reached 75-100% at all other follow up periods. However, a comparison of dAXP levels at year 4 suggested ADA enzyme activity was sufficient for metabolic detoxification. Comparable data on lymphocyte ADA activity were not available for patients after HSCT from a MUD or haploidentical donor.

For Strimvelis patients CD3+ T cell counts increased substantially at 1 year from baseline and these improvements were maintained up to 8 year follow up. However, data on CD19+ B cells and CD16+ CD56+ NK cells were more variable. CD19+ cell counts remained below baseline levels throughout the duration of follow up. Geometric means for CD16+ CD56+ cell counts remained below baseline levels up to year 5 but then increased above baseline levels in years 6-8 (median levels were more variable but consistently above baseline between years 5-8). Differences in reporting made comparisons with HSCT challenging, however there was evidence that a high proportion of HSCT patients were able to return to normal counts for CD3+ (71% for HSCT from a MUD and 63% from a haploidentical donor) and CD4+ (86% for HSCT from a MUD and 100% from a haploidentical donor) cells. The presence of T cell receptor excision circles (TREC) is considered a marker of thymic activity. TREC in peripheral blood lymphocytes increased from baseline at Years 1-3 post treatment in Strimvelis patients, but declined from years 5-8 (although remaining above baseline levels). Comparable data for either HSCT comparator was not identified and therefore meaningful comparisons with Strimvelis were not possible.

The company submission reported nine Strimvelis patients discontinuing IVIG, however, in response to a request for clarification by the ERG, the company reported 11 patients had currently discontinued IVIG: in total, 11/17 (65%) Strimvelis patients discontinued IVIG during the follow up period (8 before 3 years follow up and 3 after 3 years follow up).

Most of the 11 Strimvelis patients that discontinued IVIG exhibited antibodies to a number of infectious antigens (e.g.10 patients had detectable antibodies to pertussis, 11 for tetanus toxoid, and 8 for hepatitis B). Although data is limited, vaccination response appears comparable for patients receiving HSCT from a MUD. [32-36]Comparable data were not identified for patients receiving HSCT from a haploidentical donor.

Of the six patients who did not discontinue IVIG, three patients experienced an unsuccessful response to Strimvelis treatment. No data were available for the Named Patient Programme.

A slightly higher discontinuation rate was found for HSCT from a MUD with 5/7 (71%) patients discontinuing over time.[3] All patients with data available (7/7, 100%) who received HSCT from a haploidentical donor discontinued IVIG treatment.[3]

Table 6 Summary of key secondary endpoints

Outcomes	Strimvelis Integrated Population	Strimvelis Named Patient Programme	HSCT from a MUD	HSCT from a haploidentical donor
Severe infection	Patients with an event: pre-GT 14/17 (82%) post-GT 10/17 (59%) Total events post-GT: 15 Severe Infection Rate: pre-GT 1.17 4 months to 3 year 0.26 8 years 0.17	Not reported	No comparable data reported	No comparable data reported
Metabolic detoxification	dAXP responders (<100 nmol/mL): 100% Lymphocyte ADA activity responders: ≥ 210 nmol/h/mg): 56% at year 2 20% at year 4 75-100% all other follow up periods	Not reported	Hassan 2012[3]: median dATP =56.5µM (range 0-227 µM) (n=6)	Hassan 2012[3]: two patients who received HSCT from a haploidentical donor both showed evidence of metabolic detoxification (dATP values of 5 µM and 37 µM).
Lymphocyte counts	CD3+ improved from year 1and maintained till year 8 CD19+ cell counts below baseline levels throughout follow up CD16+ CD56+ cell counts variable – geometric means below baseline until year 5 and above baseline years 6-8	Not reported	CD3+ 71% reached normal levels (Hassan 2012[3]) CD4+ 86% reached normal levels (Hassan 2012[3])	CD3+ 63% reached normal levels (Hassan 2012[3]) CD4+100% reached normal levels (Hassan 2012[3])
Thymopoiesis	TREC in peripheral blood lymphocytes increased from baseline at Years 1-3 post treatment, but declined from years 5-8 (although remaining above baseline levels)	Not reported	Not reported	Not reported

Discontinued IVIG	Total: 11/17 (65%) < 3 years: n=8 > 3 years: n=3	Not reported	5/7 (71%) (Hassan 2012[3])	7/7 (100%) (Hassan 2012[3])
Vaccination response	109 patients had detectable antibodies to pertussis, 9 11 for tetanus toxoid, and 7 8 for hepatitis B	Not reported	appears comparable to Strimvelis patients (Bhattacharya, 2005[32]; Grunebaum, 2006[33]; Honig, 2007[34]; Patel, 2009[35]; Baffelli, 2015[36]).	No comparable data available

4.2.7 Non-immunological events

Almost all (17/18) of the Strimvelis Integrated Population experienced a neurological, CNS or hearing event during treatment or follow up. Cognitive disorders were the most common event (n=5). Deafness was also a common problem with two patients reporting deafness and a further two patients reporting bilateral deafness. Three patients reported psychomotor hyperactivity.

High incidence of non-immunological problems was also found for ADA-SCID patients following HSCT.[7] The CS concluded that neither gene therapy nor HSCT appear to be effective in reducing non-immunological problems.

4.2.8 Patient and Carer Health Related Quality of Life results

Strimvelis

Lansky performance index data were available at year 4 (n=8), year 5 (n=9), year 6 (n=6), year 7 (n=6), year 9 (n=1) and year 13 (n=1) for the Strimvelis Integrated Population. All were rated as 'fully active, normal' at these follow up periods with the exception of one patient who had minor restrictions on strenuous physical activity at year 7. Although this patient did not experience neurological deficits, they had a foot deformity and muscle atrophy. Patient [redacted] completed the Paediatric Quality of Life Inventory at year 13 with a total score expected in an average healthy adolescent of that age. This quality of life data is potentially inconsistent with other data showing that 17/18 patients experienced a neurological, CNS or hearing impairment.

Additional data (although not pre-specified) showed that most (12/14) patients reported on-time vaccinations, attendance at school or preschool as appropriate for their age. However, most patients reported not participating in sports. The CS stated that this was mainly due to the wishes of parents however the ERG noted this may potentially be reflective of impairment of health.

The ERG requested if the company had collected data on families and carers of Strimvelis patients. The company responded that the Telethon Foundation (the charity responsible for care services in the Milan treatment centre providing Strimvelis treatment) had begun an anonymous formal assessment in July 2017. The company provided an example quote of a parent reporting that their stay in Milan was "…just like home". In addition, further quotes of positive feedback from patients on the experiences of families were provided:

"The biggest help was to find a babysitter for my daughter. It was a wonderful evening and we were really happy to go out together"; "We are so grateful for all that you did for us. We really felt welcomed by friends. We would never have imagined to receive all this. Now we only hope that all will be good for our son"; "Me and my family did not thank you enough for all the things you brought to us, it was too much and it helped us a lot, so thank you so much for everything."

HSCT from a MUD or haploidentical donor
Data on quality of life for patients receiving HSCT from a MUD or haploidentical donor were limited. A study of quality of life in SCID patients treated with HSCT in Newcastle included 12 patients with ADA-SCID.[15] Patients with ADA-SCID had significantly lower quality of life (except for the emotional domain) compared with published UK norms. However, as this was a poster presentation very limited data was provided including no information about the type of HSCT performed.

ADA-SCID patients treated with HSCT were associated with IQ levels more than two standard deviations below the general population mean (100) and had greater risk of behavioural problems as indicated by the Strengths and Difficulties Questionnaire. [37] However, since there is no comparable IQ data for Strimvelis patients and behavioural problems are measured differently, comparisons between treatments are not possible.

4.2.9 Summary of Critique

Summary of Survival data
Data on the effectiveness of Strimvelis are based on a total of [redacted] patients collected in a series of open label single arm trials. Of these, 18 comprised the Strimvelis Integrated Population which was the focus of the CS narrative synthesis (data for the [redacted] patients in the Named Patient Programme are summarized in Appendix 6 of the CS). Overall survival was 100% across the [redacted] patients (follow up time ranged from 2.3 to 13.4 years in the Strimvelis Integrated Population). Intervention free survival was [redacted] for all patients but rates differed substantially between the Strimvelis Integrated Population (82.3%) and the Named Patient Programme ([redacted]). Small open label single arm trials are

inherently at a high risk of bias and lack precision. A small number of deaths or treatment failures can lead to substantial changes in survival estimates making such estimates highly uncertain.

Historical controls for HSCT from a MUD and from a haploidentical donor were provided by Hassan et al (2012).[3] Overall survival was 67% (10/15 patients) for those receiving HSCT from a MUD between 1995 and 2009. For HSCT from a haploidentical donor, overall survival was 71% (5/7 patients) based on transplants from 2000-2009. The main limitation of these historical controls is that overall survival from HSCT has improved substantially over time. Therefore, these published estimates of overall survival (particularly for HSCT from a MUD which includes data from 1995) from HSCT are likely to be an underestimate compared with current provision and therefore potentially overestimate the comparative benefits of Strimvelis. In addition, other case reports or case series were narratively reviewed, overall survival estimates in these studies range from 0-100% for both treatments. As with Strimvelis, overall survival estimates for HSCT from a MUD and HSCT from a haploidentical donor are very uncertain and based on small sample sizes.

Summary of other outcomes

Although there was some variability across outcomes and over time, generally there was positive data supporting the benefits of Strimvelis for improving immune function (e.g. 100% responders based on dAXP levels, reduction in severe infections over time, high discontinuation rates of IVIG). Although there were challenges in comparing data on immune function after HSCT from MUD or haploidentical donors with Strimvelis all three treatments appeared to improve immune function and there was no strong evidence of differences in effectiveness between them.

None of the treatments included in the narrative synthesis found evidence of effectiveness in reducing non-immunological symptoms of ADA-SCID including CNS, neurological and hearing deficits.

Generalisabilty

The ADA-SCID treatment population in the UK is very small and epidemiological data for this population is also limited. Therefore it is difficult to draw firm conclusions on the representativeness of the data to the UK.

Although no patients from the UK have yet received Strimvelis, in consultation with a clinical advisor Dr Andrew Gennery (who treats ADA-SCID patients at one of the two specialist centres in the UK), the ERG judged that there did not appear to be substantial concerns regarding the representativeness of the Strimvelis Integrated Population to ADA-SCID patients in England. However, there still remain substantial uncertainties. Data were not available on numbers screened or excluded for six patients in

the Strimvelis Integrated Population in addition to the [redacted] patients in the Named Patient Programme which in total reflects almost half of all patients treated with Strimvelis. It is therefore unclear if patients at greater risk were excluded from these studies.

Similarly, there were no concerns that the patients included in Hassan et al[3] differed from current patients receiving HSCT in the UK. Similar limitations regarding reporting of viral infections and numbers of patients screened for inclusions were found for this study. However, the nature of the study (a survey of treatment outcomes in usual practice) suggests a lower potential for selection bias.

4.3 Adverse events

Strimvelis

All patients in the Strimvelis Integrated Population reported an adverse event (see table C27 in the company submission for further details). In addition, all patients experienced an infection or infestation. The most common infection adverse events were upper respiratory tract infections, gastroenteritis, and rhinitis. Fifteen patients experienced serious adverse events, these were most frequently due to infections (e.g. device-related infections, gastroenteritis, and pneumonia). For further discussion of serious infections see section 4.2.6 above.

As discussed above (see section 4.2.7) 17/18 of the Strimvelis Integrated Population experienced neurological, CNS or hearing impairment which is potentially inconsistent with the quality of life ratings which suggested patients returned to normal health.

Twelve patients experienced 27 adverse events potentially related to auto-immunity. Antinuclear antibody positive was the most frequent event. Four patients experienced six serious auto-immunity adverse events (anti-neutrophil antibody-induced neutropenia, autoimmune thrombocytopenia [2 events], autoimmune aplastic anaemia, autoimmune hepatitis, and Guillain-Barre syndrome). Of these, two required reintroduction of PEG-ADA to restore immune function.

Other Gene Therapy

The CS included information on the adverse events associated with other gene therapies. Cases have been reported of SCID patients developing leukaemia after gene therapy.[38, 39] Although no cases of leukaemia have been reported yet in ADA-SCID patients receiving gene therapy further long term follow up is needed to confirm the risk in this population. There is also a theoretical risk of gene

silencing leading to a loss of therapeutic benefit although this requires further study to confirm the risk in ADA-SCID patients.

HSCT from a MUD or haploidentical donor

Table C28 in the company submission summarises adverse events for HSCT from MUD and haploidentical donors. A key adverse event focused on in the company systematic review was graft versus host disease (GvHD).

Eight case reports/case series contributed to the estimation of GvHD rates following HSCT from a MUD in the company submission providing data on 28 patients, although data from Booth[7]was not used as numbers of events were not reported (Table C28). Nine patients experienced GvHD (Grade I, n=1; Grade II, n=2; Grade III, n=4 and Grade not reported, n=2). One patient was reported to have experienced chronic GvHD (grading not reported) and seven patients acute GvHD, and chronicity not reported for one patient.

The company submission used an unweighted pooling of these events across studies to estimate rates of GvHD. They reported a summary total of 32.1% (9/28) of patients experiencing GvHD across studies. In addition, they estimated number of acute (3/28) and chronic GvHD (1/28) Grade III or IV events.

Five case reports/case series contributed to the estimation of GvHD rates following HSCT from a haploidentical donor in the company submission providing data on nine patients. As above, data from Booth [7] was not used as number of events were not reported. Similarly, an unweighted pooling of events across studies was conducted with 3/9 patients in these studies experiencing GvHD. One patient experienced Grade III GvHD and since it was not reported whether this was acute or chronic the company submission conservatively assumed acute GvHD.

There are a number of limitations to the GvHD data which makes these estimates very uncertain. As the company submission notes, definitions for categorising GvHD differ widely in the literature which makes comparisons across studies challenging. For example, definitions and reporting of acute and chronic GvHD differ across studies and also some studies did not report the grade. Despite acknowledging these substantial differences the company decided to conduct an unweighted pooling of these data across studies (i.e. number of events was added up across studies as if the data constituted a single study). This was not considered appropriate as this ignores important between-study differences such as varied definitions of GvHD, differences in usual care over time and across centres. In addition, the summaries did not include an estimation of the precision associated with the

estimated rates which is important because these estimated rates are likely to be highly imprecise and this is not clear in the submission.

A further important limitation was that rates of Grade III or IV acute and chronic GvHD events following HSCT from a MUD reported in the company submission lacked justification. While it is clear that three acute Grade III events were reported across studies, there is no justification provided why the fourth patient (for whom it was not reported whether the event was acute or chronic) was assumed to experience chronic Grade III GvHD.

Summary
Infections were common after Strimvelis, however, severe infection rates reduced over time, potentially due to improvement in immune function. There is no evidence that rates of infection after treatment differ between Strimvelis, HSCT from a MUD, and HSCT from a haploidentical donor, but variability in reporting makes comparisons difficult.

A major difference between Strimvelis and HSCT was that some patients experienced GvHD events after HSCT, whereas no GvHD events were reported for Strimvelis-treated patients. However, there were important limitations in how estimates of GvHD were calculated in the company submission and some rates lacked justification.

A potential risk of gene therapy identified in other SCID patients was the risk of leukaemia but no events have occurred in ADA-SCID patients. However, given the small sample size of patients who have received Strimvelis, this cannot yet be ruled out as an important potential risk.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

Not applicable

4.5 Additional work on clinical effectiveness undertaken by the ERG

Not applicable

4.6 Conclusions of the clinical effectiveness section

The clinical effectiveness section in the company submission was based on a systematic review of Strimvelis, HSCT from a MUD and HSCT from a haploidentical donor. The ERG considered the submitted evidence largely reflected the decision problem provided in the final scope.

For Strimvelis, the narrative synthesis included data only from the Strimvelis Integrated Population although limited data from the Named Patient Programme was provided in Appendix 6. Although

there were some limitations in the comprehensiveness of the search for HSCT clinical effectiveness data, the ERG judged it was unlikely important studies had been missed.

Overall survival rate was substantially higher for Strimvelis patients (100%) than historical comparator data for HSCT from a MUD (67%) and HSCT from a haploidentical donor (71%). However, there are important limitations to these data:

- Firstly, this is based on a very small sample of patients: [redacted] patients receiving Strimvelis, 15 patients receiving HSCT from a MUD and seven patients receiving HSCT from a haploidentical donor. Therefore there is substantial uncertainty regarding the precision of these estimates of overall survival. A small number of deaths during further follow up would substantially impact on conclusions of the efficacy of Strimvelis.
- Secondly, the overall survival outcome overestimates the benefits of Strimvelis as patients who survived but required an alternative treatment (such as long-term PEG-ADA or an HSCT) due to lack of efficacy are still counted as a treatment success. Intervention-free survival was lower for Strimvelis ([redacted] and there was no comparable data for this outcome in HSCT from a MUD or a haploidentical donor. In agreement with the European Medicines Agency, the ERG considered intervention-free survival to be a more relevant outcome for evaluating the clinical effectiveness of Strimvelis.
- Thirdly, empirical data and clinical expert opinion suggest overall survival from HSCT has improved substantially over time. Therefore, the historical comparator probably provides an underestimate of the likely survival rate in HSCT from a MUD or from a haploidentical donor and therefore likely overestimates the comparative benefits of Strimvelis.

On key secondary endpoints, there was positive evidence for improved immune function in Strimvelis, HSCT from a MUD and HSCT from a haploidentical donor. There was no evidence of substantial differences on immune function between these treatments. Similarly, there was no evidence of substantial differences in non-immunological outcomes (such as neurological and developmental effects of ADA-SCID). None of the included treatments showed strong improvements from baseline.

Comparisons of adverse events between Strimvelis, HSCT from a MUD and HSCT from a haploidentical donor were limited due to variable reporting across studies. However, the most frequent adverse events were similar such as infections. Key differences were in terms of the presence

of GvHD events which were experienced by some patients receiving HSCT but not by those receiving Strimvelis.

On the other hand, adverse events reported in gene therapy trials in other conditions have identified important potential risks. For example, leukaemia has been reported in some patients included in gene therapy trials. Although similar data have not yet emerged in ADA-SCID patients continued follow up is needed before this can be ruled out as a potential risk of Strimvelis treatment given the small sample size of included studies (a total of [redacted] patients). If such adverse events were identified in future studies this would substantially change the risk-benefit profile of the treatment. Theoretically, there is also a potential risk of gene silencing that could lead to a loss of therapeutic benefit over time.

5 Cost Effectiveness

This section focuses on the economic evidence submitted by the company and the additional information provided in response to the ERG's points for clarification. The submission was subject to a critical review on the basis of the company's report and by direct examination of the electronic version of the economic model. The critical appraisal was conducted with the aid of a checklist to assess the quality of the economic evaluation[40] and a narrative review to highlight key assumptions and areas of uncertainty. Section 6 presents additional analyses and scenarios independently undertaken by the ERG to further explore these uncertainties.

The company's economic submission included:

- A description of a systematic review conducted to identify published HRQoL data (CS, Section 10.1.5) with further details presented in separate appendices (CS, Appendices 3, 5).
- A report on the de novo economic evaluation conducted by the company. The report included a description of the patient population, the model structure and assumptions used in the economic model (CS, Section 12.1); the clinical, quality-of-life and resource use parameters used in the economic model (CS, Section 12.2); the measurement and valuation of health effects and quality-of-life data used in the cost-effectiveness analysis (CS, Section 10.1.9); the cost and healthcare resource use identification, measurement, and valuation (CS, Section 12.3); the approach to sensitivity analysis (CS, Section 12.4); the cost-effectiveness results for the base-case and sensitivity analyses (CS, Section 12.5); an overview of any subgroup analyses (CS, Section 12.6); the methods of validation (CS, Section 12.7); and the final interpretation and conclusion of the economic evidence (CS, Section 12.8).
- An electronic copy of the company's economic model developed in Microsoft Excel®.

In response to a number of points for clarification raised by the ERG, the company further submitted:

- A descriptive reply to the ERG's points for clarification, alongside additional data and analyses requested by the ERG.

5.1.1 Searches

The CS contained the search strategies used to identify relevant economic studies concerning ADA-SCID. The search strategies were briefly described in the main body of the submission in Section 11.1.1 and Section 10.1.5. Full details were provided in Appendix 3, Section 17.3.

The electronic database EMBASE was searched on 28th February 2017 via the Elsevier host. The search combined terms for ADA-SCID with terms for cost-effectiveness.

The sources searched to find economic evidence are limited. The NHS Economic Evaluation Database, EconLit and PubMed are all relevant databases that could have yielded further economic studies. In addition, no searches for unpublished economic studies were carried out. Sources such as Research Papers in Economics (RePEc) and abstracts from relevant conferences may have been worth searching to capture any unpublished economic literature.

The EMBASE search strategy could not be fully appraised by the ERG as we do not have a subscription to the Elsevier version of EMBASE. However, it was possible to note some general limitations of the EMBASE search strategy presented in the CS.

The subject heading (EMTREE term) adenosine deaminase deficiency/ was not included in the EMBASE strategy which may have limited the comprehensiveness of the search. In addition, the terms used for the cost-effectiveness section of the strategy are very limited. No subject headings (EMTREE terms) have been included, a very narrow range of text word searches are included and truncation has not been used. The search could have been improved by utilising an economic study design search filter or a recognised search strategy for the retrieval of economic studies such as those listed on the ISSG Search Filters Resource website. This would have ensured a more comprehensive search strategy for economic studies of ADA-SCID and minimised the risk of missing studies.

