

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Final appraisal document

Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years

1 Recommendations

- 1.1 Tisagenlecleucel therapy is recommended for use within the Cancer Drugs Fund as an option for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years, only if the conditions in the managed access agreement are followed.
- 1.2 This recommendation is not intended to affect both treatment in preparation for and treatment with tisagenlecleucel that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop. For young people aged under 18 years, this decision should be made jointly by the clinician and the young person, or the young person's parents or carers.

Why the committee made these recommendations

Current treatment for relapsed or refractory acute lymphoblastic leukaemia is usually blinatumomab or salvage chemotherapy.

Tisagenlecleucel is a CAR T-cell therapy. It contains the patient's own T cells that have been modified to attach to and kill cancer cells.

Clinical trial evidence suggests that compared with current treatment, people having tisagenlecleucel may live for longer, or have more time before their disease relapses. However, the evidence is uncertain and it is not known whether tisagenlecleucel can cure acute lymphoblastic leukaemia.

There is also not enough evidence to determine the costs of treating side effects and whether people will need a subsequent stem cell transplant.

The most plausible cost-effectiveness estimates for tisagenlecleucel are higher than what NICE normally considers acceptable. The life expectancy of people with relapsed or refractory acute lymphoblastic leukaemia is uncertain. It does not meet both of NICE's criteria to be a life-extending treatment at the end of life. Therefore tisagenlecleucel cannot be recommended for routine use in the NHS.

Collecting more data on overall survival, subsequent stem cell transplant rates, and immunoglobulin usage will reduce the uncertainty in the clinical- and cost-effectiveness evidence. Therefore tisagenlecleucel is recommended for use in the Cancer Drugs Fund.

2 Information about tisagenlecleucel

Marketing authorisation indication	<p>Tisagenlecleucel (Kymriah, Novartis) is indicated for treating 'paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse'.</p> <p>Tisagenlecleucel is an immunocellular CAR T-cell therapy. It contains the patient's own T cells (a type of white blood cell) that have been modified genetically in the laboratory so that they make a protein called chimeric antigen receptor (CAR). CAR can attach to another protein on the surface of cancer cells called CD-19. When tisagenlecleucel is given to the patient, the modified T cells attach to and kill cancer cells, thereby helping to clear the cancer from the body.</p>
Dosage in the marketing authorisation	<p>Treatment with tisagenlecleucel comprises a single-dose intravenous infusion of tisagenlecleucel. It is intended for autologous use only and at the following dosage:</p> <ul style="list-style-type: none"> • For patients ≤ 50 kg: 0.2 to 5.0×10^6 CAR-positive viable T cells per kg body weight. • For patients > 50 kg: 0.1 to 2.5×10^8 CAR-positive viable T cells (non-weight based).
Price	<p>The list price for tisagenlecleucel is £282,000 per infusion (company submission).</p> <p>The company has a managed access agreement including a commercial arrangement (patient access scheme). This makes tisagenlecleucel available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.</p>

3 Committee discussion

The appraisal committee ([section 6](#)) considered evidence submitted by Novartis and a review of this submission by the evidence review group (ERG). See the [committee papers](#) for full details of the evidence.

New treatment option

People with relapsed or refractory B-cell acute lymphoblastic leukaemia would welcome a new treatment option

- 3.1 Outcomes for people with relapsed or refractory B-cell acute lymphoblastic leukaemia are poor. The disease has low levels of response to treatment, and is associated with limited survival. Common symptoms include fatigue, breathlessness, infections, bleeding, bruising, fever and sweating. The patient experts explained that the cycle of remission and relapse when having successive treatments has a substantial psychological and physical effect on people with the disease and the people caring for them. They further explained that stem cell transplants are associated with a slow and laborious recovery over the course of around a year. The committee understood that chimeric antigen receptors (CAR) T-cell therapies (such as tisagenlecleucel) are advanced treatments for cancer and belong to a new generation of personalised cancer immunotherapies that are based on collecting and modifying patients' own immune cells to treat their cancer. The committee heard from the patient experts that treatment with CAR T-cell therapies involves intense and challenging side effects immediately after infusion, but can enable recovery within a few months. The committee concluded that people with relapsed or refractory acute lymphoblastic leukaemia would welcome new treatment options such as CAR T-cell therapies that improve the chance of survival.

Treatment pathway

The company's positioning of tisagenlecleucel in the pathway is appropriate

- 3.2 The company proposed 4 potential positions for tisagenlecleucel in the treatment pathway for this indication. Specifically, for use in people aged up to 25 years with B-cell acute lymphoblastic leukaemia:

- whose disease was refractory after 1 systemic chemotherapy ('primary refractory')
- whose disease