5.2 ERG's summary and critique of company's submitted economic evaluation

Table 7: ERG's summary and critique of company's submitted economic evaluation

	Approach	Source / Justification	Location in CS
Model	A short term decision tree is used to establish the proportion of patients who achieve each outcome from initial procedure (HSCT or Strimvelis); Markov health states calculate quality adjusted survival and costs in those who have successful treatment procedures. At the outset, patients are assigned to HSCT treatment or to Strimvelis treatment and all patients begin receiving PEG-ADA treatment (19 weeks vs 9 weeks respectively). The pathway probabilities dictate the initial transplant outcomes (see states and events). Surviving patients are assumed to have mortality and health-related quality of life in line with the general population. Those who fail initial treatment are assigned further rescue treatments, delays and costs. 100 year (lifetime) time horizon is used.	The structure reflects the UK's treatment pathway for ADA-SCID for patients without a MRD. The structure was formed on the basis of expert clinical and health economic advice sought by the company.	Section 12.1.3; p136-1377 Section 12.1.4; p138-140
States and events	The model includes four main outcomes: (i) Success, long term survival; (ii) unsuccessful engraftment, PEG-ADA, awaiting rescue HSCT; (iii) death; (iv) long term survival after rescue HSCT. Patients with unsuccessful engraftment (ii) are assumed to undertake a rescue MSD HSCT two years after initial procedure.	The modelling approach was reported to be validated by expert advice.	Section 12.1.3; p136-1377 Section 12.1.4; p138-140
Comparators	For patients without a MRD, current treatment options for ADA-SCID include: • HSCT from a matched unrelated donor (MUD) • HSCT from a haploidentical donor • Long term enzyme replacement therapy Long-term ERT is not seen as a preferred treatment option in England	Aligned with NICE's final scope: "*Bone marrow transplant (including HSCT from an HLA - matched unrelated donor or HSCT from an HLA - haploidentical donor)"*	Section 12.1.2; p136
Natural History	It was assumed that all patients survive the wait to the initial procedure. QALYs gained in the wait period are added as a lump sum those calculated in the Markov process for extrapolation. The survival outcomes from initial procedures are applied to the simulated cohort at the end of the initial wait period.	The estimates of survival, modelling approach and associated cure assumptions were reported to be validated by expert clinical advisors.	Section 12.2.1; p149-150

	Three years after a successful treatment Strimvelis and HSCT patients were assumed to be cured with general population mortality risks from lifetables. Thus the treatment benefits of Strimvelis and HSCT are assumed to be life-long.		
Treatment effectiveness	Strimvelis and HSCT survival outcomes were derived from the long-term integrated population study (n=18) and a historic cohort [Hassan et al (2012)] respectively. Patients in the integrated population of the Strimvelis clinical programme (median follow-up of 6.9 years) had a 100% survival rate and an 82.4% intervention-free survival rate. Three patients suffered failed engraftment. Two patients received a HSCT from a HLA-matched sibling donor a third patient continues to receive PEG-ADA following unsuccessful gene therapy. The NPP also recorded 100% survival. Patients analysed in Hassan et al (2012) (median follow-up 6.5 years) reported an overall survival from patients who received a MUD and haploidentical HSCT of 67% (10/15) and 43% (13/30) respectively. However, the 71% (5/7) OS after HSCT from a haploidentical donor recorded in Hassan (2012) for the 2000-2009 cohort (N=7) was deemed a better reflection of survival than the 43% recorded for the entire Hassan cohort by the manufacturer and NICE at a HST scoping meeting. From those patients that survived initial therapy, three Strimvelis patients (3/17) two haploidentical patients (2/7) and one MUD patient (1/15) required rescue therapies after unsuccessful engraftment. [redacted] Approach to modelling OS as described in natural history. GvHD treatment benefit described in adverse events.	The chief driver of QALY gain with Strimvelis is higher rates of survival. Alternative treatment benefits include circumventing the need for a stem cell donor search, no risk of immune rejection (GvHD) and a reduced wait time to procedure. The company acknowledged the limited data available concerning ADA-SCID patients' long-term outcomes and provides an additional two-way sensitivity analysis to explore the uncertainty around the mean life expectancy and utility scores of ADA-SCID patients.	Section 12.2.1; p149-151
Adverse events	GvHD rates (acute and chronic) were sourced from the ADA-SCID literature and case reports which were included in the model as a treatment-related AE after MUD or haploidentical HSCT. The expected duration of aGvHD or cGvHD was sought by clinical advisors. The disutility of incurring GvHD was taken from the published literature. The product of the duration of GvHD and its disutility provided a one-off QALY burden applied to the model. The cost of GvHD was taken from the literature also. The Strimvelis Integrated population was the primary source of adverse event (AE) data. Infections were the most common SAEs and were included as a cost in the model. The cost of infection was taken from the literature. Rates of severe infection were 26% for the first 3 years, 7% for years 4-8 per person per year as observed in the Strimvelis integrated population. It was assumed this rate of severe infections was equal to that experienced by patients having a HSCT from a MUD or haploidentical donor. It was assumed patients do not experience a HRQoL decrement when incurs a serve infection.	GvHD rates and the utilities used in the model were based on values sourced from the literature. The duration of GvHD was informed by expert clinical advice. The safety findings of Strimvelis are in line with those expected in an ADA-SCID population that has undergone conditioning and is undergoing immune	Section 12.2.4; p155

	AEs related to conditioning regimens or specific to gene therapy were not included in the cost-effectiveness model.	reconstitution. AEs related to conditioning regimens were not included in the model due to data limitations.	
Mortality	Mortality stemmed from only two sources in the model: first, as a direct result of an initial HSCT; second, from general all-cause mortality. The rates of mortality for each procedure used in the model are as follows: Strimvelis: 0% HSCT - MUD: 33.3% Haploidentical donor: 28.6% MSD: 0% Only procedural mortality was captured in first three years. It was assumed patients incurred no mortality risk between diagnosis and initial procedure or while awaiting rescue transplant.	General population all-cause mortality rates for England and Wales were taken from national life tables and applied 3 years after a successful procedure. Expert clinical advice deemed this assumption reasonable.	Section 12.1.5; p140-141 Section 12.2.1; p149-151
Health-related quality of life	No disutility was applied to patients prior to initial procedure (i.e. Strimvelis or HSCT). Post-procedural morbidity was assumed to result in a utility decrement for six months for both initial and rescue procedures. One time QALY losses were applied for instances of GvHD. GvHD QALY losses were calculated as the product of the utility decrement of a GvHD event and the expected duration of an episode. Treatment with IVIG, occurrence of severe infection, AEs related to conditioning regimens and the systematic sequelae of ADA-SCID were assumed not to impact on HRQL. For patients six months beyond initial or rescue procedure the model applies general population EQ-5D scores by age band. Bereaved parent QALY loss associated with child's death was explored in a scenario analysis.	For simplicity no disutility was applied to patients prior to initial procedure (i.e. Strimvelis or HSCT). External acute myeloid leukaemia literature was used to estimate the utility of patients during the first six months after receiving initial or subsequent therapies (i.e. Strimvelis, an initial HSCT or a rescue HSCT).	Section 12.2.6; 163-164 Section 12.4.2; p179

		External literature was used to inform the relevant utility decrement of a GvHD event and the expected average duration of a GvHD episode was sourced through clinical advice. Uncertainties in GvHD related values were explored through scenario analysis. Uncertainties in health related quality of life values were explored through scenario analysis, including a lower HRQL for those receiving IVIG.	
Resource utilisation and costs	Resource use and costs included: Strimvelis' drug acquisition cost (unit price), administration and follow-up; management of adverse events; HSCT costs (initial procedure and follow-up) and subsequent treatment costs. The costs of conditioning therapies and adverse events not related to GvHD or severe infection were excluded from the model. Costs for GvHD events were applied across all patients in year 1 whilst severe infection costs were applied over 1-7 years post-procedure. Rescue therapy costs were applied as a lump sum to patients in the year 3. PEG-ADA costs were incorporated over the period preceding the initial procedure and during the wait to rescue procedure for those that failed engraftment. Strimvelis follow-up costs were assumed to be equal to those applied to HSCT, although an adjustment was made for VCN tests and the first two months of follow-up being conducted in Italy. The costs of follow-up extend for two years post-HSCT procedures and three years for gene therapy on account of VCN tests.	Unit costs were based on the literature, NHS Reference costs, the British National Formulary (BNF) / Medicine Complete and expert opinion. Where appropriate, unit costs were inflated to 2015/2016 prices and converted to British pounds using the exchange rate €1=£0.85. The price of the technology is set in euros and is to be paid to the San Raffaele Hospital. Administration costs for Strimvelis were based on a length of stay assumption	Section 12.2.6; p156-168 Section 12.3.6; p169-175

		informed by assumed administration periods for baseline patient preparation (31 days), treatment (50 days) and outpatient follow-up (60 days). Cost per severe infection was informed from the literature using a figure representing the proportion of hospital costs attributable to severe infections. The IVIG dosage was calculated using an exponential curve across the 25th percentile of the average weight of boys and girls in the UK. Resource use and costs associated with PEG-ADA drug acquisition was based on a dosage and unit cost acquired from expert advice. Initially the model applied the following annual cost for PEG-ADA: Annual PEG-ADA doses *(Average price of PEG-ADA per week + Infusion cost for PEG-ADA) However, in response to a request made by the ERG, the company estimated the dosage and costs of PEG-ADA based	

		on weight, as was undertaken for IVIG dosing. Administration costs of PEG-ADA and IVIG were assumed to follow NHS reference costs for "Consultant Led. Paediatric Clinical Immunology and Allergy Service". In response to clarification from the ERG, the company provided alternative administration costs calculated as the product of the PSSRU defined unit cost for nurse's time and the expected administration times for each drug. Costs associated with the HSCT procedure were assumed to follow NHS references costs for 'Bone Marrow Transplant, Allogeneic Graft (Haplo-Identical), 18 years and under' and 'Bone Marrow Transplant, Allogeneic Graft (cord blood), 18 years and under' for haploidentical and MUD transplants respectively. The procedural cost of a rescue transplant was assumed to equal the cost of a MUD transplant. Long term follow duration and costs was taken from the literature.	

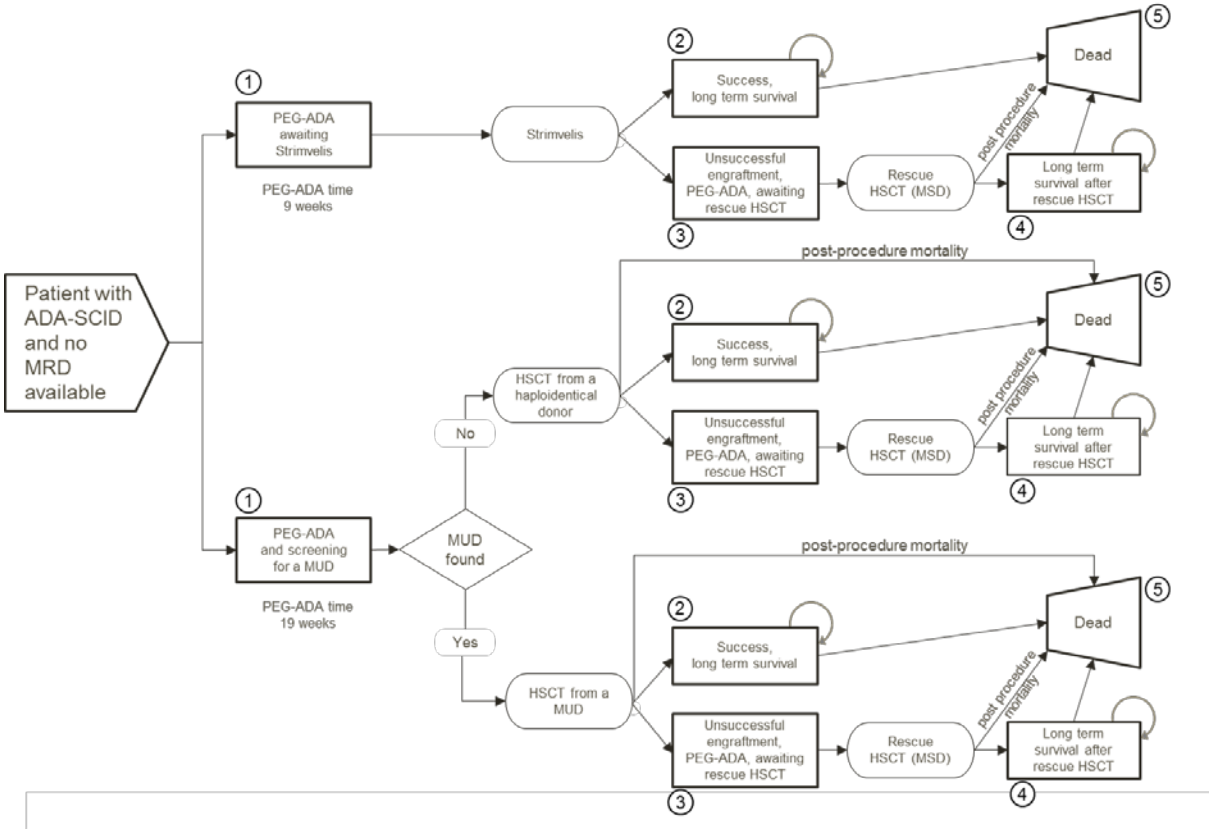
Discount rates	1.5% for utilities and costs (base case). 3.5% discount rates were presented as a scenario.	NICE Methods Guide	Section 12.1.7; p146-147
Population and Subgroups	No formal subgroups were presented due to the small numbers of patients in each treatment group.	The final scope did not specify specific populations and subgroups.	Section 12.6.1; p219
Sensitivity analysis	Deterministic sensitivity analysis and threshold analyses were performed on a series of model parameters. Probabilistic sensitivity analysis and scenario analyses were also performed. Tornado diagrams were produced on request.	NICE reference case	Section 12.5.11; p197-208 Section 12.5.12; p209-210 Section 12.5.13; p210-211 Section 12.5.14; p211-216
Key: HSCT: Haematopoietic stem cell transplant; OS: Overall survival; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; IVIG: Intravenous immunoglobulin; PEG-ADA: Adenosine deaminase conjugated with polyethylene glycol; VCN: Vector copy number; GVHD: Graft versus host disease; ERG: Evidence Review Group; QALY: Quality adjusted life year; CVC: Central venous catheter; AE: Adverse event; SAE: Serious adverse event; MUD: Matched unrelated donor; ADA-SCID: Adenosine deaminase deficiency severe combined immune deficiency: HLA; Human leukocyte antigen; ERT: Enzyme replacement therapy; EQ-5D; EuroQol 5-dimension questionnaire			

5.2.1 Model structure

In the absence of previously published cost-effectiveness analyses for Strimvelis or any other ADA-SCID treatment (CS, Section 11), the company undertook a *de novo* economic evaluation. The submission is based on a decision tree model, with long-term survival extrapolated using a Markov modelling approach. The decision tree characterises the first three year period and is used to establish the proportion of patients successfully treated with each initial procedure (HSCT or Strimvelis) and the proportion that require rescue transplant following failed engraftment. A Markov model approach is used to calculate quality adjusted survival and costs in patients who survive to the end of three years. Figure 1 reports the model structure used by the company. The post-procedural model structure comprises four main outcomes:

(i) *Success, long term survival*
(ii) *Unsuccessful engraftment, PEG-ADA, awaiting rescue transplant*
(iii) *Death*
(iv) *Long term survival after rescue HSCT*

Figure 1: Schematic of company model structure



CS, Figure 5 - p137

At entry to the model patients are assigned to either Strimvelis or HSCT and assumed to start enzyme replacement therapy (ERT) with PEG-ADA immediately to 'bridge' them to the transplant procedure. All patients assigned to Strimvelis go on to receive gene therapy, and hence the model does not incorporate a pathway for patients unable to donate adequate CD34+ cells. While the schematic of the model structure implies that patients allocated to HSCT are split between transplants from a MUD or a haploidentical donor, the model does not estimate the proportion of patients for whom no suitable MUD is available; hence the model compares Strimvelis with either HSCT from a MUD or HSCT from a haploidentical donor.

The model assumes the time between diagnosis and procedure differs between HSCT (19 weeks) and Strimvelis (9 weeks). The time between diagnosis and HSCT procedure characterises the process of searching for and obtaining stem cells from an appropriate donor. In patients who are allocated to receive HSCT from a haploidentical donor it is assumed that a search for a MUD is undertaken. The time between diagnosis and Strimvelis procedure characterises the process of determining eligibility for Strimvelis, arranging travel to Milan, and baseline patient preparation, and assumes no donor screening is undertaken. All patients are assumed to survive the initial wait to procedure.

After the initial procedure, patients are divided into one of three outcomes: (i) *Success, long term survival*; (ii) *Unsuccessful engraftment, PEG-ADA, awaiting rescue transplant*; (iii) *Death*. The decision tree incorporates only procedural based mortality, and patients who die as a result of their procedure are assumed to do so at the point of the procedure. Patients that survive the initial procedure with successful engraftment survive until entry to the Markov process after year 3. Patients that survive the initial procedure, but have unsuccessful engraftment, commence ERT with PEG-ADA and wait for a rescue HSCT ("*Unsuccessful engraftment, PEG-ADA, awaiting rescue transplant*"). All patients waiting for a rescue transplant are assumed to survive two years before receiving the transplant from a MSD. The company recognise that not all rescue treatments may take the form of transplant from a MSD and so include a sensitivity analysis in which the rescue transplant is from a MUD. Following rescue transplant patients are divided between two health outcomes (iii) *Death* and (iv) *Long-term survival after rescue HSCT*.

In the model, all patients who survive either an initial or rescue procedure begin IVIG treatment, the rate of which gradually reduces to zero at 8 years after the procedure. Patients who survive an initial procedure are also at risk of severe infection until 8 years have passed. It is assumed that the rate of severe infections and IVIG usage post-procedure is the same for Strimvelis and HSCT. A proportion of patients who survive an initial HSCT from a MUD or haploidentical donor are assumed to

experience GvHD, which may be acute or chronic. The onset of GvHD was associated with a one-off cost, and a QALY loss dependent on the severity of a GvHD event. Neither risk of GvHD nor severe infection was incorporated for rescue procedures. Surviving patients from the decision tree in (i) *"Success, long term survival"* and (iv) "*Long term survival after rescue HSCT*" enter a Markov process to model subsequent long-term health outcomes and costs from three years following the initial procedure, and are assumed to follow the survival rates and health related quality of life of the general population.

In summary, the decision model allocates procedural outcomes within the first three years plus 9 weeks for Strimvelis, and three years plus 19 weeks for HSCT; thereafter extrapolation occurs over a lifetime horizon with a cycle length of one year.

The ERG is not aware of any existing economic models for this condition and considers that the use of a decision tree with a Markov approach to extrapolating long term survival is appropriate for comparing the costs and health outcomes of alternative treatments for ADA-SCID. However, while the company model structure was stated to be "verified" by an expert modeller, the company provides no details concerning how the initial structure was informed. The simple pathway characterised in the company model provides an incomplete description of the routes by which patients may arrive to treatment. The alternative routes to treatment may imply additional pathways and/or additional treatment strategies. Furthermore, the company model may oversimplify the procession of events after the initial procedure. Both of these factors may obscure potentially important differences in cost and outcome between alternative treatment strategies and are discussed in more detail below.

The model assumes that all patients allocated to Strimvelis proceed to receive gene therapy. However, in practice the recommended minimum dose of Strimvelis is between 2 and 20 million purified CD34+ cells/kg, and patients must be assessed by bone marrow biopsy to determine their ability to donate sufficient CD34+ cells before any treatment can commence. The company report that one patient from the Strimvelis integrated population was unable to deliver the minimum purified CD34+ cells/kg (company response to clarification A6), and suggest that in practice the initial screening process would identify this patient as unsuitable to continue to treatment with Strimvelis. On this basis, if Strimvelis were approved it may be expected that a proportion of patients would incur the cost of an initial baseline assessment for gene therapy but would not subsequently receive treatment with Strimvelis. These costs are not accounted for within the model.

The model assumes that a decision to use gene therapy will be made before any search for a MUD is undertaken. While this reflects some recent clinical guidelines,[26] it does not necessarily reflect clinical practice (see Section 2.2.4). Some patients and their families may first wish to explore the potential for a MUD and reconsider gene therapy if no appropriate donor is found. For those patients the screening and wait time for Strimvelis would be in addition to, and not instead of, the screening and wait time for HSCT. For patients that undertake a search for a MUD and do find an appropriate donor, gene therapy might be considered as a second line treatment following failure to engraft. A proportion of patients who received Strimvelis in the integrated population did so after an unsuccessful HSCT from a MUD. In these patients the screening and wait time for Strimvelis would be in addition to the screen and wait time for HSCT, and the cost of both procedures would be incurred.

The probability of identifying an appropriate MUD, and the potential wait time for an HSCT, may differ according to patient characteristics such as ethnicity and the patient's HLA type. The ability to wait may depend on patient characteristics such as the presence of an active viral infection, which may indicate greater urgency in finding a donor. The clinical advisor to the ERG described that in UK practice, concurrent with tests undertaken to confirm a diagnosis for ADA-SCID, tissue samples are taken from the patient's parents and immediate family for typing and a search of the Anthony Nolan registry would be initiated. The results of the tissue sample tests would be expected within approximately one week, and information regarding the existence of a cord blood match would be expected within approximately two weeks. The ERG found evidence to suggest that the wait time for HSCT from a MUD using cord blood is approximately 2 weeks, and is shorter than the wait time for transplant using adult bone marrow.[18] Hence shortly after it is established that patients do not have a suitable MRD, information regarding the potential wait time and cord blood match should be available. The clinical advisor to the ERG described that the search process for a MUD would be paused if at this point the patient decides to undergo gene therapy.

The ERG therefore note that the expected wait time, and the potential difference in wait time between gene therapy, HSCT from a MUD and HSCT from a haploidentical donor may be predictable by, and differ according to, known patient characteristics. If a reduction in wait time is an important factor in either the choice of treatment or in establishing the value for money of Strimvelis, then these factors could have been reflected in the model structure, for example by including branches with different expected wait times (e.g.to indicate the existence of a cord blood match in the bone marrow registry), or with the use of subgroups (e.g. to indicate longer expected wait times in certain ethnic groups).

In the process of preparing for treatment with Strimvelis, patients are required to donate and have stored a 'back up' bone marrow transplant that could be used in the event of failure. Similar 'back up' transplants may be used in HSCT. The model does not incorporate the usage of such back up, which may be associated with additional resource use and impact on health related quality of life.

The decision to include only procedural based mortality in the first three years of the model may be inadequate to describe the possible sequence of events for sicker patients, including those with active viral infections and who require urgent treatment. These patients may have worse prognosis regardless of treatment received, and may experience mortality during the wait for the initial or rescue procedure. Omission of non-procedural mortality may therefore overestimate quality adjusted survival, and correspondingly overestimate the benefits of avoiding deaths attributed to transplant procedures. Similarly, the characterisation of procedural based mortality as immediate does not reflect the experience of patients who die months after a procedure having undergone substantial further treatment for infection and multiple rescue attempts. The assumption of immediate mortality may underestimate both the health care resource use and the quality adjusted survival of patients who die as a consequence of their HSCT or gene therapy procedure. The potential overestimation of quality adjusted survival in patients that survive transplant procedures combined with the underestimation of quality adjusted survival in those that suffer post-procedural mortality will overestimate the benefits of treatments that reduce procedural mortality.

The ERG believes that following an unsuccessful transplant not all patients would find a MSD to provide a rescue transplant. In practice many rescue transplants come from a MUD (and potentially even haploidentical donor), and this may be especially likely in patients for whom the decision was made to use gene therapy before a search for a MUD was complete. The ERG therefore considers that the type of rescue therapy could differ between patients initially allocated to gene therapy and those initially allocated to HSCT, as the former would be more likely than the latter to identify a suitable MUD for rescue transplant, having not already exhausted that option. Another concern is that some patients may fail to identify any appropriate donor, and these patients in the UK could continue to receive PEG-ADA for an extended period. Compared to the model structure in which transplant from a MSD is the mode of rescue, in practice use of haploidentical donors may be greater, and for some patients duration of PEG-ADA may be longer than is characterised in the model. The implication is that QALYs may be overestimated and health care resource use underestimated for patients requiring rescue transplants.

5.2.2 The company's economic evaluation compared with the NICE reference case checklist

Table 8: Comparison of the company economic evaluation against the NICE reference case checklist

Attribute	Reference Case	Included in CS	Comment on whether *de novo* evaluation meets requirements of NICE reference case
Comparator(s)	The NICE scope defined comparators as follows: Bone marrow transplant including HSCT from an: - HLA matched unrelated donor - HLA haploidentical donor	Yes	Yes
Type of economic evaluation	Cost-effectiveness analysis	Yes	Yes
Perspective - costs	NHS and PSS	Yes	Yes
Perspective – benefits	All health effects on individuals	Yes	
Time horizon	Sufficient to reflect any differences in costs or outcomes between the technologies being compared.	Yes	The economic model had a life-time horizon of 100 years. No patients were expected to be alive beyond this period.
Synthesis of evidence on outcomes	Systematic review	Yes	
Outcome measure	QALYs	Yes	
Health states for QALY measurement	Described using a standardised and validated instrument	Partial	All utility values were derived from the external literature, with duration of utility decrements informed by expert opinion. Utilities for the states defined by long term survival were derived from the general population EQ-5D scores. Health states for the 6 months post-procedure and for GvHD were described using vignettes in the corresponding source studies.
Benefit valuation	Time Trade Off or Standard Gamble	Partial	Utility values for long-term survival and for GvHD were based on time trade off. Utility values for post-procedural morbidity were based on visual analogue scale.
Source of preference data	Representative sample of the public	Partial	Utility values for long-term survival and GvHD were based on a sample of the public. Utility values for post-procedural morbidity were based on physician preferences.
Discount rate	3.5% on costs and health benefits	No	Costs and benefits have been discounted at 1.5% per annum in the base case analysis. A 3.5% discount rate is explored in scenario analyses.
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes	
Sensitivity analysis	Probabilistic sensitivity analysis	Yes	Yes

NHS: National Health Service; NICE: National Institute for Health and Care Excellence; PSS; Personal Social Services; IVIG: Intravenous immunoglobulin; HSCT: Haematopoietic stem cell transplant; ADA-SCID: Adenosine deaminase deficiency severe combined immune deficiency: HLA; Human leukocyte antigen; EQ-5D; EuroQol 5-dimension questionnaire QALY: Quality adjusted life year; GVHD: Graft versus host disease

5.2.3 Population

The primary sources of data used to inform the cost-effectiveness model was the Strimvelis Integrated Population long-term follow-up study and selected patients from a retrospective international study.[3] As previously stated in Section 3.1, the populations in these studies can be considered to match the NICE scope, but some differences may exist between patients in the Strimvelis Integrated Population and those eligible to receive Strimvelis treatment in England. Further differences exist between the modelled patient population in the company's cost-effectiveness analysis and the patients observed in the primary data sources.

The model population is a cohort aged 1, with 50% male and 50% female patients. No further information is provided as to the assumed population characteristics, for example whether they may have received prior therapy. The Strimvelis Integrated Population are older (mean 2.1 years at gene therapy), more frequently male (61%) and a proportion had already undertaken a HSCT prior to gene therapy (22.2%) or received PEG-ADA (83% PEG-ADA of any duration; 67% PEG-ADA of duration >3 months). The ERG considers the modelled patient cohort broadly reflects the licenced indication for treatment of patients with ADA-SCID for whom no suitable human leukocyte antigen (HLA) - matched related stem cell donor is available.

In line with the final scope issued by NICE, no subgroup populations were considered. The company justified this on the basis of small numbers of patients in each treatment group. While the ERG considers this a reasonable argument, it is noted that certain patient characteristics may alter expected outcomes. Age at transplant and presence of an active viral infection, pre-existing respiratory impairment and septicemia are associated with lower expected survival following HSCT. [3, 27, 28] The clinical advisor to the ERG noted that age may be a proxy for the presence of an active viral infection, [27] and that while the published survival data for HSCT certainly include patients who received transplant with active infection, it was unclear whether any patients in the Strimvelis integrated population received gene therapy in the presence of active viral infection. In response to clarification, the company stated that no patients had active viral infection at screening for inclusion in the Strimvelis integrated population (company response to clarification A1). Age is a factor that may determine suitability and success of gene therapy; in response to clarification, the company noted that cellularity typically decreases with age, and patients with lower cellularity may be unable to deliver the minimum amount of cells required for treatment with Strimvelis (company response to clarification A6). Finally, a key component of the model is the reduction in usage of PEG-ADA to bridge to transplant. As doses of PEG-ADA and IVIG are determined by patient weight, older patients would be expected to incur greater costs while being maintained on ERT, and to incur greater

costs for IVIG post-procedure. Overall, the ERG considers that mortality and health care costs would be expected to increase with patient age, and that the results of the company model are not generalisable to older patient populations.

Given the importance of a number of the uncertainties in the treatment pathway and patient population, additional analyses which consider the potential impact of these uncertainties on the cost-effectiveness results were undertaken by the ERG and are presented in Section 6.

5.2.4 Interventions and comparators

The intervention assessed is the retroviral-transduced cell product Strimvelis. While the transduced cell product is separate from the transplant procedure that utilises the product, in practice the short shelf life means that Strimvelis can only be transplanted in SR-TIGET, Milan. Patients cannot be treated with Strimvelis without also travelling to, and additionally pay for the transplant procedure, in the specialist centre in Milan.

The comparators included in the economic evaluation are HSCT from a MUD and HSCT from a haploidentical donor, as specified in the NICE scope. While HSCT from a haploidentical donor was incorporated into the company's economic analysis, the company considers MUD transplants to be the only relevant comparator on the basis of expert clinical advice.

"*We have assumed that Strimvelis will be replacing 1 HSCT from a MUD based on clinical expert explanation that HSCT from a haploidentical donor has not been performed in England in the last 15 years.*" CS, p225

Long term enzyme replacement therapy (ERT) can act as an efficacious alternative to transplantation.[30] However, the company report that long-term ERT is not seen as a preferred treatment option in England, which may be due to the inconvenience of the weekly or bi-weekly treatment schedule, significant long-term cost, limited availability, and uncertainty regarding the development of antibodies that could reduce efficacy with prolonged use. In line with the NICE scope, this comparator was omitted from the cost-effectiveness analysis. The ERG's clinical expert agreed with the conclusions drawn by the company.

The ERG note that the rarity of observed haploidentical transplants may be attributable in part to the small number of ADA-SCID patients over time and the preference in clinical practice to consider first transplant from a MUD or entry into available trials of gene therapy. Recent developments in the techniques for HSCT with a haploidentical donor are associated with improving rates of survival,[4, 6]

and it offers the advantage of being available to nearly all patients with ADA-SCID without the need to undergo a lengthy search procedure. The ERG therefore considers haploidentical donor bone marrow transplants as a relevant comparator, although recognises that based on current clinical guidelines it may be considered as second-line alternative to transplant from a MUD. The ERG notes that the company submission does not characterise the costs and health outcomes of avoiding search costs and wait times through first-line use of haploidentical donors.

The comparison of Strimvelis with HSCT from a MUD is appropriate if the availability of a MUD is known before choosing between gene therapy and HSCT. This is inconsistent with company's assumption that this information is not available at the point of the treatment decision. To inform decisions made without knowledge of the availability of MUD the relevant comparator may be a weighted combination of MUD for the proportion of patients that find a suitable donor, with haploidentical donor restricted to those who fail to find an appropriate MUD.

5.2.5 Perspective, time horizon and discounting

The perspective of the company's analysis was the NHS and Personal Social Services (NHS & PSS). The time horizon used in the model was assessed over a life-time (100 years). This was justified on the basis that expert clinical advice sought by the company suggests a successful engraftment from Strimvelis or HSCT related procedures offer a cure from ADA-SCID, and that patients surviving after three years would revert to the mortality of the general population.

A discount rate of 1.5% per annum was applied to both costs and outcomes in the company's base case. The NICE Methods Guide states that a discount rate of 1.5% for costs and benefits may be considered in cases when the treatment restores individuals who would otherwise die or have a very severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years).[41] The company justified the use of a 1.5% discount rate on the basis that patients treated with Strimvelis are expected to have a long and sustained benefit, regaining normal life expectancy.

The ERG considers that the time horizon used in the model adequately encapsulates all the benefits and costs related to Strimvelis and HSCT. However, the ERG note that the different wait time before the initial procedures in the decision tree means that the model time horizon is 10 weeks shorter for Strimvelis compared to HSCT. In response to clarification the company asserted that the 10 weeks difference would be realised at the end of a patient's life, and that with discounting the impact on the model results would be negligible (company response to clarification B15). The ERG agrees that this

10 week differential is unlikely to be influential on the results if realised at the end of the time horizon. The ERG considers the 1.5% discount rate applied to the model may be reasonable according to NICE guidance, but is concerned that many patients with ADA-SCID will not return to general population life expectancy and morbidity after successful transplant.

5.2.6 Treatment effectiveness and extrapolation

The company's base case model assumes that gene therapy with Strimvelis will alter the outcomes of patients who would otherwise have received HSCT from a MUD or haploidentical donor in four ways:

- Wait time to procedure and duration of ERT
- Survival
- Rate of rescue therapy
- Rates of GvHD

5.2.6.1 Wait time to procedure and duration of ERT

The wait time between diagnosis and procedure determines the duration of ERT with PEG-ADA, which is assumed to be used in all patients to stabilise them and 'bridge' to procedure. The wait times for HSCT were taken from Gaspar et al (2013), which reported an average wait time of 129 days.[17] The company rounded this figure to 19 weeks. Based on the clinical schedule defined by San Raffaele Telethon Institute for Gene Therapy, the company assume a 9 week wait time between diagnosis and treatment with Strimvelis. This 9 week wait time differs from the length of the 'pre-treatment phase' observed for patients recruited to the Strimvelis pivotal study (average 5.7 months, equivalent to 25 weeks).

As part of the clarifications stage the ERG requested the company justify the discrepancy between recorded and modelled time to treatment. The company response noted concerns about the age of the data '*The pivotal study treated its first patient in October 2002 and its last patient in June 2008*', and that '*Time to treatment will be shorter now post-authorisation as the need for ethical approval and other such delays will be eliminated*'. The company also note that, '*If Strimvelis receives positive approval from NICE, then NHS England will be obliged to provide funding so that there will be no need for further approvals in order to refer a patient to Milan for treatment with Strimvelis*' (company response to clarification B8).

The ERG notes that the data from the Strimvelis pivotal study is contemporary with that used to inform the wait time to HSCT. Furthermore, the ERG understands that for most clinical studies

ethical approval would be required prior to recruitment, and would not introduce delay between recruitment of a patient to a study and receipt of study treatment. It is unclear what role funding barriers may have played in the length of the pre-treatment phase in the pivotal study, which included no patients from the UK. The ERG notes that the company's preference for using the clinical schedule of the San Raffaele Telethon Institute for Gene Therapy (SR-TIGET) to determine the wait time to Strimvelis in preference to observed wait times could be considered inconsistent with the preference to use observed wait times for HSCT and not the UK Stem Cell Forums recommendations of 6-8 weeks wait to HSCT (company response to clarification B1). The ERG does not consider that the assumed treatment benefit of reducing PEG-ADA usage was adequately justified by the company on the basis that no evidence was provided to demonstrate that Strimvelis will be delivered within the quoted 9 week schedule. The ERG assesses the potential impact of a treatment independent time to procedure on cost-effectiveness in Section 6.

The company model assumes all patients receive PEG-ADA for the duration of the wait to the initial procedure, and throughout the wait between an unsuccessful engraftment and a rescue transplant. The company note that PEG-ADA '*is usually stopped 20 days before infusion of Strimvelis*' and that they have overlooked this in the model for the sake of simplicity (company response to clarification B1). The ERG is also aware that PEG-ADA may be stopped to allow cellular immunity to wane in preparation to receive HSCT, in order to reduce the risk of graft rejection.[19] The company submission highlights the limited availability of PEG-ADA and the reluctance to supply it as a long-term treatment option. The ERG notes that many patients with ADA-SCID did not receive ERT prior to HSCT, including 83/106 (78%) of those reported in Hassan 2012.[3] In contrast the majority of patients in the Strimvelis Integrated Population did receive ERT prior to gene therapy (15/18; 83%). As UK centres contributed 44 patients to the Hassan study, even with the extreme assumption that all of the 23 patients that did receive ERT were from the UK, this would give a maximum rate of PEG-ADA use of 23/44 (52%) prior to HSCT. The ERG note that there is little data on the use of PEG-ADA as secondary therapy following a failed HSCT, with Gaspar 2009 reporting use in fewer than 10% of patients.[30] Thus there is uncertainty not only regarding the duration of PEG-ADA use, but also the rate of PEG-ADA use. Clinical advice to the ERG indicated that most patients in the UK would be expected to receive PEG-ADA while awaiting transplant. The ERG therefore accepts the simplifying assumption that patients will receive PEG-ADA for the duration of the wait until transplant, but cautions that this likely overestimates any savings from reducing the duration of time between diagnosis and transplant procedure.

5.2.6.2 Survival

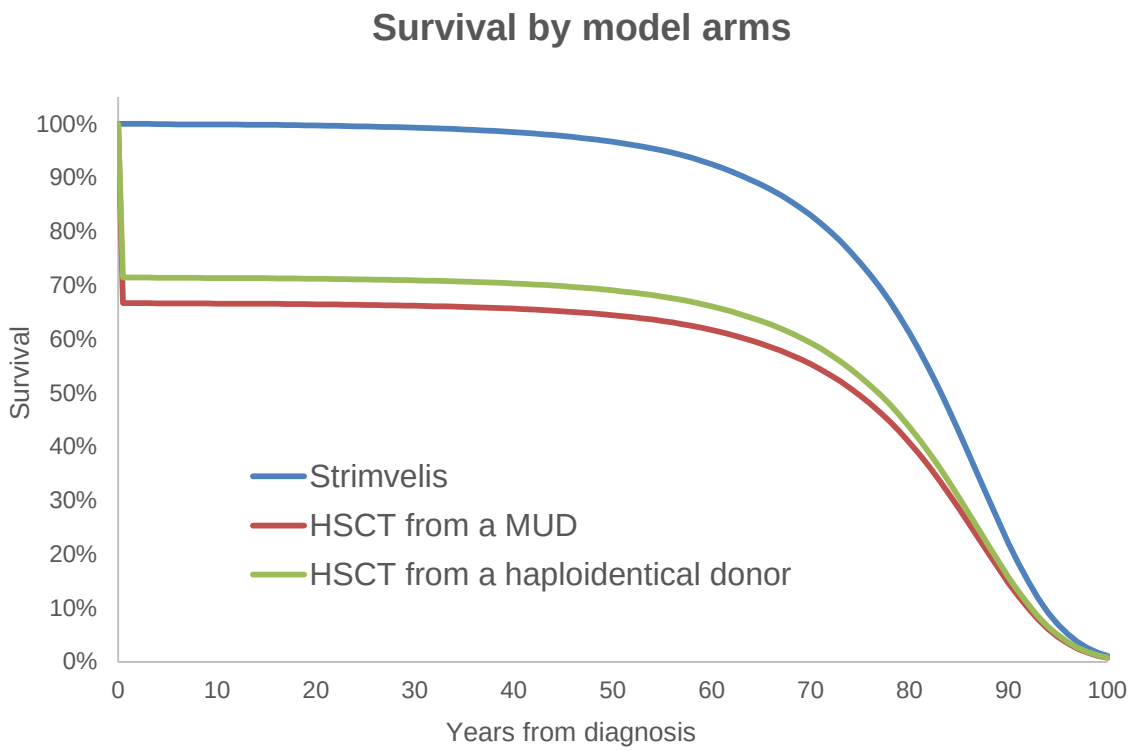
The primary clinical effectiveness parameters used in the model are the survival probabilities for each initial procedure. The source used to inform survival probabilities for Strimvelis is the long-term follow-up study of the Strimvelis Integrated Population. The source used to inform survival after HSCT is a retrospective survey of 16 international transplant centres, which included 44/106 (44%) HSCTs provided in the UK.[3] Overall survival after Strimvelis is reported to be 100%; however this includes three patients with unsuccessful response to Strimvelis and who required further intervention. Intervention-free survival, defined in the Strimvelis clinical programme as survival without post-gene therapy PEG-ADA use for a continuous period of ≥3 months, SCT, or death, was 82.4%. Survival probabilities for transplants performed between 2000-2009 was used for haploidentical donors (5/7 patients, 71%) while survival for MUD patients was informed from by the entire duration of the study (10/15 patients, 66.6%) (see Section 4.2.5).

Given the small sample sizes the ERG consider it important to utilise all available data on patients receiving Strimvelis, including data from the Named Patient Programme ([redacted]) to inform model parameters. All patients from the Named Patient Programme remain alive, and [redacted] are considered to be intervention-free. This leaves overall survival unchanged at 100%, and [redacted].

The ERG has concerns that data selected by the company to inform survival following HSCT suggests that survival after transplant from a MUD is lower than that from a haploidentical donor, which lacks face validity. A further concern is whether the historical data provided in Hassan appropriately characterises current survival rates following HSCT. As noted in Section 4.2.5, survival rates with HSCT are widely considered to be improving over time, with the UK Stem Cell report showing sustained year on year improvements in one year survival following unrelated donor stem cell transplantation from 2003 to 2012.[4] A recent study from a transplant centre in Sweden showed that five year survival following transplant from a MUD for children with non-malignant diseases improved from 72% in the period 1992-2002 to 93% in the period 2003-2013 (p=0.02), with a corresponding drop in transplant related mortality.[6] The ERG believes that overall survival following HSCT may now be higher than that reported in Hassan. In contrast, survival with Strimvelis can only reduce from 100%, and this is not implausible given the severe nature of ADA-SCID as a condition and the less than 100% response rate to gene therapy. The ERG is therefore concerned that the absolute difference in overall survival between Strimvelis and HSCT may be overestimated in the company model.

Mortality stemmed from only two sources in the company base case: first, as a direct result of an initial HSCT; second, from general all-cause mortality. The company assume after a successful treatment using Strimvelis or HSCT patients are cured from ADA-SCID and experience the same mortality risk as the general population. Figure 2 displays the survival outcomes by treatment arm within the model.

Figure 2: Modelled survival outcomes by treatment arm



Company model, "*Inputs Survival*"

The company justify the ways in which mortality is incorporated into the model on the basis that:

- Procedural survival is informed using the most recent evidence
- Kaplan-Meier overall survival curves for patients who received HSCT from a MUD or haploidentical donor, do not show deaths after approximately 1 year

The ERG are concerned that the underlying message from the model is that all ADA-SCID patients without a matched related donor can be cured and return to general population mortality and morbidity if they survive the initial procedure, regardless of engraftment success, patient characteristics or prior health state. Expert clinical advice confirmed the assumption that patients surviving beyond three years since the time of initial procedures could return to the mortality risk for

the general population. However, it was noted that HSCT has only been provided to patients with ADA-SCID within the last 25 years, and so data on life expectancy is not available.

It is observed that a proportion of patients require immune support with IVIG and experience severe infections for up to 8 years following transplant, which is suggestive of less than full health. Furthermore, the systemic sequelae of ADA-SCID remain even after successful transplant, and patients continue to be underweight. In general being underweight may compromise health, and is associated with increased all-cause mortality. The Royal College of Paediatrics and Child Health BMI centile charts indicate that children on the 25th percentile have a BMI of approximately 15, increasing slowly over time to a BMI of approximately 20 at age 19. BMI of less than 20 is associated with increased hazard ratio for all-cause mortality in adults compared to those with a BMI between 22.5 and 24.9. [42] Individuals who have ADA-SCID are more likely to experience hearing loss, respiratory complications and neurologic abnormalities compared to the general population.[1, 8, 34, 43, 44] Fourteen (78%) patients in the Strimvelis Integrated Population had ongoing neurological impairments at baseline and 10 of these experienced further events after gene therapy (56%). [45] These factors all indicate that ADA-SCID patients with successful engraftment may not be entirely comparable with the general population after a period of three years. While many long-term adverse events and the systemic sequelae of ADA-SCID consequences are assumed not to differ between gene therapy with Strimvelis and HSCT from a MUD or haploidentical donor, omitting these from the model risks overestimating the QALY gain from any deaths avoided and underestimates the health care resource use of survivors. This would be expected to overestimate the cost-effectiveness of treatment strategies that reduce initial procedural mortality.

5.2.6.3 Rescue transplant

The same sources used to inform the rates of overall survival are used to inform the rates of rescue therapy for each comparator. Following unsuccessful engraftment, two patients from the Strimvelis integrated population (patients 8, 17) started continuous PEG-ADA post-gene therapy before receiving a HSCT from a HLA-matched sibling donor whilst a third patient (patient 2) continues to receive PEG-ADA. On the basis of expert clinical advice, the company assumed the latter patient would eventually receive a rescue transplant in UK practice.

Table 9 displays the treatment specific pathway probabilities for each of the three procedural outcomes used in the model along with the patient numbers used to inform them.

Table 9: Summary of primary efficacy data reported by the company

	Success, long term survival	Unsuccessful engraftment, PEG-ADA, awaiting rescue transplant	Death	Source
Strimvelis	14/17 (82.4%)	3/17 (17.6%)	0/17 (0%)	Strimvelis long-term integrated population study
MUD	9/15 (60.0%)	1/15 (6.7%)	5/15 (33.3%)	Hassen et al (2012)
Haploidentical	3/7 (42.9%)	2/7 (28.6%)	2/7 (28.6%)	Hassan et al (2002) [using 2000-2009 cohort]

The ERG notes that [redacted] patients in the Named Patient Programme required rescue therapy, and inclusion of these data would give a rescue transplant rate of [redacted] and a corresponding successful engraftment rate of [redacted].

The ERG has concerns regarding the calculation of rescue therapy rates conducted by the company as they are not conditional on survival following the initial procedure. Further to this, the use of overall survival rather than transplant related mortality means that deaths from all causes, including rescue treatment attempts, are applied at the point of the initial procedure in the model. Consequently, the outcomes in the company model structure are not mutually exclusive. In the sensitivity analysis that explores rescue using transplant from a MUD with 66.67% survival, the failure to use transplant related mortality and conditional probabilities of rescue transplant is particularly problematic, as it may double count fatal events.

For the outcomes in the decision tree to be mutually exclusive the rescue therapy rates ought to be calculated from the number of patients who survived initial procedure rather than from the initial sample size. Since Strimvelis is recorded as having a 0% mortality rate, the rates of rescue therapy for Strimvelis are by default based only on survivors. Transplant related mortality, defined as death within 100 days of transplant, was reported in Hassan et al to be 4/15 (27%) from a MUD. For haploidentical donors transplant related mortality was only reported for the full cohort at 10/30 (33%) and was not available for the subset of transplants conducted between 2000-2009. The conditional rate of rescue therapy following HSCT from a MUD is 1/10 (10%) based on overall survival and 1/11 (9%) based on transplant related mortality. The conditional rate of rescue therapy following transplant from a haploidentical donor is 2/5 (40%) based on overall survival. These rates are

somewhat higher than those applied in the company model (6.7% for MUD and 28.6% for haploidentical). However, the sample size in Hassan is very small and there may be other relevant evidence as to the rate of rescue transplant following HSCT.[27] The ERG note that while the limited evidence suggests that the rate of rescue transplant may be higher following HSCT from a haploidentical donor compared to a MUD, it is highly uncertain as to whether there is any difference in the rate of rescue therapy between Strimvelis and HSCT. The potential impact of a treatment independent rate of rescue therapy on cost-effectiveness is explored in Section 6.2.

5.2.6.4 Rates of GVHD

A further treatment benefit incorporated into the model was the avoidance of GvHD in patients treated with Strimvelis. This treatment benefit is clinically justified on the basis that Strimvelis is made from a patient's own cells and as such incurs no risk of rejection due to HLA mismatching or minor antigen incompatibility. This conclusion is in line with what was observed in the clinical programme.

The company calculated rates of any GvHD, chronic GVHD and acute GVHD by summing the number of events reported across the literature. A summary of the sources referenced in the company submission and the company's calculated rates of GvHD are shown in Table 10. The ERG express concerns regarding the derivation of the rates of GvHD applied in the economic model (see Section 4.3). It is unclear from the company submission which GvHD events may have resulted in death and whether these events were then used to calculate GvHD rates. Including GvHD events resulting in death would double count the negative consequences of GvHD given that the company apply HSCT procedural mortality that incorporates mortality from GvHD and assumes death is immediate. Although the ERG has concerns regarding the approach to calculation for the rates of GvHD applied in the company model, the rates themselves appear reasonable in comparison to broader studies assessing GvHD following HSCT for SCID.[27]

Table 10: Rates of GvHD used in the company submission

Donor	GvHD grade		N	Rates	Source
MUD	Grade I/II		5	17.9%	Baffelli, 2015; Serana, 2010; Dvorak, 2014; Gennery, 2001
	Grade III/IV	Acute	3	10.7%	Dvorak, 2014; Grunebaum, 2006
		Chronic	1	3.6%	
	Total GvHDs		9	32.1%	
	Total patients		28		

Haploidentical	Grade I/II		2	22.2%	Honig, 2007; Borghans, 2006
	Grade III/IV	Acute	1*	11.1%	Honig, 2007
		Chronic	0	0%	
	Total GvHDs		3	33.3%	
	Total patients		9		

5.2.6.5 Costs and outcomes not included in the model

The model does not include costs or health outcomes related to the use of conditioning regimens prior to HSCT or gene therapy. Conditioning regimens used before Strimvelis and HSCT are a source of adverse events. Clinical advice to the ERG suggested that busulfan would be the most common conditioning agent in the UK, and that regimens have become less toxic over time. Low-dose busulfan is used as a pre-treatment for Strimvelis, and this may be lower intensity on average compared to the conditioning regimen used for HSCT. Therefore, the company assert that the omission of conditioning regimens from the economic analysis can be regarded as conservative and would underestimate the benefits of gene therapy compared to HSCT. Clinical advice to the ERG supports this assumption.

Following the initial procedure, the company assume that the rates of IVIG use and severe infections are the same across treatment arms. This was considered to be a reasonable assumption by the clinical experts and ERG. While IVIG use is included after both the initial procedure and any rescue procedure, severe infections are incorporated only following the initial procedure. Adverse events not related to GvHD or severe infections were omitted from the analysis. The model does not characterise any particular adverse events that may be connected to use of gene therapy such as leukemic events, and assumes that retroviral insertion site testing and replication competent retrovirus testing will not be undertaken. The company state that no leukemic adverse events have been observed in the Strimvelis clinical programme, and assume that adverse events so far observed are attributable to the conditioning regimen used and other factors common to both HSCT and gene therapy transplant procedures, such as the placement of a central venous catheter. The ERG note that the assumption of no risk of adverse event associated with gene therapy is based on a small population thus far treated with Strimvelis, and that these adverse events have been observed with retroviral vector gene therapy for other SCIDs (see Section 4.6).

The form of rescue therapy was assumed to be the same regardless of initial transplant procedure. In the base case rescue transplant was assumed to come from a MSD donor, with 100% survival, 100% successful engraftment and no risk of GvHD or severe infection. The ERG note that transplant from MSD donor is associated with less than 100% survival, less than 100% success and carries a risk of GvHD.[27] A scenario analysis considered the use rescue transplant from a MUD, using the same survival rate as initial transplant from a MUD (66.67%), but again without further consideration of GvHD or risk of severe infection. As the company use the data from overall survival to model deaths from the initial procedure, any deaths following rescue transplants received have already been incorporated in the initial post-procedural survival rate. Consequently, scenarios that add further mortality at the point of rescue transplant risk double counting mortality events in patients assigned to HSCT. Double counting is so far not possible for Strimvelis as no deaths are attributed to the initial procedure. The ERG thinks that it is reasonable to assume that there will be similar mortality rates from a given rescue transplant procedure among patients who have failed to engraft following gene therapy as for those who fail to engraft following HSCT. The ERG believes that the current scenario that explores mortality associated with rescue transplant is favourable to Strimvelis by overestimating mortality in patients assigned to HSCT. Further to this the ERG believes that the form of, and pathway, to rescue transplant could differ between patients who fail gene therapy without ever having completed a search for a MUD and those who fail initial HSCT after having completed such a search.

The ERG noted several other relevant treatment related events not considered by the company that could have been included in the model structure, including the proportion of patients who could produce sufficient CD34+ cells to be eligible for Strimvelis, the proportion of ADA-SCID patients expected to find no appropriate MUD, and the use of 'back up' bone marrow transplantation. In response to clarification the company reported that one patient from the Strimvelis integrated population was unable to produce sufficient CD34+, which would provide a rate of 1/18 (6%) patients with ADA-SCID who may be considered unsuitable to progress to treatment following a bone marrow biopsy (company response to clarification A6). In response to clarification the company provided further information on the use of 'back up' bone marrow transplantation. The company note that, '*In the integrated population, 1 subject (6%) received back up bone marrow cells because the subject was unable to receive the scheduled infusion of Strimvelis at the first attempt due to contamination, and 3 subjects (17%) received stored back up of unmanipulated bone marrow cells due to events after Strimvelis.* [redacted] *There is no further information on the use of back up bone marrow in the available NPP data (company response to*

clarification A7).' The observed use of 'back up' bone marrow transplant is therefore 4/18 (22%) in the Strimvelis Integrated Population, which [redacted] if the Named Patient Programme is included. The company submission does not contain any evidence to determine whether the rate of 'back up' bone marrow transplant differs between Strimvelis and HSCT.

5.2.7 Health related quality of life

The LTFU study AD1115611 collected general HRQL evidence from participants using both the Lansky performance status index (collected for all LTFU patients) and the Paediatric Quality of Life Inventory (PedsQL) (not collected for subjects younger than 5 years old). The company submission also contained three search strategies used to identify: 1) HRQL studies concerning ADA-SCID; 2) health-related utility values after HSCT, and; 3) health-related utility values in GvHD. The search strategies were briefly described in the main body of the submission in Section 10.1.5. Full details were provided in Appendix 3, Section 17.3 and Appendix 5, Sections 17.5.1 and 17.5.2.

1) Health-related quality of life studies concerning ADA-SCID

The results of the search for economic evidence were used to identify HRQL studies. The electronic database EMBASE was searched on 28th February 2017 via the Elsevier host. The search combined terms for ADA-SCID with terms for cost-effectiveness. This search did not contain any terms for quality of life or measurement tools for quality of life so may not have identified all relevant studies on HRQL in ADA-SCID. Reliable search filters to restrict retrieval to utility values are available and the ERG considers that a search using terms for ADA-SCID combined with a utility values search filter would have been a more appropriate.

In addition to this search, the company note on page 123 of the submission that they also searched the results from the clinical data literature search in an attempt to identify HRQL data. However this clinical data search was restricted to studies in patients with ADA-SCID treated with gene therapy, stem cell transplants or bone marrow transplants.

2) Health-related quality of life values after HSCT

The electronic database EMBASE was searched on 10th March 2017 via the Elsevier host. The search combined terms for quality of life with terms for HSCT. Retrieval was restricted to studies from 2007 onwards. The search contained both textword searches and subject heading searches of the main terms

relating to quality of life. However more reliable search filters to identify utility values are available and it would have been more appropriate to utilise a tried and tested filter within the strategy. In addition a lack of truncation within the strategy presented may have restricted retrieval of relevant studies.

3) Health-related quality of life values in GvHD

The electronic database EMBASE was searched on 6th March 2017 via the Elsevier host. The search combined terms for quality of life with terms for GvHD. Retrieval was restricted to studies from 2007 onwards. The search contained both textword searches and subject heading searches of the main terms relating to quality of life. However more reliable search filters to identify utility values are available and it would have been more appropriate to utilise a tried and tested filter within the strategy. The subject heading Graft versus host reaction/ is missing from the strategy. In addition a lack of truncation within the strategy presented may have restricted retrieval of relevant studies.

The systematic searches identified no relevant utility related articles for the ADA-SCID patient population. Instead, the company identified one article directly reporting preference-based utilities in GvHD for patients with relapsing/refractory Hodgkin lymphoma (R/R HL) and R/R systemic anaplastic large-cell lymphoma (Swinburn, 2015) and two HSCT articles deemed to have potential utility information assessing patients with chronic lymphocytic leukaemia (Kharan-Dabaja, 2012) and chronic myelogenous leukaemia patients (Rochau, 2015). Results reported in the clinical and economic systematic literature reviews did not contain any relevant HRQL data. Each systematic literature review reported only one final relevant study. This was partly due to the exclusion criteria only permitting articles reporting preference-based utilities directly. The subsequent health-related quality of life review was conducted with three reports, none of which were those deemed relevant in the systematic literature reviews for preference based utilities.

In the absence of relevant preference-specific utilities for ADA-SCID patients in the Strimvelis Integrated Population, the utility values applied in the model were derived from a combination of alternative patient populations and studies sourced in the systematic literature review and expert clinical opinion. Table 11 provides a summary of the utility values used within the model, including the source and justification.

Table 11: Utilities applied in the cost-effectiveness model

	Value	Reference in submission	Justification
Health utility in the period before HSCT or Strimvelis	0.98		Assumed equal to the general population utility at age 1. We do not consider the potential disutility patients incur whilst waiting for Strimvelis or HSCT (e.g. due to being in isolation and receiving PEG-ADA). Given that patients receiving Strimvelis are likely to wait less than patients receiving HSCT, this is a conservative assumption.
Utility decrement during the first 6 months after Strimvelis, HSCT from a MUD or haploidentical donor, or rescue transplant	0.57	Sung, 2003	In the absence of information on utilities after treatment for ADA-SCID, utility values after BMT in leukaemia were considered the best available information
Utility values for surviving patients with ADA-SCID	Age-specific utility	Jones-Hughes, 2016 Ara, 2010	No specific values on utilities of patients with ADA-SCID were identified. Age-specific normal values were used, and the possibility of lowering utilities was explored in the sensitivity analysis
One-off QALY loss due to a utility decrement from acute GvHD	0.41	Swinburn, 2015	The utility value for patients with acute GvHD and complete remission from relapsed/refractory Hodgkin lymphoma or systemic anaplastic large cell lymphoma was used to calculate a utility decrement and then adjusted based on the expected average duration of an episode of acute GvHD (8 months) based on expert clinical advice.
One-off QALY loss due to a utility decrement from chronic GvHD	1.44	Swinburn, 2015	Utility value for patients with chronic GvHD and complete remission from relapsed/refractory Hodgkin lymphoma or systemic anaplastic large cell lymphoma was used to calculate a utility decrement and then adjusted based on the expected duration of an episode of chronic GvHD (3 years) based on expert clinical advice.

CS, Table C29 – p127-128

The HRQL of patients in the model is comprised of three separate stages:

- pre-treatment;
- 0-6 months after transplant; and
- 6 months post-procedure for the remaining life time horizon.

The health utility applied in the period before HSCT or Strimvelis did not consider decrements in patients' utility. The health related quality of life estimate applied in the first 6 months post-procedure was based on a study by Sung (2003) which surveyed 12 physicians with experience of bone marrow transplant using visual analogue scale to determine a HRQL 'disutility' of 0.57 for transplant in patients with acute myeloid leukaemia. The utility values applied from 6 months after transplant for the remainder of the time horizon were age-specific normal population values taken from the Jones-Hughes analysis of the Health Survey for England (2012). Patients with failed engraftment are assigned two 6 month periods with a utility of 0.57. The first period coincides with the 6 months following the initial failed procedure and the second occurs after rescue therapy. The remaining time between initial and rescue procedure follows the age-specific normal population values.

Utility values are not differentiated by treatment in the model with the exception of GvHD events, which apply to HSCT procedures only. GvHD of grade III or IV is associated with a one-off QALY decrement applied as a lump-sum. The average QALY losses for acute and chronic GvHD were calculated as the product of their assumed duration and associated disutility. The expected duration of a GvHD event was informed by expert clinical advice whilst the utility value was taken from an international valuation survey that used time trade off to determine public preferences for health states relating to relapsing/refractory Hodgkin lymphoma.[46] Acute GvHD was assumed to last for eight months, and during those eight months patients were assumed to have a utility score of 0.39. Chronic GvHD was assumed to last for three years, during which patients experience a utility of 0.52.

The model assumes no disutility in relation to severe infections, IVIG administration or central venous catheter placement. The company had identified a cost-effectiveness study that estimated a mean health utility of 0.66 associated with use of IVIG in patients with chronic lymphocytic leukaemia. However this was not incorporated due to the age of the study and the fact that health utility value was based on a small sample of physicians (company submission p130).[47] The company did provide a one-way sensitivity analysis in which a disutility weight of 0.75 was applied to patients receiving IVIG. Adverse events related to conditioning regimens were not included in the cost-

effectiveness analysis. The economic evaluation incorporated the HRQL of parents as an additional scenario, and conducted a range of further one-way sensitivity analyses for HRQL values.

The ERG considers that prior to transplantation the HRQL of patients awaiting treatment may be lower than that of the general population. Establishing HRQL values for very young patients is challenging, and the rarity of ADA-SCID compounds this. As the period before transplantation constitutes a very small proportion of the modelled time horizon, the ERG expects that the results are unlikely to be sensitive to the simplifying assumption that health related quality of life in this initial period is equal to that of the general population.

The ERG noted that the assumed duration of three years for chronic GvHD means that the impact extends beyond the assumed timing of the rescue transplant. In response to clarification the company confirmed that rescue transplant would not normally be provided to patients with ongoing chronic GvHD (company response to clarification B22). The company provided an additional sensitivity analysis to show the impact on the ICER of either delaying rescue transplant to year 4 or year 5, or reducing the duration of chronic GvHD to two years. The company also note in their response that as Strimvelis carries no risk of GvHD that the timing of rescue transplant could potentially be earlier following failed engraftment with gene therapy compared to failed engraftment of HSCT.

The ERG consider that the company's justification for omitting the health related quality of life impact of IVIG is inconsistent with their acceptance of physician survey as a source of the health-related quality of life value for HSCT. Both values were obtained using a similar methodology and sample, and the ERG therefore considers that a health related quality of life value for IVIG use could have been incorporated in the base case analysis. The ERG note that where the company submission applies absolute health utility values taken from source studies in different disease areas it would have been preferable to calculate the decrement from the reference population in the respective studies. This would suggest utility weights of 0.43 (0.39/0.91) for acute GvHD, 0.57 (0.52/0.91) for chronic GvHD[46] and 0.76 (0.66/0.87) for IVIG.[47]

The ERG considers that the searches to identify utility values may not have picked up the full range of potentially relevant studies. A pragmatic search by the ERG identified two recent reviews of health related quality of life in children who undergo HSCT.[13, 14] One study from these reviews directly assessed the impact of severe chronic GvHD using a generic multidimensional self-reported instrument, the SCHQ-CF87, in a cohort of 52 children at least three years beyond HSCT.[48] In this

study seven patients continued to experience GvHD related symptoms three to nine years following transplant.

The ERG identified one longitudinal study of quality of life in paediatric recipients of allogenic stem cell or bone marrow transplant that applied the HUI Mark 2/3 to estimate health related quality of life at 35 and 7 days prior to, and 10, 28, 100, 180 and 360 days after bone marrow transplantation.[49, 50] This study provides a preference based measure of health-related quality of life derived from children aged three years and older. The study did not report the mean HUI global utility score for each time point, although it is noted that 10 days after transplant is the nadir for observed quality of life. The reported difference in HUI global utility score from 35 days prior to bone marrow transplant to 360 days after bone marrow transplant was -0.13 (standard error 0.16; $p \leq 0.01$) as rated by children aged at least 10 (n=21), and -0.08 (not significant) as rated by parents (n=26) or physicians (n=27).

While these reviews did not identify alternative values that could directly replace those applied in the company model, they do offer support for the company assumption that quality of life decrement from receipt of HSCT lasts for about 6 months.[14] However, evidence cited in the company submission contradicts the assumption that quality of life for patients with ADA-SCID returns to population norms thereafter[15, 37]. Patients with ADA-SCID have been reported to have a high incidence of bilateral sensorineural deafness (58%).[43] A pragmatic search by the ERG identified a study that used the HUI Mark 3 to estimate a mean health-related quality of life decrement for bilateral permanent hearing impairment of -0.294 ($p<0.01$) compared to children with normal hearing. Children with SCID exhibit worse emotional and behavioural outcomes compared to population norms as measured by the strengths and difficulties questionnaire (SDQ), and ADA-SCID is predictive of a worse SDQ score compared to other SCIDs.[37] The SDQ score has been linked directly to a preference based measure of health-related quality of life [51].

5.2.8 Resources and costs

The company submission provided details of the resource use and costs associated with each relevant strategy of care. The company highlight the three elements of cost associated with sending a patient to Milan for gene therapy:

1. The cost of Strimvelis itself;
2. Related hospital procedures, including screening, baseline tests, bone marrow sample, chemotherapy, infusion of Strimvelis, recovery in isolation room and outpatient follow-up; and

3. Patient support, such as accommodation, food, and transport services as well as travel to/from Milan.

The costs and resource use for HSCT include: (1) the cost of searching for and obtaining stem cells; (2) related hospital procedures; and (3) costs related to GvHD. Additional elements of resource use common across all strategies of care include drug acquisition and administration costs for PEG-ADA and IVIG, follow-up costs for patients who have successful engraftment, and costs related to severe infection.

To identify cost and resource use data to inform the assessment of cost-effectiveness, the company performed a pragmatic review of the literature for ADA-SCID patients. The CS did not contain any searches for resource data on ADA-SCID. The company stated that this was due to a scarcity of published data on ADA-SCID. However, it would have been useful if the search strategies to demonstrate that published data was not available were included in the company submission. The costs reported in the CS are denoted in pound sterling by applying an exchange rate of €1= £0.85).

5.2.8.1 Treatment and administration costs

The price of the Strimvelis technology, which constitutes the transduced stem cells for transplant, is set in euros (€594,000) and is to be paid to the Ospedale San Raffaele (OSR) Hospital, Milan. The company are reported to be in discussion with NHS England to determine a fixed price in local currency for Strimvelis, and funding arrangements are anticipated to align with the EU directive route which is currently paying for proton beam therapy outside of the UK.

Administration costs for Strimvelis, i.e. the transplant procedure and related hospitalisation, were based on a length of stay schedule informed by the expected administration periods for baseline patient preparation (31 days), treatment (50 days) and outpatient follow-up (60 days). This schedule was revealed during the clarification stage to be defined by the San Raffaele Telethon Institute for Gene Therapy (SR-TIGET) and OSR (company response to clarification B5). The administration costs of Strimvelis are shown in Table 12. The company assume that the [redacted] per patient screening cost, which comprises an outpatient visit for informed consent and clinical tests along with a hospital diagnostic bone marrow aspirate to determine ability to produce sufficient CD34+ cells, would be incurred in England prior to travel to Italy. The initial hospitalisation cost of [redacted] (baseline + treatment + follow-up, month 1 and 2 from discharge) requires a fixed payment to OSR for those patients who go on to receive Strimvelis.

Table 12: Schedule of Payments by Ospendale San Raffael

ADA SCID – Patient's Procedural Phases and Reimbursement	
SCREENING	[redacted]
BASELINE	[redacted]
TREATMENT	[redacted]
FOLLOW-UP, month 1 and 2 from discharge	[redacted]
Total	[redacted]

Response to ERG clarifications, Table 8 p36

The ERG requested clarification as to whether the technology cost (€594,000) and cost of initial hospitalisation ([redacted]) would apply to all patients, or whether different charges may apply in a range circumstances applicable to the patient population under consideration. Table 13 presents the response from the company.

Table 13: Costs of patients with unplanned complications

Circumstance	Company Response/Costs
Extended hospitalisation resulting from severe infection.	Estimated technology cost of €594,000 (£505,000) and the initial hospitalisation cost of [redacted] would apply in this case. Additional days in the hospital beyond the assumed clinical schedule (i.e., > 55/days standard stay) would be charged at [redacted] per day for Italian statutory patients. If the patient does not come with an approved S2 form, then they would be charged for each procedure conducted during that period.
Patients for whom the product contains less than 2 million CD34+ cells/kg Cases of product failure e.g. contamination	If Strimvelis was not administered the Strimvelis product cost of €594,000 (£505,000) and the initial hospitalisation cost of [redacted] would not apply. The patient may receive its own back-up as rescue therapy as he/she has already received chemotherapy. In this scenario, i) If the patient is supported through an S2 Form (i.e. the patient would be treated as an Italian statutory patient), the administration of the back-up will fall under the autologous transplantation and the tariff/DRG for the autologous transplantation will be charged to the NHS (i.e., [redacted]; DRG 481, Oct 2016). ii) If the patient does not come with an approved S2 form, the administration of the back-up would fall under the autologous transplantation, but in this case, any clinical service paid in advance and not provided will be reimbursed after the patient is discharged.
Cases of transplant failure, or prolonged bone marrow aplasia after treatment with Strimvelis which require the use of the rescue product	Estimated technology cost of €594,000 (£505,000) and the initial hospitalisation cost of [redacted] would apply in this case. In the case of treatment failure, if the back-up bone marrow is used to facilitate hematopoietic recovery, then this cost is covered by the initial hospitalisation cost up to 55/days standard stay. Additional days in the hospital beyond the assumed clinical schedule (i.e., > 55/days standard stay) would be charged at [redacted] per day for Italian statutory patients. If

	the patient does not come with an approved S2 form, then they would be charged for each procedure conducted during that period.

A cost of public transport and support necessary for a patient and their parent(s)/carer(s) to relocate to Milan was estimated by the company in their original submission but not applied in the model (company submission Section 12.3.9). In clarification, the company acknowledge that the NHS may support travel arrangements (company response to clarification B9). Clinical advice to the ERG indicated that some patients require transfers by ambulance depending on their clinical condition. At clarification the ERG requested the method of transport by which patients arrived for treatment with Strimvelis and the estimated cost of ambulance transfers within the UK and Italy, and by air between UK and Italy. It was reported that 1 patient required ambulance transportation, and none air ambulance (company response to clarification B10). The company provided updated travel costs and additional scenario analyses in response to the ERG's request. The updated travel costs consisted of: air travel at £200 per round trip per person, assuming each patient travels with two additional persons; ambulance transfer from and to the airport within the UK at £472 per patient (based on NHS reference cost code ASS02); and ambulance transfer from and to airport within Italy at £340 per patient (based on communication with OSR). This provided a total travel cost of £1,412 per patient treated with Strimvelis if it is assumed that all patients are funded for within country travel to and from the airport using ambulance (and do not use self-funded public transport). The company estimated that the cost of air ambulance with respiratory assistance would be in the range €11,000 to €17,500 (£9,350 to £14,875 @0.85£/1€) per one way trip. However, they comment that the likelihood of air ambulance being needed is small if it is assumed that patients are always stabilised before they travel (company response to clarification B10).

The cost of obtaining stem cells for HSCT was included in a £45,127 cost of screening for a MUD. The source of this cost was omitted from the original company submission and provided in a separate response to clarification which cited van Agthoven (2002), who reported the screening cost for a MUD transplant of €47,063 (company response to clarification B2).[52] The estimate was based on costs observed in the Netherlands in 1999, which the company inflated to a 2016 value using a health inflation adjustment of 12.8% reported by Statistics Netherland and converted to British pounds using an exchange rate of €1= £0.85. The company consider these costs "*reasonably transferable to the English reality*". A summary of the costs related to screening for a donor are presented in Table 14.

Table 14: Cost components for donor screening from Van Agthoven

Cost Component	Cost (€)
Family HLA typing	6,842
Requesting blood samples	5,506
Sample typing	12,232
Requesting donor graft	15,971
Europdonor intermediation	1,920
CD34 selection/T cell depletion	4,592
Total costs (excluding personnel costs)	47,063

Response to ERG clarifications, Table 3 p20

The 'Family HLA typing' component assumes four non-sibling family members are typed for every patient, and for 15% of patients on average an additional six cousins are typed. The total cost estimated for family HLA typing includes the costs of typing undertaken for the 55% of MUD patients assumed not to undergo transplantation. The 'Requesting blood samples' component includes an average of four fulfilled blood samples requests on potential donors with a weighted average cost of €620 per sample. The 'Sample typing' component includes HLA retyping for the four blood samples, and includes the costs of retyping for patients who do not undergo transplantation. The 'Requesting donor graft' comprises a weighted average cost of stem cells, which are reported to be generally sourced from bone marrow.[52]

The administration of stem cells for HSCT was based on NHS reference costs. The unit cost applied for a HSCT from a MUD was £95,516, which is the national average unit cost for 'Bone Marrow Transplant, Allogeneic Graft (Cord Blood), 18 years and under' Currency Code SA22B. The corresponding cost used for HSCT from a haploidentical donor is £108,760, which is the national average unit cost for 'Bone Marrow Transplant, Allogeneic Graft (Haplo-Identical), 18 years and under' Currency Code SA23B.[53]

The ERG identified two potentially relevant uncertainties regarding the reported costs for Strimvelis. The first is the funding arrangement for Strimvelis, as VAT may be payable dependent on whether a patient arrives in Milan via the S2 or EU directive route. The NICE methods guide (2013) states that value added tax (VAT) should be excluded from all economic evaluations as the NHS does not pay VAT for drugs purchased locally.[41] Whether a fixed price in euros agreed between the company and NHS England will include any taxes remains unknown to the ERG. The second uncertainty is the exchange rate at the time of purchase. The ERG has concerns that this uncertainty is not addressed in the CS but deserves consideration. The ERG has conducted further analyses to explore the impacts of these uncertainties in Section 6.

The ERG is concerned that by applying only the standard hospitalisation charge to all patients in the Strimvelis arm the company model significantly underestimates the potential costs to the NHS of treatment with Strimvelis. For patients that remain in hospital in Milan for longer than the standard stay of 55 days additional hospital costs would be incurred at a rate of [redacted] per day, and the cost of any additional procedures. The median and mean length of hospitalisation in the Strimvelis Integrated Population was 45 days and 53 days. One patient stayed hospitalised for a maximum of 110 days, which would increase the hospitalisation charge by [redacted] (company submission p234). If it is conservatively assumed that only 6% (1/18) patients have hospital stay exceeding 55 days and that they receive no further procedures during this time, the hospitalisation charge is underestimated by a minimum of [redacted] per patient treated with Strimvelis. Where back-up marrow is administered outside of the 55 day standard hospitalisation the charge would be [redacted]. These costs are not accounted for in the company model. In response to clarification the company state that 1 subject received back up marrow cells due to product contamination and 3 subjects (17%) received stored back up due to events after Strimvelis from the Strimvelis Integrated Population, [redacted] (company response to clarifications A7). Assuming that 3/18 subjects from the Strimvelis Integrated Population (17%) receive back up outside the 55 day window would produce an additional cost of [redacted] per patient treated with Strimvelis, while assuming that all [redacted] subjects who received back up bone marrow did so outside of the 55 day window would produce an additional cost of [redacted] per patient treated with Strimvelis. The company submission does not contain any evidence to determine whether excess hospitalisation costs and back up bone marrow transplantation may similarly occur for patients undergoing HSCT.

The ERG considers that had the patient who required ambulance transport for treatment with Strimvelis been travelling from the UK, an air ambulance may have been required, and so travel costs may have been underestimated. Including air ambulance travel could increase average travel costs for Strimvelis by approximately 1/18*£12,113=£673 using the mid-range of the company air ambulance costs and assuming a one way trip. However, the ERG note that the additional scenario analysis provided by the company incorporated travel costs assumes within country ambulance transfer for all patients, which the company consider to overestimate the rate of ambulance transfer. The ERG considers that the underestimation of air ambulance use may be balanced by the overestimation of

ambulance transfer within country, and that this scenario analysis may be reasonably representative of the expected travel costs to be reimbursed by the NHS.

To determine whether the per patient cost of screening for Strimvelis is applicable to UK practice the ERG identified that the cost of a diagnostic bone marrow extraction based on NHS reference costs is £493.90 (ref Total HRG's code SA33Z).[53] Depending on the nature of the outpatient visit and additional tests required for determining eligibility for Strimvelis, the [redacted] based on estimates from OSR may be reasonably representative of costs to the NHS. To address concerns as to whether costs taken from van Agthoven were representative to current UK practice the ERG requested further information from the Anthony Nolan register, who provided an average price of £18,300 for stem cells from bone marrow or PBSC, £28,200 for stem cells from cord blood, and £650 per blood sample for confirmatory typing (Louise Nazir, personal communication). These prices appear broadly comparable with the corresponding unit costs from van Agthoven.

The NHS main schedule of reference costs includes two estimates for the cost of bone marrow transplant, allogeneic graft, that differ based on whether the stem cells are from cord blood (£95,517 code SA22B as applied in company base case) or from volunteer unrelated donor (£79,199 code SA21B).[53] The company submission does not contain any information regarding the proportion of transplants that are from cord blood compared to adult bone marrow. In Hassan 2012 the majority of stem cells were sourced from bone marrow (88/106, 83%) and the same is noted in van Agthoven 2002.[3, 52] Therefore the ERG considers that the cost of HSCT from a MUD may be overestimated in the company model.

5.2.8.2 Drug acquisition costs

The company's original model assumed administration costs of PEG-ADA and IVIG in line with NHS reference costs for "Consultant Led. Paediatric Clinical Immunology and Allergy Service", £306. In response to clarification the company provided an alternative estimate of administration costs of £54 for PEG-ADA based on 30 minutes of Grade 6 hospital nurse time, and £216 for IVIG based on two hours of nurse time (company response to clarification B6).

After consultation with a clinical expert, the company base case assumed a cost of £9,000 per vial of PEG-ADA, and that on average patients would require 1.5 vials per week, giving a cost per dose of PEG-ADA of £13,500. In response to a request from the ERG, the company provided an alternative estimate for the weekly cost of PEG-ADA as a function of body weight, assuming the average patient was on the 25th percentile for weight. Table 15 displays the weekly cost of PEG-ADA based on

weight using an estimated dosage consistent with the maximum dose recommended by the manufacturer of PEG-ADA (30 units per kg).

Table 15: Weekly cost of PEG-ADA based on weight

Age	Weight * (25th percentile)	Units per patient per week **	Vials per patient per week ***	Vials rounded	Weekly cost of PEG-ADA
1 year	8.6 kg	258	0.69	1.0	£9,000
2 years	10.9 kg	326	0.87	1.0	£9,000
3 years	13.0 kg	389	1.04	1.0	£9,000

Response to ERG clarifications, Table 8 p36

The duration of PEG-ADA in the model is dependent on the initial treatment procedure (i.e. Strimvelis or HSCT from a MUD or haploidentical donor) and the rates of rescue therapies required post-procedure (see Section 5.2.1). The model assumes patients undergoing Strimvelis require only 9 weeks of PEG-ADA to bridge to treatment and that 17.6% of Strimvelis patients will require 21 months of PEG-ADA to bridge to rescue therapy after failed engraftment. HSCT procedures are assumed to require 19 weeks of PEG-ADA prior to initial procedure and that 6.7% and 28.6% of MUD and haploidentical patients respectively require 21 months of PEG-ADA to bridge to rescue therapy after failed engraftment.

The annual costs of IVIG were estimated based on the cost per gram of IVIG sourced from a medical data base (medicines complete). IVIG dosing was calculated using the 25th percentile of weight by age in the United Kingdom with an exponential curve fitted to the data. The duration of IVIG in the model was calculated based on rates observed in the Strimvelis integrated population. At the time of data cut (08-May-2014) information regarding IVIG use existed at 0, 3 and 8 years since receipt of Strimvelis. It was assumed the rates of IVIG usage diminished at a constant rate between observations, and that no patients would continue use beyond 8 years. This was justified by the assumption that the patient administered with IVIG for at least 8 years in the Strimvelis integrated population would have received a rescue transplant in the UK. The rates of IVIG drug use were assumed to be equal between patients treated with Strimvelis and those treated with HSCT. This assumption is consistent with expert clinical advice received by the ERG. Table 16 displays the rates of IVIG usage applied to each comparator in the model.

Table 16: Proportion of patients on IVIG by year in company model

Year 1	100.0%
Year 2	79.4%
Year 3	58.8%
Year 4	47.0%
Year 5	35.3%
Year 6	23.5%
Year 7	11.8%
Year 8	0%
Year 9	0%
Year 10	0%

Company model, "*parameters*"

The ERG note that the weight based costs applied in the company model would be higher for patients who are older, such as those included in the NPP.

5.2.8.3 Follow up costs

The company assume equivalence in long-term follow-up requirements for Strimvelis, MUD and haploidentical HSCTs (including use as rescue therapies), with the exception of vector copy number (VCN) testing which is required only for gene therapy. However, the company base the follow up costs for Strimvelis directly on the figures provided in the UK Stem Cell Oversight committee report, and calculate follow up costs for HSCT directly from van Agthoven 2002.[4, 52] In response to clarification the company explained that the estimates from the UK Stem Cell Oversight report (which themselves are extrapolated from van Agthoven) were considered to include other types of transplant, but van Agthoven refers specifically to transplants from a MUD (company response to clarification B13, p34). The average post-transplant care costs in the UK Stem Cell Oversight report are reported as: [redacted] (0-6 months); [redacted] (6-12 months) and [redacted] (12 to 24 months). The company model appears to incorporate a minor typographical error in which the first 6 month period is costed at [redacted] rather than [redacted]. The company assume that the first two months of follow up for Strimvelis is provided in Italy and are incorporated in the [redacted] initial hospitalisation cost for Strimvelis, and so adjust the first six month cost from [redacted] to [redacted], reducing the total follow-up cost to from [redacted] to [redacted] per living patient after Strimvelis.

In contrast, the total follow up cost per living patient after HSCT is assumed to be £59,541 using van Agthoven directly. Gene therapy follow-up included an additional 6 VCN tests (two per year for three years). Each test was costed at £1,199 which amounted to a total cost of £7,194. The company

model appears to include a minor typographical error in which the cost per VCN test applied is £1,207 rather than £1,199. No reference is given in the submission or response to clarifications regarding the source of the unit cost or recommended VCN test schedule.

Table 17 provides a summary of the average costs associated with Strimvelis and HSCT in the company's economic model.

Table 17: Company base case cost per treatment per patient.

Items	Strimvelis	HSCT from a MUD	HSCT from a haploidentical donor
Confirmation of Eligibility for Strimvelis Treatment	[redacted]	-	-
Cost of Strimvelis	£505,000	-	-
Cost of screening, including stem cells	-	£45,127	£45,127
Initial PEG-ADA before procedure and screening	£124,254 (10 weeks)	£262,314 (19 weeks)	£262,314 (19 weeks)
Hospitalisation for transplantation	[redacted]	£95,516	£108,760
Follow-up costs	[redacted] per living patient*	£59,541 per living patient	£59,541 per living patient
Total cost per treatment/patient	[redacted]	**£462,498**	**£475,742**

*Assumes first 2 months' follow up incorporated in cost of hospitalisation for transplantation and includes VCN testing

In response to clarifications the company provided updated costs that determined dose of PEG-ADA based on patient weight, an updated administration cost for PEG-ADA and for IVIG, and updated travel costs for patients travelling to Milan for treatment. The rationale for the changes to unit costs is summarised in the company response to clarifications Table 12, p60. The updated costs for PEG-ADA reduce the 'Initial PEG-ADA before procedure and screening' from £124,254 to £81,486 for Strimvelis, and from £262,314 to £172,026 for HSCT. With the addition of travel costs for Strimvelis, this gives an alternative lower total cost per treatment per patient of [redacted] (including VCN testing) for Strimvelis, £417,371 for HSCT from a MUD and £430,615 for HSCT from a haploidentical donor (company response to clarification Tables 15, 16 and 17).

5.2.8.4 Adverse event costs

Adverse events deemed relevant to the economic evaluation were severe infections after any transplant procedure and GvHD after HSCT from a MUD or a haploidentical donor. The incidence of severe infections was drawn from the Strimvelis Integrated Population. It was assumed that the rates of severe infection observed after receipt of Strimvelis were also applicable to patients who received HSCT from a MUD or haploidentical donor. The rates of severe infections were 26% between years 1 and 3 and 7% between years 4 and 8 post-procedure. The company based the cost per severe infection on a US study that estimated that infection increased allogeneic transplantation costs by $15,300, and that the median inpatient cost was $105,300.[54] The company assume that severe infection costs can be estimated as 15% of hospitalisation costs and apply a cost per severe infection of £12,143.

The same unit cost was applied to all GvHD events, with the rates determined in a literature review (company submission, Table C28). For HSCT from a MUD the rate of GvHD of any grade was 32.1% (9/28) while for HSCT from a haploidentical donor the rate was 33.3% (3/9). The unit cost was based on a single UK study which reported hospital readmission costs associated with GvHD.[55] The company took the mean cost of readmission for patients without GvHD (£13,405) and the cost of readmission with severe (Grade III/IV) GvHD (£40,012) and inflated the difference from £26,607 to £29,420 to represent 2016 prices. The cost for GvHD events was applied across all patients in year 1 of the model. The company assumes no risk of severe infection of GvHD after rescue transplant.

Table 18 presents the average undiscounted costs of managing each of the adverse events deemed relevant to the decision problem.

Table 18: Summary of total adverse event costs

Treatment	Average cost of severe infection	Average cost of GvHD	Total
Strimvelis	£13,719	£0	£13,719
MUD	£9,146	£7,880	£17,026
Haploidentical	£9,799	£8,406	£18,205

The ERG consider it inappropriate to apply a cost of severe (Grade III/IV) GvHD to GvHD events of all grades as this will overestimate the adverse event costs associated with HSCT. The study by Dignan 2013 provides a mean readmission cost separately for Grade I/II and Grade III/IV GvHD

events, and also reports an estimate for any GvHD event, which gives a lower cost per GvHD event of £15,455 (£28,860 - £13,405), which would be £17,089 inflated to 2016 prices.

The company note that retroviral insertion site testing is expected to cost €7,299 per test (£6,204 @ 1€ = £0.85), and replication competent retrovirus testing would be expected to cost €1,420 per test (£1,207 @ 1€ = £0.85). However, these costs are not included in the company base case as they would only be incurred in the event of a leukemic adverse event, which has not yet been observed in the Strimvelis clinical programme (company response to clarification B11, p32).

The ERG is concerned that the model underestimates the ongoing healthcare costs of patients with successful engraftment. The ongoing systemic sequelae of ADA-SCID and any long-term adverse events from conditioning regimens may imply higher healthcare costs compared to the general population. A pragmatic search by the ERG found a UK study that estimated the increase in mean annual NHS (£83) and PSS (£1368.20) healthcare costs of £1,451 associated with bilateral permanent childhood hearing impairment.[56]

5.2.9 Cost effectiveness results

5.2.9.1 Base case results

The company base case cost-effectiveness results are presented in Table 19. The base case results used a discount rate of 1.5% for costs and QALYs and a life time horizon (CS, Section 5.2.5). The company found Strimvelis to be more costly (cost difference of £494,255 and £170,668) but also more effective (gains of 13.6 and 11.7 QALYs) compared with HSCT from a MUD and haploidentical donor respectively. The estimated deterministic ICER for Strimvelis is £36,360 per QALY gained compared to HSCT from a MUD, and £14,645 per QALY gained compared to HSCT from a haploidentical donor.

Table 19: Company base case results

Technologies	Costs (£)	LYs gained	QALYs gained	Incremental			
				Costs (£)	LYs gained	QALYs gained	ICER (£/QALY)
Strimvelis	£1,059,425	46.1	41.4				
MUD	£565,170	31.0	27.8	£494,255	15.1	13.6	£36,360
Haplo	£888,757	33.2	29.7	£170,668	12.9	11.7	£14,645

CS, Table D14 – p185

Table 20 provides the disaggregation of accrued QALYs and life years, which shows that the majority of QALYs are accrued within the *Post-procedure, successful engraftment* state. The *Rescue transplant and post-transplant* state was the secondary source of QALYs accrued in the model.

Table 20: Summary of discounted QALY gain by health state

Strimvelis		
Outcome	LY	QALY
Pre-procedure (PEG-ADA)	0.2	0.2
Post-procedure, successful engraftment	37.8	34.0
Failure to engraft, PEG-ADA	0.3	0.3
Rescue transplant and post-transplant	7.8	6.9
Total	46.1	41.4
HSCT from a MUD		
Outcome	LY	QALY
Pre-procedure (PEG-ADA)	0.4	0.4
Post-procedure, successful engraftment	27.6	24.7
Failure to engraft, PEG-ADA	0.1	0.1
Rescue transplant and post-transplant	2.9	2.6
Total	31.0	27.8
HSCT from a haploidentical donor		
Outcome	LY	QALY
Pre-procedure (PEG-ADA)	0.4	0.4
Post-procedure, successful engraftment	19.7	17.7
Failure to engraft, PEG-ADA	0.6	0.4
Rescue transplant and post-transplant	12.6	11.2
Total	33.2	29.7

CS, Table D17 – p190

The HST interim methods process guide indicates that the magnitude of therapeutic improvement, as revealed by the QALY gain, determines the acceptability of a technology as an effective use of NHS resources. The methods guide indicates that an increased weight can be applied to QALYs gained where there is compelling evidence that the improvement in health exceeds 10 QALYs. The ERG and company were informed by NICE that the magnitude of the QALY gain should be based on undiscounted QALYs. In response to clarification the company report that the undiscounted QALY gain for Strimvelis compared to HSCT from a MUD is 23.2 QALYs, which would imply a weight of

2.3, or alternatively an increase in the cost-effectiveness threshold from £100,000 to £230,000 per QALY gained (company response to clarifications B19, p43). The undiscounted QALY gain for Strimvelis compared to HSCT from a haploidentical donor is 19.9, which would imply a weight of 2 to be applied to QALY gains or an increase in the cost-effectiveness threshold from £100,000 to £200,000 per QALY gained (Company submission Section 12.5.7, Table D 21).

The costs by category and their contribution to the total cost for each comparator are shown in Table 21. The cost of Strimvelis is the major cost component of total Strimvelis costs, followed by rescue PEG-ADA costs. In contrast PEG-ADA pre-procedure is the major component of total cost for HSCT from a MUD, followed by hospitalisation costs. For HSCT from a haploidentical donor the major component of total cost is rescue PEG-ADA costs followed by PEG-ADA pre-procedure costs (Company submission Section 12.5.16).

Table 21: Total costs by cost category

Cost category	Costs for Strimvelis therapy (% of total)	HSCT from a MUD (% of total)	HSCT from a haploidentical donor (% of total)
Screening pre-procedure	£0 (0.0%)	£45,127 (8.0%)	£45,127 (5.1%)
Confirmation of eligibility for Strimvelis treatment	[redacted]	£0 (0.0%)	£0 (0.0%)
PEG-ADA pre-procedure	£124,254 (11.7%)	£262,314 (46.4%)	£232,314 (29.5%)
Product	£505,000 (47.7%)	£0 (0.0%)	£0 (0.0%)
Severe infection cost	£13,103 (1.2%)	£8,735 (1.5%)	£9,359 (1.1%)
Rescue transplant cost	£16,119 (1.5%)	£6,090 (1.1%)	£26,098 (2.9%)
Rescue PEG-ADA cost	£217,055 (20.5%)	£81,999 (14.5%)	£351,423 (39.5%)
Hospitalisation cost	[redacted]	£95,516 (16.9%)	£108,760 (12.2%)
Follow-up cost (includes VCN in Strimvelis)	[redacted]	£43,027 (7.6%)	£58,259 (6.6%)
GvHD	£0 (0.0%)	£7,834 (1.4%)	£8,354 (0.9%)
IVIG cost	£23,041 (2.2%)	£14,529 (2.6%)	£19,063 (2.1%)
Total	**£1,059,425 (100%)**	**£565,170 (100%)**	**£888,757 (100%)**

Abbreviations: HSCT= HSCT=haematopoietic stem cell transplantation; GvHD=graft-versus-host disease; IVIG=intravenous immunoglobulin; MUD=matched unrelated donor; PEG-ADA=polyethylene glycol-modified bovine adenosine deaminase.

The company report that the product cost for Strimvelis is responsible for most of the increased cost compared to HSCT from a MUD, and is only somewhat offset by lower pre-procedure PEG-ADA and avoidance of MUD screening (Company submission Section 12.5.8). The product cost is compensated somewhat by a reduction in rescue transplant and rescue PEG-ADA costs when Strimvelis is compared to HSCT from a haploidentical donor, but not from a MUD.

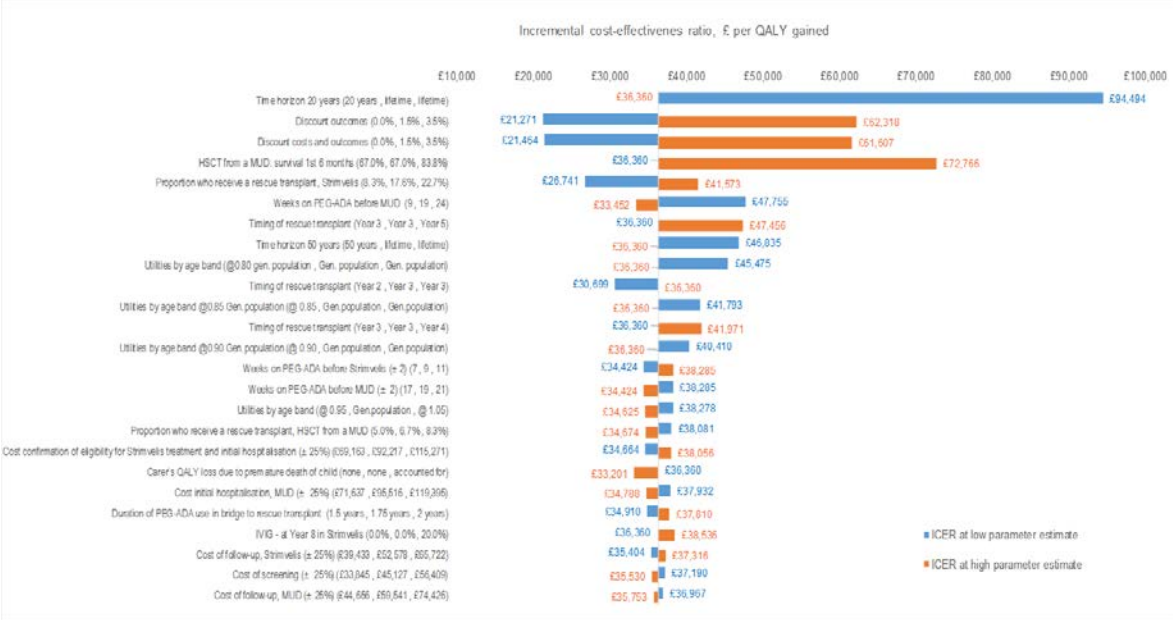
5.2.9.2 Deterministic sensitivity analysis

The company presented a series of one-way deterministic sensitivity analyses to assess the impact of varying key model input parameters on the ICER. Model parameters varied included the discount rate and time horizon, survival rates, clinical probabilities, timing and duration, costs, drug dosages, and utilities. The interval range applied for the parameters varied, though the majority of variables were adjusted by +/- 25%. A summary of the variables and ranges used in the company's one-way and two-way sensitivity analyses were provided in Tables D12 and D13 of the CS.

The results from all 1-way deterministic univariate sensitivity analyses are presented in Table D24 and Table D25 of the CS, with the results applying alternative discount rates presented in Appendix 8. In response to clarification the company provided tornado diagrams, shown in Figure 3 and Figure 4, summarising the 25 most influential parameters on the company ICER for Strimvelis compared to HSCT from a MUD and haploidentical donor respectively. The five most influential parameters for the comparison of Strimvelis against HSCT from a MUD were the time horizon (20 years compared to lifetime), the discount rate (0% or 3.5% compared to 1.5%), overall survival following HSCT from a MUD (83.75% compared to 66.7%), the proportion requiring rescue transplant following Strimvelis (8.3% or 22.7% compared to 17.6%) and the weeks on PEG-ADA before MUD (9 or 24 compared to 19). The five most influential parameters for the comparison of Strimvelis against HSCT from a haploidentical donor were the time horizon (20 years compared to lifetime), cost of PEG-ADA (10% of base case), the discount rate (0% or 3.5% compared to 1.5%), weeks on PEG-ADA before Haplo (9 or 24 compared to 19) and the proportion who require a rescue transplant following Strimvelis (0 compared to 17.6%).

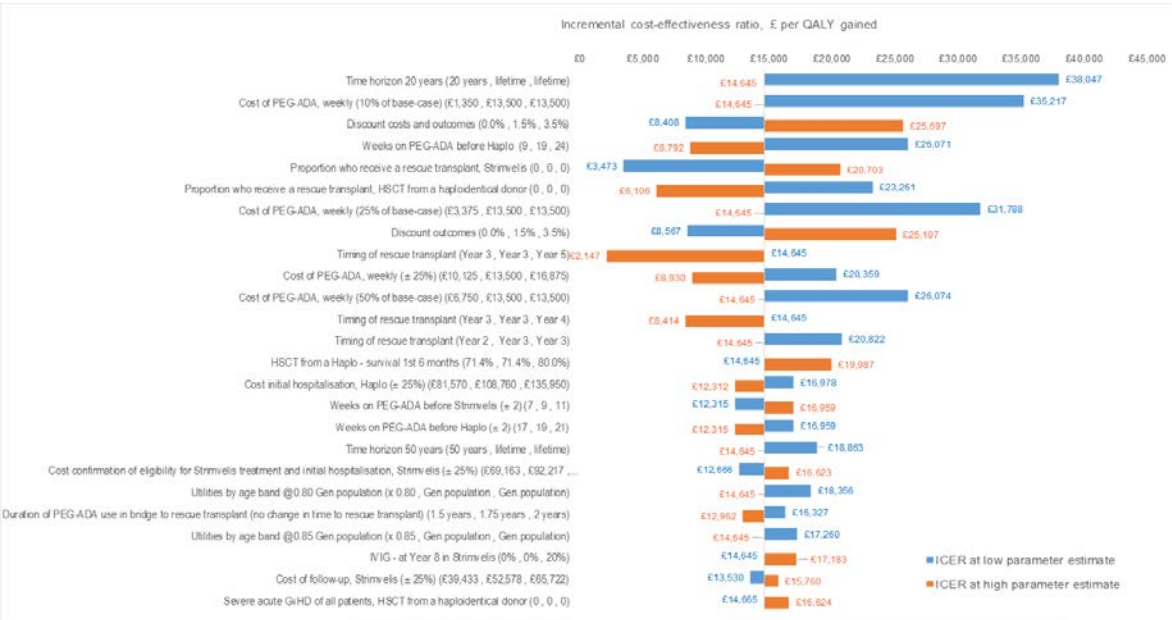
Table 22 displays the two-way sensitivity analysis conducted by the company to explore the joint uncertainties in long-term utility scores and mean life-expectancy for survivors (MLS). Overall the ICERs did not exceed £100,000 in response to the company sensitivity analyses.

Figure 3: Company tornado diagram Strimvelis vs HSCT from a MUD (base case: £36,360 per QALY)



Response to ERG clarifications, Figure 1 p48

Figure 4: Company tornado diagram Strimvelis vs HSCT from a haploidentical donor (base case: £14,645 per QALY)



Response to ERG clarifications, Figure 2 p49

Table 22: Two-way scenario analysis

	MLS*1 (79.9 yrs)	MLS*0.9 (71.9 yrs)	MLS*0.8 (63.9 yrs)
Strimvelis vs HSCT from a MUD			
Utility Score by Age * 1	£36,360	£38,375	£40,987
Utility Score by Age * 0.9	£40,410	£42,650	£45,554
Utility Score by Age * 0.8	£45,475	£47,997	£51,266
Strimvelis vs HSCT from a Haploidentical donor			
Utility Score by Age * 1	£14,645	£15,456	£16,508
Utility Score by Age * 0.9	£16,290	£17,194	£18,366
Utility Score by Age * 0.8	£18,352	£19,371	£20,694

CS, Table D26 p209; MLS = mean life expectancy of survivors

In response to clarification the company provided an additional scenario analysis that incorporated the updated cost of PEG-ADA, the updated administration costs for PEG-ADA and IVIG, and travel costs (company response to clarification Appendix, p59). This reduced the total costs for all comparators and had minimal impact on the estimated ICERs.

In response to a request from the ERG the company provided additional sensitivity analyses to explore the impact of lower rates of overall survival with Strimvelis. The ICER for Strimvelis compared to MUD increased to £41,387 using overall survival of 95% for Strimvelis, and increased to £48,601 using overall survival of 90%. The corresponding ICER for Strimvelis compared to haploidenitcal donor increased to £16,027 when survival after Strimvelis is 95% and £18,166 when survival after Strimvelis is 90% (company response to clarification B17, p40-41). The company declined to provide a sensitivity analysis that explored survival rates of 90% following HSCT from a MUD (company response to clarification B24, p50-51).

The company performed a range of threshold analyses in their original submission and in response to clarification, which are summarised in Table 23.

Table 23: Company threshold analysis

Variable	ICER compared to	Threshold		
		>£100,000/QALY	>£120,000/QALY	>£140,000/QALY

Post-procedure survival in Strimvelis and HSCT procedures	MUD	Survival after MUD >88% or survival after Strim <77%	-	Survival after MUD >92% or survival after Strim <74%
	Haplo	-	Survival after Haplo >97% or survival after Strim <73%	-
The acquisition cost of the Strimvelis procedure (baseline £505,000)	MUD	£1,370,092	-	£1,913,831
	Haplo	-	£1,732,803	-
The long-term post-procedure utility values for Strimvelis and HSCT procedures	MUD	<0.37	-	<0.26
	Haplo	-	<0.13	-

5.2.9.3 Probabilistic sensitivity analysis

The company performed a probabilistic sensitivity analysis (PSA) where parameters were sampled probabilistically from distributions based on 2,000 simulations. No justification was provided for the assigned distributions to the input parameters, although the ERG felt that those chosen were reasonable. The ERG identified a methodological error in the estimation of the probabilistic ICER in which the company provided the arithmetic mean of PSA ICERs as opposed to ICERs derived from the ratio of the mean costs and mean QALY. In response to clarification the company calculated the correct probabilistic ICERs at £36,161 ICER for Strimvelis compared with HSCT from a MUD and £14,964 when compared against HSCT from a haploidentical donor. As the decision model is linear, the probabilistic ICER is almost identical to the deterministic ICER. The company report that the ICER for exceeded £100,000 in 2% of the PSA simulations when compared to HSCT from a MUD and in 3% of the PSA simulations when compared to HSCT from a haploidentical donor (CS Section 12.5.14). The probability of Strimvelis being cost-effective at a threshold of £100,000 per QALY gained was reported to be 97% when compared to HSCT from a MUD and 99% when compared to HSCT from a haploidentical donor. The ERG considers that the slight discrepancy in the proportion of ICERs reported to exceed £100,000 per QALY is due to stochastic variation between PSA runs.

5.2.9.4 Additional sensitivity analysis undertaken by the ERG

Using the company base case results the ERG conduct a simple sensitivity analysis to inform the reduction in procedural mortality required for the ICER with Strimvelis to remain below £100,000 per QALY gained. In the company base case model each death avoided from the initial transplant procedure is associated with an additional 41 QALYs (41.4 QALYs per surviving patient using a

discount rate of 1.5%). Thus the company model estimates that for every percentage point reduction in procedural mortality there is an improvement of 0.41 QALYs. As Strimvelis is estimated to cost an additional £494,255 compared to HSCT from a MUD, the percentage point reduction in procedural mortality required to produce an ICER below £100,000 per QALY is (£494,255/£100,000)/0.41 = 12. Compared to HSCT from a haploidentical donor Strimvelis is expected to increase costs by £170,668, and so the percentage point reduction in procedural mortality must be at least (£170,668/£100,000)/0.41 = 4.

5.2.10 Model validation and face validity check

5.2.10.1 Internal consistency

The company did not provide any details on quality checks performed on the health economic model to validate its functionality. The ERG conducted a range of checks for the key calculations in the model and to examine whether varying input parameter values would generate intuitive results. A comprehensive check of all cells in the model was not performed. Overall, the company model appeared accurate, although errors existed in the estimation of probabilistic ICERs.

5.2.10.2 External consistency

The company did not conduct data validation of the economic model against existing literature on the basis that the model itself uses the most recent long term evidence on the natural history of ADA-SCID. The company states the economic model, its assumptions and results were validated by a UK clinical expert. The ERG recognises the challenges in externally validating the model results given the ultra-rare nature of the disease and the dearth of studies analysing long-term patient outcomes specific to ADA-SCID.

5.3 Conclusions of the cost effectiveness section

The ERG considered the company's economic submission to meet the requirements of the NICE reference case. The ERG considers that the company base case model applies only to younger patients in whom the decision to use Strimvelis is made immediately following diagnosis with ADA-SCID. The ERG identified a number of issues with the company model which indicate that it may underestimate the ICERs for Strimvelis compared to HSCT. The main concerns relate to four key areas:

1. *Underestimation of treatment costs with Strimvelis*
   The ERG noted that not all patients screened would be deemed eligible for treatment with Strimvelis, and the model does not incorporate the cost of initial baseline assessments in

patients unable to produce sufficient CD34+ cells. The company base case applies the standard hospitalisation charge to all patients treated with Strimvelis, and does not incorporate the additional costs incurred by the proportion of patients that exceed the standard 55 day length of stay. The model also fails to include any costs incurred for transplantation of back up bone marrow due to failure of the product or in order to facilitate recovery. However, the ERG acknowledge that excess hospital costs and use of back up bone marrow following HSCT are also excluded from the model. The company base case omits travel costs that would be reimbursed by the NHS, although these were included in a separate scenario analysis.

2. *Overestimation of costs associated with HSCT*

   The company base case assumes that the wait time before transplant is 10 weeks longer with HSCT compared to Strimvelis and that all patients are maintained on ERT using PEG-ADA during this period. The ERG consider that the available evidence does not support the assumption of greater use of PEG-ADA prior to HSCT compared to Strimvelis in terms of differential wait times and note that in practice not all patients have received ERT prior to HSCT. The company applied the higher cost of bone marrow transplant using stem cells from cord blood to all HSCT from a MUD, despite the majority of these being sourced from bone marrow, which is associated with a lower hospitalisation cost. The company also applied the cost of severe (Grade III/IV) GvHD events to GvHD events of any grade.

3. *Position of Strimvelis in the treatment pathway*

   The ERG note that some patients may utilise Strimvelis after having completed a search for a MUD. These may include patients unwilling to travel to Milan unless no appropriate MUD is found or until failure of a first-line MUD. For these patients the decision to use Strimvelis will not avoid the search costs for a MUD, but the company model structure assumes this search is avoided for all patients.

4. *Overestimation of health gains with Strimvelis*

   The company base case characterises a 33 percentage point reduction in procedural mortality with Strimvelis compared to HSCT from a MUD, and a 29 percentage point reduction compared to HSCT from a haploidentical donor. The ERG acknowledges that this is based on the best available evidence but considers that it is highly uncertain and may be an

overestimate based on improvements in survival rates following HSCT over time and the potential for overall survival following Strimvelis to fall below 100%.
The company base case assumes that patients who survive an initial transplant procedure are returned to general population longevity, and general population morbidity after three years. The ERG considers this to be unsupported by the available evidence, which indicates that following successful engraftment patients with ADA-SCID remain underweight, continue to experience cognitive and neurodevelopmental deficits and have a lower health-related quality of life compared to the general population. Following unsuccessful engraftment the ERG considers that the company base case fails to appropriately characterise the morbidity and additional health care costs associated with rescue transplant procedures.

Additional analyses based on scenarios undertaken by the company and independent analyses undertaken by the ERG are presented in Section 6 to address these uncertainties and provide an alternative set of cost-effectiveness results.

6 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

6.1 Overview

This section focuses on the additional analyses used to explore the key areas of uncertainty and concern highlighted in Section 5. The additional work undertaken by the ERG includes changes to the economic model to develop an ERG base case analysis, and a range of sensitivity and threshold analyses undertaken to explore the impact of key uncertainties.

The main changes made by the ERG to the economic model include:

1. Utilising a number of scenario analyses undertaken by the company:
    - Disuility weight of 0.75 applied for patients treated with IVIG
    - Duration of GvHD 2 years consistent with timing of rescue transplant
    - Revised PEG-ADA dose determined by patient weight
    - Revised administration costs for PEG-ADA and IVIG
    - Inclusion of travel costs
2. Incorporating the NPP to inform procedural outcomes
3. Minor corrections to the company model
4. Assuming equal wait times and pre-procedure PEG-ADA use across treatment arms
5. Assuming rescue therapy has same cost and health outcomes as initial MUD
6. Including ongoing healthcare costs and morbidity associated systemic sequelae of ADA-SCID
7. Adjusting unit costs for:
    - HSCT from a MUD to reflect proportion sourced from bone marrow
    - GvHD events to make cost per event consistent with severity
8. Incorporating cost of baseline screening for proportion of patients ineligible for Strimvelis

After demonstrating the impact of the various scenarios on the ICER, the ERG presents its preferred base-case analysis. The ERG's additional scenario analyses thereafter assess the impacts the following four uncertainties have on cost-effectiveness:

1. Survival rates for Strimvelis and HSCT
2. Cost of Strimvelis and initial hospital care in OSR
3. Strimvelis' position in the treatment pathway
4. Rescue transplant rates

6.2 ERG corrections and adjustments to the company's base case model

6.2.1 Company sensitivity analyses and alterations

The company submission recognised many of the uncertainties discussed in Section 5 and incorporated a range of scenario analyses that assessed the impact of alternative assumptions on the company's base case results.

The ERG consider that the company sensitivity analysis that incorporates a health related quality of life impact associated with IVIG use is more representative of the experience of patients with ADA-SCID. The company sensitivity analysis applies a utility weight of 0.75, which is approximately in line with the ratio of IVIG use to chronic lymphocytic leukemia without infection reported in the literature (0.66/0.87).[47]

In the company base case the duration of chronic GvHD exceeds the assumed time to rescue transplant. The ERG prefers to maintain consistency between these as rescue transplant is only performed once chronic GVHD is resolved. In response to clarification the company provided alternative results assuming rescue transplant occurred at year 4, which would maintain consistency between duration of GvHD and timing of rescue transplant. However, the company did not provide an updated economic model with this adjusted timing of rescue transplant. Instead, the ERG therefore apply the company's analysis which reduced the duration of chronic GvHD to 2 years, although noting that the impact on the ICER is much smaller than delaying rescue transplant.

In response to points for clarification, the company provided a further scenario analysis incorporating: weight based PEG-ADA dosages, cost of drug administration in line with expected administration times and the costs of travel to and from the OSR, Milan (Section 5.2.9.2 and company response to clarification Appendix p59-60). The ERG accepts this additional scenario analysis as a more appropriate account of the dosing and costs of administration and travel likely to occur in practice.

6.2.2 Incorporating the NPP

As previously discussed in Section 4.2.1, the ERG believes that it is important to use all available data on patients that have been treated with Strimvelis to inform the model parameters and considers that incorporating the NPP is consistent with the merger of studies that the company used for the Strimvelis Integrated Population. Table 24 illustrates the difference this makes to the numbers of patients informing procedural outcomes.

Table 24: Modelled procedural outcomes by patient population

	Company base case	ERG preferred
	Integrated Strimvelis population	NPP + Integrated Strimvelis population
Patients	17	[redacted]
Rescue transplants	3	[redacted]
Died	0	[redacted]
Survived	17	[redacted]
Rescue transplant	17.6%	[redacted]
Survived	100%	100.0%

6.2.3 Parameter corrections

The ERG identified and corrected minor errors in the company model for the cost applied to the first six months' follow up after Strimvelis and the cost per test for vector copy number. Table 25 provides a summary of the identified discrepancies in the company submission and the company model. The ERG's preferred base case applies the corrected values for each parameter in Table 25.

Table 25: Parameter discrepancies

	Company submission	Company model	Corrected value
Cost of follow-up (Months 0-6)	[redacted]	[redacted]	[redacted]
Cost of VCN	£1,199	£1,207	£1,199

The ERG also has concerns regarding the calculation of rescue therapy rates in the company model. As discussed in Section 5.2.6.3, the company's calculated rescue transplant rates are not conditional on survival following the initial procedure. The ERG's base case applies rescue therapy rates conditional on survival from the Strimvelis Integrated Population and the NPP. Table 26 reports the conditional and non-conditional rates of rescue therapy for each population under study.

Table 26: Conditional and non-conditional rates of rescue therapy

	Strimvelis Integrated Population			Strimvelis Integrated Population + NPP		
	Strimvelis	MUD	Haplo	Strimvelis	MUD	Haplo
Patients	17	15	7	[redacted]	15	7
Rescue transplant	3	1	2	[redacted]	1	2
Died	0	5	2	[redacted]	5	2
Survived	17	10	5	[redacted]	10	5

Non-conditional rescue transplant rates	3/17 (17.6%)	1/15 (6.7%)	2/7 (28.6%)	[redacted]	1/15 (6.7%)	2/7 (28.6%)
Conditional rescue transplant rates	3/17 (17.6%)	1/10 (10.0%)	2/5 (40%)	[redacted]	1/10 (10.0%)	2/5 (40%)

6.2.4 Equal wait times across treatments

The ERG considers that there is insufficient evidence to support a difference in wait time between Strimvelis and HSCT (see Section 5.2.6.1). The ERG preferred base case therefore assumes no difference in wait time to transplant across all comparators, which is applied by setting wait time to 0 weeks.

6.2.5 Rescue therapy

The ERG believes it is unrealistic to assume all patients following an unsuccessful engraftment would find a MSD for rescue transplantation, and unrealistic to assume that patients receiving rescue transplants will have 100% survival and 100% successful engraftment. The company had included a sensitivity analysis in which the survival rate from a rescue transplant is taken from a MUD procedure, but this did not include the risk of GvHD nor severe infections post-procedure. The ERG's preferred base case assumes that patients who receive a rescue transplant experience the health outcomes and costs associated with using a MUD. The ERG provides an alternative rescue transplant scenario which incorporates:

- The survival rate from a MUD transplant (66.6%)
- The expected cost and QALY impacts of GvHD
- The expected cost of severe infections
- Patients who fail to engraft following rescue transplant go on to receive long term PEG-ADA (≥0.3% of modelled patient cohort)

Table 27 reports the changes in costs and QALYs which result from the ERG's alternative base case for rescue therapies.

Table 27: Changes in costs and QALYs for the ERG's alternative rescue therapy scenario

	Change in costs			Change in QALYs		
	Strimvelis	MUD	Haplo	Strimvelis	MUD	Haplo
ERG alternative rescue scenario	+£186,511	+£70,460	+£301,970	-2.3	-0.9	-3.8

6.2.6 Long-term cost and health-related quality of life outcomes

As discussed in Section 5.2.7, both the company and the ERG identified evidence contradicting the assumption made in the CS that ADA-SCID patients return to the HRQoL observed in the general population 6 months post-procedure. The ERG utilise studies identified in a pragmatic review to provide an indication of the cost and HRQoL impacts of the common long-term sequelae of ADA-SCID.

As discussed in Section 5.2.7, Petrou et al estimated a mean health-related quality of life decrement for bilateral permanent hearing impairment of -0.294 ($p<0.01$) compared to children with normal hearing.[57] Schroeder et al calculated mean annual costs (relevant to the NHS & PSS) of bilateral permanent hearing impairment at £1,451.20, which is £2,095.82 inflated to 2016 prices using the PSSRU hospital and community health service index.[56]

Titman et al reported that 25% of SCID patients who survive HSCT experience higher levels of difficulties in emotional and behavioural function, as defined by a total difficulties score ≥17 on the SDQ. This was compared to 10% in the general population.[37] Using a mapping algorithm to predict preference-based utility scores based on clinical bandings of the SDQ, the ERG estimate a decrement of 0.14 for difficulties in emotional and behavioural function among SCID patients.[51]

Table 28 presents evidence sourced by the ERG relevant to the long-term expected costs and HRQoL of patients with ADA-SCID.

Table 28: Long-term ADA-SCID related cost and HRQoL values from the literature

	Decrement in HRQoL		Cost		Rates		Expected Value	
Condition	Value	Source	Value	Source	Value	Source	HRQoL	Cost
Bilateral permanent hearing impairment	-0.294	Petrou et al (2007)	£2,095.82	Schroeder et al (2006)	58.3%	Albuquerque and Gaspar (2004)	-0.172	£1221.86
Emotional and behavioural dysfunction	-0.14	Furber et al (2014)	-	-	15%	Titman et al (2008)	-0.021	-

Table 29 displays the resultant changes in costs and QALYs if these estimates are applied in the company model. Given uncertainty surrounding the application of mapping to determine the health related quality of life impact of emotional and behavioural problems, the ERG's preferred base case applies the expected costs and HRQoL impacts from bilateral permanent hearing impairments only,

while noting that these are not the only long-term sequelae of ADA-SCID that may imply ongoing costs and morbidity.

Table 29: Change in costs and QALYs from long-term ADA-SCID morbidities

	Change in costs			Change in QALYs		
Condition	Strimvelis	MUD	Haplo	Strimvelis	MUD	Haplo
Bilateral permanent hearing impairment	+£56,167	+£37,444	+£40,119	-7.8	-5.2	-5.5
Emotional and behavioural dysfunction	£0	£0	£0	-1.0	-0.6	-0.7
Total	+£56,167	+£37,444	+£40,119	-8.8	-5.8	-6.2

6.2.7 Updated unit costs

As discussed in Section 5.2.8.1, the company submission applies a unit cost derived from cord blood bone marrow transplants to all MUD transplants. However, the ERG expects that a significant proportion of MUD transplants will be undertaken using bone marrow, in line with the rate observed in Hassan 2012 (88/106, 83%) and the national schedule of reference costs (51/62, 82%).[3, 53] The NHS reference cost of bone marrow transplant, allogeneic graft, is £95,517 using stem cells from cord blood (code SA22B as applied in company base case) and £79,199 using stem cells from volunteer unrelated donor (£79,199 code SA21B). The weighted average cost used in the ERG's base case analysis is £81,973, based on the proportion of transplants sourced from bone marrow in Hassan.

As previously detailed in Section 5.2.8.4 the ERG consider it inappropriate to apply a cost of severe (Grade III/IV) GvHD to GvHD events of all grades since this will overestimate the adverse event costs associated with HSCT. The ERG believe a more appropriate unit cost per GvHD event would be calculated by the difference between the mean readmission cost of any GvHD event (£28,860) and the mean cost of readmission for patients without GvHD (£13,405). After inflating the difference of £15,455 to 2016 prices, the resultant unit cost applied in the ERG's preferred base case is £17,089.

6.2.8 Cost of ineligibility to Strimvelis

In the company's economic model, all patients assigned to Strimvelis are assumed to receive gene therapy, and hence the model does not incorporate forgone screening costs for patients unable to donate adequate CD34+ cells. Given that 1 of the 18 patients in the Strimvelis Integrated population was deemed ineligible after screening, the ERG considers it appropriate to include these costs in the Strimvelis treatment arm. The ERG's preferred base case makes a simplified adjustment in the cost of screening so that for every 18 patients tested, 17 patients advance to Strimvelis. This alteration

prompts a revised cost of [redacted] per successfully treated patient as supposed to [redacted] used in the company's original base case.

While the ERG have made adjustments to the base case company model costs for Strimvelis related screening the ERG still considers there remains a large degree of uncertainty surrounding the treatment pathway for those patients who fail screening for Strimvelis. The duration of time these patients remain on PEG-ADA is unknown and it is unclear whether inability to produce sufficient CD34+ cells will also impact on success of HSCT.

6.2.9 ERG preferred base case

Table 30 shows the effect of each individual change to the company base case ICER and how these are combined to produce the ERG's preferred base case estimates. It should be noted that the results were conducted using the company's base case discount rate (1.5%).

Table 30 - Results of the relevant scenarios and additional calculations for the ERG base cases

	Costs	QALYs	Inc. cost	Inc. QALY	ICER	Δ ICER
Company base case						
Company original base case (deterministic)						
Strimvelis	£1,059,425	41.4				-
MUD	£565,170	27.8	£494,255	13.6	£36,360	-
Haploidentical	£888,757	29.7	£170,668	11.7	£14,645	-
Company's secondary analysis (after clarifications requested to the company by NICE and the ERG)						
Weekly cost of PEG-ADA set using 1 vial @ £9,000 (from £13,500)						
Strimvelis	£948,177	41.4				
MUD	£452,943	27.8	£495,234	13.6	£36,432	+£72
Haploidentical	£688,712	29.7	£259,465	11.7	£22,264	+£7,619
PSSRU cost of administration of IVIG @ £216 (from £306)						
Strimvelis	£1,055,311	41.4				
MUD	£562,590	27.8	£492,722	13.6	£36,247	-£113
Haploidentical	£885,311	29.7	£170,001	11.7	£14,587	-£57
PSSRU cost of administration of PEG-ADA @ £54 (from £306)						
Strimvelis	£1,053,195	41.4				
MUD	£558,885	27.8	£494,310	13.6	£36,364	+£4
Haploidentical	£877,554	29.7	£175,641	11.7	£15,071	+£427
Including company's specified cost of travel to Milan						
Strimvelis	£1,060,837	41.4				

MUD	£565,170	27.8	£495,667	13.6	£36,464	+£104
Haploidentical	£888,757	29.7	£172,080	11.7	£14,766	+£121
Company's total secondary analysis						
Strimvelis	£939,245	41.4				
MUD	£444,078	27.8	£495,167	13.6	£36,427	+£67
Haploidentical	£674,064	29.7	£265,182	11.7	£22,755	+£8,110
Company's IVIG disutility scenario (utility = 0.75)						
Strimvelis	£1,059,425	40.5				
MUD	£565,170	27.2	£494,255	13.3	£37,158	+£799
Haploidentical	£888,757	29.1	£170,668	11.5	£14,865	+£221
ERG Scenario Analyses						
SA1. Named Patient Population (NPP) included to inform procedural outcomes						
Strimvelis	£1,161,783	41.3				
MUD	£565,170	27.8	£596,613	13.6	£42,950	+£7,590
Haploidentical	£888,757	29.7	£273,026	11.6	£23,465	+£8,820
SA2. Parameter corrections and conditional probabilities for rescue therapy						
Strimvelis	£1,059,381	41.4				
MUD	£611,649	27.8	£447,732	13.6	£32,917	-£3,443
Haploidentical	£1,048,115	29.7	£11,267	11.7	£964	-£13,680
SA3. Equalising duration of initial PEG-ADA prior to initial procedure (0 days)						
Strimvelis	£935,171	41.2				
MUD	£302,856	27.4	£632,315	13.8	£45,881	+£9,522
Haploidentical	£626,443	29.4	£308,728	11.8	£26,071	+£11,426
SA4. Rescue therapy transplants conducted from a MUD (reduced survival, GvHD and severe infection risk, PEG-ADA for failed engraftment)						
Strimvelis	£1,245,936	39.0				
MUD	£635,630	26.9	£610,306	12.1	£50,246	+£13,886
Haploidentical	£1,190,727	25.9	£55,209	13.1	£4,216	-£10,428
SA5. Utilities accommodating for permanent childhood hearing impairment						
Strimvelis	£1,059,425	33.6				
MUD	£565,170	22.6	£494,255	11.0	£44,913	+£8,553
Haploidentical	£888,757	24.2	£170,667	9.4	£18,121	+£3,476
SA6. Costs of permanent childhood hearing impairment						
Strimvelis	£1,155,592	41.4				
MUD	£602,615	27.8	£512,977	13.6	£37,737	+£1,377

Haploidentical	£928,876	29.7	£186,716	11.7	£16,022	+£1,377
SA7. Updated unit costs for HSCT (with bone marrow donation) and GvHD events (average costs applied)						
Strimvelis	£1,057,140	41.4				
MUD	£547,480	27.8	£509,659	13.6	£37,493	+£1,133
Haploidentical	£881,555	29.7	£175,584	11.7	£15,067	+£422
SA8. Cost of ineligibility for Strimvelis						
Strimvelis	[redacted]	41.4				
MUD	£565,170	27.8	[redacted]	13.6	[redacted]	[redacted]
Haploidentical	£888,757	29.7	[redacted]	11.7	[redacted]	[redacted]
ERG preferred base case						
Strimvelis	£1,236,768	30.1				
MUD	£425,656	20.7	£811,195	9.3	£86,815	+£50,455
Haploidentical	£1,052,166	19.0	£184,686	11.1	£16,704	+£2,060

The ERG preferred base case predicts lower QALYs for all comparators compared to the company base case. This is attributable to the increased mortality and morbidity associated with rescue transplants and the application of HRQoL decrements for IVIG use and bilateral hearing impairment. The ERG's preferred base case predicts higher costs for Strimvelis, lower costs for HSCT from a MUD and higher costs for HSCT from a haploidentical donor compared to the company base case. This is attributable to the higher rates of rescue transplant for Strimvelis and HSCT from a haploidentical donor combined with the increased health care costs per rescue transplant to reflect risks of severe infection and GvHD. As shown in Table 30, the ERG's base case ICERs are higher than the company base case, rising to £86,815 for Strimvelis compared to HSCT from a MUD and to £16,704 for Strimvelis compared to a haploidentical donor. The ERG's preferred ICER remains below the £100,000 lower tier threshold for both comparators.

Recent consultation published by NICE on arrangements for funding in highly specialised technology programmes states that the threshold used for decision making is now conditional on the size of the QALY gain the treatment offers. Table 31 reports the adjusted cost-effectiveness thresholds for both the company's and ERG's base cases.

Table 31: Relevant decision making threshold for the company and ERG base cases

	Comparator	Strimvelis' undiscounted QALY gain	Weighting of QALY	Adjusted threshold
Company base case	MUD	23.2	2.32	£232,000
	Haploidentical	19.9	1.99	£199,000
ERG base case	MUD	15.9	1.59	£159,000
	Haploidentical	18.8	1.88	£188,000

6.3 Additional ERG analyses

6.3.1 Survival rates

As discussed in Section 5.2.6.1 the rates of survival for ADA-SCID patients is highly uncertain. Figure 5 and Figure 6 show the results of two-way sensitivity analysis comparing the rates of survival following Strimvelis to overall survival following HSCT from a MUD and from a haploidentical donor respectively.

Figure 5 indicates that the ERG base case ICER is sensitive to the survival rate following HSCT from a MUD. The comparison of the results of sensitivity analyses around survival rates against adjusted cost-effectiveness thresholds is complicated by the fact that adjusting the survival rate will alter the expected QALY gain with Strimvelis. Table 32 provides a one way sensitivity analysis for overall survival following HSCT from a MUD. This indicates that Strimvelis must reduce procedural mortality by at least 23 percentage points compared to a MUD in order for the undiscounted QALY gain to exceed 10 QALYs, and that it must reduce procedural mortality by at least 30 percentage points to result in an ICER less than £100,000.

Table 32: ICER and undiscounted QALY gain dependent on overall survival with initial MUD

Survival with MUD	ICER Strimvelis vs MUD	Undiscounted QALY gain Strimvelis compared to MUD	Adjusted threshold
0.66	£84,936	16.25	£163,000
0.67	£87,787	15.70	£157,000
0.68	£90,848	15.14	£151,000
0.69	£94,143	14.58	£146,000
0.70	£97,699	14.02	£140,000
0.71	£101,549	13.46	£135,000
0.72	£105,731	12.90	£129,000
0.73	£110,289	12.35	£124,000

0.74	£115,277	11.79	£118,000
0.75	£120,759	11.23	£112,000
0.76	£126,812	10.67	£107,000
0.77	£133,529	10.11	£101,000
0.78	£141,027	9.56	£100,000 (no adjustment)

Figure 6 displays how insensitive the ICER for Strimvelis is with respect to survival outcomes of patients undergoing transplant from haploidentical donors. Increasing the rate of survival for haploidentical transplants decreases the ICER for Strimvelis. The underlying reason for this is the high rates of rescue therapy following HSCT from a haploidentical donor. Increasing survival following HSCT increases QALYs but is associated with large increases in the costs of PEG-ADA when awaiting rescue therapy and the cost and mortality risks of the rescue transplant. Given the very small numbers that inform the rates of rescue therapy the results of Figure 6 should be taken with caution.

Figure 5: Two way sensitivity analysis for initial procedure survival rates showing ICER for Strimvelis compared to MUD

Strimvelis Survival ↓ **MUD Survival →** **ERG base case***

	1.00	0.96	0.92	0.88	0.84	0.80	0.76	0.72	0.68	0.667
1.00	Dominated	Dominated	£736,937	£330,448	£214,116	£158,982	£126,812	£105,731	£90,848	**£86,815**
0.98	Dominated	Dominated	£1,696,417	£436,228	£251,934	£177,911	£137,979	£112,996	£95,890	£91,327
0.96	Dominated	Dominated	Dominated	£652,004	£308,197	£202,869	£151,788	£121,627	£101,720	£96,507
0.94	Dominated	Dominated	Dominated	£1,335,165	£400,749	£237,285	£169,301	£132,051	£108,536	£102,513
0.92	Dominated	Dominated	Dominated	Dominated	£581,415	£287,790	£192,240	£144,889	£116,613	£109,560
0.90	Dominated	Dominated	Dominated	Dominated	£1,090,350	£369,109	£223,589	£161,092	£126,337	£117,944
0.88	Dominated	Dominated	Dominated	Dominated	£11,704,595	£521,819	£269,009	£182,180	£138,268	£128,088
0.86	Dominated	Dominated	Dominated	Dominated	Dominated	£913,490	£340,718	£210,755	£153,255	£140,607
0.84	Dominated	Dominated	Dominated	Dominated	Dominated	£4,121,762	£470,834	£251,666	£172,643	£156,450
0.82	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	£779,741	£315,100	£198,705	£177,140

Figure 6: Two way sensitivity analysis for initial procedure survival rates showing ICER for Strimvelis compared to Haplo

Strimvelis Survival ↓ **Haplo Survival →** **ERG base case***

	1.00	0.96	0.92	0.88	0.84	0.80	0.76	0.72	0.714
1.00	Dominant	Dominant	Dominant	£1,413	£6,707	£10,715	£13,856	£16,383	**£16,704**
0.98	Dominant	Dominant	Dominant	-£558	£5,479	£9,942	£13,376	£16,101	£16,445
0.96	Dominant	Dominant	Dominant	-£2,964	£4,024	£9,046	£12,830	£15,784	£16,153
0.94	Dominant	Dominant	Dominant	-£5,969	£2,273	£7,996	£12,202	£15,424	£15,824
0.92	Dominant	Dominant	Dominant	-£9,827	£124	£6,747	£11,473	£15,014	£15,449
0.90	Dominant	Dominant	Dominant	-£14,960	-£2,574	£5,238	£10,615	£14,542	£15,018
0.88	£1,218,861	Dominant	Dominant	-£22,127	-£6,063	£3,378	£9,592	£13,991	£14,517
0.86	£271,284	Dominant	Dominant	-£32,835	-£10,752	£1,027	£8,349	£13,342	£13,929
0.84	£160,825	£595,462	Dominant	-£50,571	-£17,387	-£2,037	£6,810	£12,565	£13,227
0.82	£118,051	£210,925	Dominant	-£85,628	-£27,497	-£6,198	£4,852	£11,617	£12,375

6.3.2 Price of Strimvelis and cost of initial hospitalisation in OSR

The product cost of Strimvelis is uncertain due to potential fluctuations in the exchange rate and the associated hospitalisation charge is still under negotiation between NHS England and the company. The ERG also identified a number of treatment relevant costs that were omitted from the company model, including additional costs for hospital stays in Milan that exceed 55 days and the costs of back up bone marrow administration. To address uncertainties in the additional costs for patients treated with Strimvelis, the ERG conducted a threshold sensitivity analysis to indicate the increase in the incremental costs for Strimvelis that would cause the estimated ICER to exceed £100,000 per QALY or the adjusted threshold indicated by the undiscounted QALY gain. An increase of £123,203 in the incremental cost of Strimvelis compared to HSCT from a MUD would result in an ICER greater than £100,000 per QALY, and an increase of £683,842 would result in an ICER greater than £160,000 compared to HSCT from a MUD. The corresponding threshold incremental cost increases are much larger when Strimvelis is compared to HSCT using a haploidentical donor, at £920,932 to produce an ICER greater than £100,000 per QALY and £1,893,876 to produce an ICER greater than £188,000 per QALY.

Figure 7 shows a two-way sensitivity analysis and provides the ICER for Strimvelis compared to MUD for variations in alternative overall survival following Strimvelis and the product cost (i.e. £505,000) of Strimvelis. It should be noted that when the survival rate following Strimvelis is reduced below 100%, the adjusted cost-effectiveness threshold in accordance with the HST methods process guide will also fall (£133,000 for overall survival at 95% and £108,000 for overall survival at 90%).

Figure 7: Two way sensitivity analysis for overall survival and product cost of Strimvelis.

Strimvelis Survival ↓ **%Change Strimvelis product cost →** **ERG base case**

	+30%	+20%	+10%	+/-0%	-10%	-20%	-30%
1.00	£103,028	£97,624	£92,219	**£86,815**	£81,410	£76,006	£70,601
0.95	£118,718	£112,277	£105,836	£99,395	£92,954	£86,513	£80,072
0.90	£141,852	£133,883	£125,914	£117,944	£109,975	£102,006	£94,036

6.3.3 Strimvelis' position in the treatment pathway

As noted in Section 5.2.1 the ERG considers that Strimvelis could take a range of different positions in the treatment pathway, each with different implications for cost and outcomes. The company decision tree structure characterises one of the possible routes in which patients arrive to treatment directly after diagnosis. The ERG highlights two alternative pathways in which patients may arrive to treatment:

- In cases where patients, families or clinicians first wish to explore the potential for a MUD before making a decision to use gene therapy;
- In cases where patients undergo HSCT but fail to engraft and subsequently undergo Strimvelis as a rescue therapy

In both these cases the costs of searching for a MUD would not be avoided in patients who go on to use Strimvelis. The ERG base case does include an alternative model structure that fully characterises these alternative pathways. Instead the ERG provide a simplistic analysis that explores the impact of assuming donor screening is undertaken before the decision is made to use Strimvelis. This simply includes the cost of donor screening in the Strimvelis arm, and leaves all other parameters such as duration of PEG-ADA unchanged from the ERG base case. Table 33 shows that incorporating donor screening costs for both Strimvelis and HSCT increases the ICERs for Strimvelis compared to HSCT by £4,830 compared to MUD and by £4,082 compared to Haploidentical donor source.

Table 33: Strimvelis incurring the cost of screening for a MUD

	Costs	QALYs	Inc. cost	Inc. QALY	ICER	∆ ERG ICER
Strimvelis	£1,281,895	30.1				
MUD	£425,656	20.7	£856,322	9.3	£91,644	+£4,830
Haploidentical	£1,052,166	19.0	£229,913	11.1	£20,786	+£4,082

In the absence of evidence regarding the proportion of ADA-SCID patients for whom no appropriate MUD can be found, it is not possible to estimate a weighted combination of HSCT from a MUD or haploidentical donor to represent the costs and health outcomes that would be expected from HSCT prior to completion of a donor search. However, the ERG note that the ICER for Strimvelis compared to a weighted combination of HSCT from a MUD and HSCT from a haploidentical donor would be lower than that estimated for Strimvelis compared to HSCT from a MUD only.

6.3.4 Equal rates of rescue therapy

To assess the effects of removing any difference between treatments in rates of rescue therapy, the ERG presents a scenario analysis in which [redacted] of patients fail to engraft, based on the rate of rescue transplant calculated in the Strimvelis Integrated Population and NPP. This implies an increase in the rate of rescue transplant following MUD from 10%, and a reduction in the rate of rescue transplant following Haplo. Table 34 displays the resultant changes in costs and QALYs. It is clear from this

scenario that the costs are highly sensitivity to the removal of differences in the rates of rescue therapy, which is predominantly driven by the assumed PEG-ADA costs required to bridge patients to rescue therapies.

Table 34: Changes in costs and QALYs when equalising rates of rescue therapy

	Costs	QALYs	Inc. cost	Inc. QALY	ICER	Δ ERG ICER
Strimvelis	£1,635,030	30.1				
MUD	£1,120,099	19.1	£514,931	11.0	£46,849	-£39,965
Haploidentical	£1,154,080	20.7	£480,950	9.4	£51,116	+£34,412

6.4 Conclusions from ERG analyses

The changes made by the ERG produce ICERs for Strimvelis compared to HSCT that are higher than the company base case, but remain below £100,000 per QALY gained. The results of the model would suggest that Strimvelis is a cost-effective alternative for patients that have no MUD available, and in whom HSCT from a haploidentical donor is the only alternative, as the ICER for Strimvelis compared to HSCT from a haploidentical donor is unlikely to exceed £100,000 per QALY for a range of sensitivity analyses.

However, the results of the comparison between Strimvelis and HSCT from a MUD are very sensitive to the assumed reduction in procedural mortality for Strimvelis compared to HSCT from a MUD. For patients with an appropriate MUD available, improvements in techniques for HSCT that increase overall survival following MUD or the occurrence of a death in a patient treated with Strimvelis, could cause the ICER for Strimvelis compared to MUD to exceed £100,000 per QALY gained. If survival following HSCT from a MUD exceeds 75%, the ICER for Strimvelis compared to a MUD would no longer fall beneath the adjusted cost-effectiveness threshold determined by the extent of the undiscounted QALY gain with Strimvelis. If overall survival with Strimvelis falls below 100%, the results are also sensitive to the additional cost of Strimvelis treatment. The rates of rescue transplant are also very influential on the estimated ICERs. Assumptions that improve the anticipated outcomes of rescue transplant after Strimvelis, for example if rescue transplantation is earlier following Strimvelis due to the avoidance of chronic GvHD or because MUD options have not yet been exhausted, this would be expected to reduce the ICER for Strimvelis compared to HSCT from a MUD.

7 Submissions from practitioner and patient groups

One submission was received from Dr Susan Walsh representing Primary Immunodeficiency UK (PDI UK). As there were no further submissions from patient groups the ERG judged there would be no added value in summarising this document and would potentially risk losing key issues. Therefore, for further details please see the submission by Dr Susan Walsh.

One submission was also received from NHS England, as above the ERG judged there would be no added value in summarising this document. For further details please see the submission by NHS England.

A further submission was also provided by Professor Aiuti an expert in the treatment of Strimvelis.

8 Overall conclusions

The ERG acknowledge that the company base case utilises appropriate available evidence to inform rates of overall survival and successful engraftment, but is concerned that the small numbers of patients mean that the extent of the estimated treatment benefit is highly uncertain. The company model was simple and straightforward, but as a consequence may have failed to appropriately characterise the cost and health differences between alternative treatment strategies and pathways.

The ERG considered that the company base case omitted potentially important costs associated with the use of Strimvelis, including the cost of screening for patients deemed ineligible to proceed to treatment with Strimvelis, travel costs, and the full health care cost implications of patients that fail to engraft and require rescue transplant. The ERG acknowledges that the company addressed some of these concerns in sensitivity analysis. While the ERG was also concerned that the omission of excess hospitalisation costs and administration of back up bone marrow in patients treated with Strimvelis, the ERG base case also omits these costs as it is uncertain whether similar costs may be incurred by patients who undergo HSCT from a MUD or haploidentical donor.

The ERG identified a number of areas where the costs associated with HSCT from a MUD or haploidentical donor may be overestimated, including the hospitalisation cost applied for HSCT from a MUD, the cost per GvHD event and the cost of PEG-ADA in terms of both duration of ERT prior to HSCT and drug acquisition and administration costs.

The ERG was very concerned with the underlying assumption in the company base case model that all ADA-SCID patients who survive the initial procedure are cured and return to general population

mortality and morbidity regardless of engraftment success, patient characteristics and prior health state. The ERG assumed greater mortality, morbidity and health care costs for rescue transplant compared to the company base case and introduced disutility associated with IVIG use and bilateral hearing impairment, and an ongoing health care cost from bilateral hearing impairment in patients that survive transplant procedures. This reduced the QALY gained predicted by the model for a given reduction in procedural mortality.

The ERG consider that the company base case applies only to younger patients in whom the decision to use Strimvelis is made immediately after diagnosis and prior to undertaking a search for a MUD. It is likely that in older patients the costs of PEG-ADA and IVIG will be increased across all comparators, and possible that overall survival and success rates will be reduced across all comparators. If the search costs for a MUD are not avoided by the time the decision to use Strimvelis is taken, the ICER for Strimvelis compared to a MUD increases, but remains below £100,000 per QALY. If assumptions about rescue transplants are more favourable to Strimvelis, this would significantly reduce the ICER for Strimvelis compared to HSCT from a MUD.

8.1 Implications for research

Overall, the ERG believes that the difference in overall survival between Strimvelis and HSCT from a MUD could well be lower than that characterised in the model or is likely to fall with time. The ERG consider that given the rarity of ADA-SCID and the changes in clinical practices over time that obtaining contemporary evidence to inform survival rates is challenging. Given the small sample sizes used to inform the key model parameters, each additional patient treated can have a large influence on estimates of overall survival and rates of successful engraftment. An update to the analysis conducted by Hassan et al. that informed more recent rates of overall survival following HSCT from a MUD may be very valuable in determining whether Strimvelis can be considered cost-effective.

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10 Appendices

10.1 Checklist

Table 35 summarises the results of the Phillips checklist applied to the company cost effectiveness submission.

Table 35: Phillips checklist for company submission

Description of quality	Response (✓,✗ or NA)	Comments	Reference
Structure			
S1 Statement of decision problem objective			
Is there a clear statement of the decision problem?	✓	The decision problem was clearly stated in the first table of the CS using the PICOS framework.	CS, Table A1, p19-22
Is the objective of the evaluation and model specified and consistent with the stated decision problem?	✓	Given the CS is submitted under the highly specialised technologies evaluation programme it is implied that the core evidence presented by the company intends to fulfil NICE's objective of determining the clinical and cost-effectiveness of Strimvelis within its marketing authorisation for patients with ADA-SCID for whom no suitable HLA-matched related stem cell donor is available.	
Is the primary decision-maker specified?	✓	Yes, NICE.	
S2 Statement of scope/perspective			
Is the perspective of the model clearly stated?	✓	Yes, the perspective of the company's analysis was the NHS and Personal Social Services (NHS & PSS).	CS, Table D4, p146-148
Are the model inputs consistent with the stated perspective?	✓	Yes.	
Has the scope of the model been stated or justified?	✓	The scope used for the company's de novo analysis was stated in the first table of the CS.	CS, Table A1, p19-22
Are the outcomes of the model consistent with the perspective, scope and overall objective of the model?	✓	Outcomes relate to life-years, quality adjusted life years and costs. The outcomes and perspective of the model are in line with NICE guidance.	
S3 Rationale for structure			

Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	×	• The structural assumption that MSDs are available for all rescue transplants is not consistent with UK clinical practice. • The underlying message from the model is that all ADA-SCID patients without a matched related donor will be cured and return to general population mortality and morbidity due to Strimvelis, regardless of engraftment success, patient characteristics or prior health state. This is inconsistent with the data provided and the theory of the health condition. • No reference to how the structure and design of the model was informed • The models design suggests Strimvelis is chosen in its own right, prior to HLA-matching and without consideration of the patients' condition or availability and match of HSCT donors. In reality it is unclear when the decision to use Strimvelis is actually made in clinical practice. A better appreciation of the context in which the decision to use gene therapy is being made is required to appreciate the extent to which matching, prior condition and patient characteristics (e.g. infections, patient age, etc.) influence decision making and/or outcomes.	CS, p137-148
Are the sources of data used to develop the structure of the model specified?	×	The model was designed in line with the NICE reference case, from the perspective of the UK NHS and PSS. No details were provided in the main submission concerning the model conceptualisation process and the role of experts in validating the final model structure.	
Are the causal relationships described by the model structure justified appropriately?	✓	The causal relationship between Strimvelis and HSCT was justified but is highly uncertain given the limited non-randomised, single-arm, open label evidence available.	
S4 Structural assumptions			
Are the structural assumptions transparent and justified?	✓	Yes.	CS, Table D2 – p140-143
Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?	×	No. See S3.	CS, Table D2 – p140-143
S5 Strategies/comparators			
Is there a clear definition of the options under evaluation?	✓	Yes *"The model was used to estimate the costs and outcomes for patients treated with Strimvelis and to compare these estimates with the corresponding costs and outcomes of the current practice of HSCT from either a MUD or haploidentical donor."*	CS, p138

Have all feasible and practical options been evaluated?	✓	Yes. The only omitted treatment option for ADA-SCID patients without an MRD is long term enzyme replacement therapy.	CS, Table D2 – p140-143 & p36
Is there justification for the exclusion of feasible options?	✓	Yes. Long-term ERT is not seen as a preferred treatment option in England, as verified by expert clinical advice.	CS, Table D2 – p140-143 & p36
S6 Model type			
Is the chosen model type appropriate given the decision problem and specified causal relationship within the model?	✓	Yes.	
S7 Time horizon			
Is the time horizon of the model sufficient to reflect all important differences between options?	✓	The time horizon used in the model was 100 years, which is assumed to represent a lifetime horizon.	CS, Table D4 – p146-148
Are the time horizon of the model, the duration of treatment and the duration of treatment effect described and justified?	✓	**Time horizon:** The time horizon is in line with NICE guidance. **Duration of treatment:** The schedule of treatment used in the model is consistent with the marketing authorisation **Duration of treatment effect:** Strimvelis was assumed as having a treatment effect over a patients' lifetime from increasing the long-term survival of patients with ADA-SCID.	CS, Table D4 – p146-148
S8 Disease states/pathways			
Do the disease states or the pathways reflect the underlying biological process of the disease in question and the impact of interventions?	×	• The rescue therapy state defined by a two year delay followed by a HSCT MSD transplant is not consistent with UK clinical practice. • A high degree of uncertainty exists regarding the long-term survival of ADA-SCID patients. Assuming no mortality risk above the general population may omit for the risks of oncogenesis and metabolic conditions reported in other severe combined immune-deficiencies.	
S9 Cycle Length			
Is the cycle length defined and justified in terms of the natural history of disease?	✓	A cycle length of one year was used in the model (except for the first year, which consists of 2 cycles of 6 months). A 1-year cycle length was chosen in order to be consistent with the time frame for clinical assessment.	CS, Table D4 – p146-148 & p139

Data			
D1 Data identification			
Are the data identification methods transparent and appropriate given the objectives of the model?	✓	Yes **Need CRD's view on the SLR's**. Although no systematic search was conducted for resource use, lack of transparency over the papers deemed relevant in the HRQoL HSCT systematic literature review.	
Where choices have been made between data sources, are these justified appropriately?	✓	Due to limited sources of data this was not a significant issue. In instances when alternative sources were available (e.g. unit costs) justifications for the choice of data was lacking.	
Has particular attention been paid to identifying data for the important parameters in the model?	×	Insufficient attention was given to identifying data for the long-term survival of ADA-SCID patients, or for SCID patients, post HSCT/gene therapy. A greater emphasis on the role of oncogenesis and metabolic disturbances would have been beneficial. Given the large cost of PEG-ADA insufficient justification was given regarding its unit cost and dosages.	
Has the quality of the data been assessed appropriately?	×	**Clinical Effectiveness:** A critical appraisal of each trial was conducted by the company with the use of questions adapted from a Critical Appraisal Skills Programme (CASP) **Cost Studies:** Resource use studies were collected from a pragmatic literature search. Each source identified was not formally assessed for quality. **HRQoL Studies**: HRQoL studies were collected from a systematic literature search. Each source identified was not formally assessed for quality.	CS, p64-72
Where expert opinion has been used, are the methods described and justified?	×	Expert opinion has been sought throughout the CS, however no details were provided concerning the methods used or the specific questions asked.	
D2a Baseline data			
Is the choice of baseline data described and justified?	✓	Yes.	
Has a half-cycle correction been applied to both cost and outcome?	✓	No.	
D2b Treatment effects			

If the relative treatment effects have been derived from trial data, have they been synthesised using appropriate techniques?	×	The treatment effects were not derived from trial data.	
Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?	✓	Yes. The assumption that patients return to general population mortality and HRQoL is justified on the basis that Kaplan-Meier overall survival curves for patients who received HSCT from a MUD or haploidentical donor, do not show deaths after approximately 1 year and that expert clinical advice sought by the company confirmed the assumption that patients surviving beyond three years since the time of initial procedures will return to the HRQoL and mortality risk for the general population.	CS, p143
Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified?	✓	Strimvelis was assumed as having a treatment effect over a patients' lifetime from increasing the long-term survival of patients with ADA-SCID. The 100% survival of Strimvelis LTFU cohort, flat Kaplan-Meier curves one-year post-HSCT and expert clinical advice were given as evidence of the robust nature of survival which Strimvelis and HSCT offer.	CS, p143
Have alternative extrapolation assumptions been explored through sensitivity analysis?	✓	The company acknowledged the limited data available concerning ADA-SCID patients' long-term outcomes and as such provide an additional two-way sensitivity analysis to explore the uncertainty around the mean life expectancy and utility scores of ADA-SCID patients.	CS, Table D26 – p209
Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis.	✓	See above.	CS, Table D26 – p209
D2c Costs			
Are the costs incorporated into the model justified?	✓	Yes.	
Has the source of the costs been described?	✓	Resource use and costs included: Strimvelis unit price, administration and follow-up; management of an adverse events; HSCT costs (initial procedure and follow-up) and subsequent treatment costs.	CS, Table D5 – p156-164 & Table D8 – p169-172
Have the discount rates been described and justified given the target decision maker?	✓	The company has given justification for using a discount rate of 1.5% in the UK decision making context to minimise the differential impact of discounting on costs and benefits, the NICE Methods Guide states that in such cases when treatment restores people who would otherwise die to near full health over a very long period, a lower discount rate of 1.5% may be considered. 3.5% discount rates were presented as a scenario.	CS, Table D4 – p146-148 & p198, p203
D2d Quality of life weights			

Are the utilities incorporated into the model appropriate?	✓	Yes.	
Is the source of the utility weights referenced?	✓	All sources are referred and described.	CS, Table D5 – p156-164
Are the methods of derivation for the utility weights justified	✓	Yes	CS, Table D5 – p156-164
D3 Data incorporation			
Have all data incorporated into the model been described and referenced in sufficient detail?	✓	All data are referred and described.	CS, Table D5 – p156-164
Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate?)	NA		
Is the process of data incorporation transparent?	✓	Data is referenced explicitly in the company's model and incorporated with the value and within the chosen distributions mentioned in Table B13 of the CS.	CS, Table B13
If data have been incorporated as distributions, has the choice of distributions for each parameter been described and justified?	✓	The chosen distributions has been described (see above) but not justified.	CS, Table
If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?	✓	Yes, parameter uncertainty has been adequately addressed by the company. However, the company have not assessed first order uncertainty (on the count of limited data).	
D4 Assessment of uncertainty			
Have the four principle types of uncertainty been addressed? If not, has the omission of particular forms of uncertainty been justified?	✓	See below.	
D4a Methodological			
Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?	✓	Only the effect of alternative discount rates on the company ICER has been assessed. The impacts of alternative methodological uncertainties (e.g. dosing methods, application of a half cycle correction, etc.) were not assessed.	CS, p198, p203
D4b Structural			
Is there evidence that structural uncertainties have been addressed via sensitivity analysis?	✓	A wide range of scenarios and sensitivity analyses were conducted which provided meaningful evidence of the key drivers of cost-effectiveness and areas of uncertainty in the base case model.	CS, p197-212

D4c Heterogeneity			
Has heterogeneity been dealt with by running the model separately for different subgroups?	×	Due to the small sample size the company did not run any sub group analyses as it was deemed unlikely to provide clinically meaningful information. The final scope did not specify specific populations and subgroups.	
D4d Parameter			
Are the methods of assessment of parameter uncertainty appropriate?	✓	In line with the NICE reference case deterministic sensitivity analyses were performed on a series of model parameters. Probabilistic sensitivity analyses were also performed.	CS, p197-219
If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	✓	All range data is reported and incorporated as distributions.	CS, Table D13 p180-183
Consistency			
C1 Internal consistency			
Is there any evidence that the mathematical logic of the model has been tested thoroughly before use?	×		
C2 External consistency			
Are any counterintuitive results from the model explained and justified?	NA	The probabilistic ICER is significantly higher in the CS. This was due to a technical issue resolved in clarification with the ERG.	
If the model has been calibrated against independent data, have any differences been explained and justified?	NA		
Have the results of the model been compared with those of previous models and any differences in results explained?	NA		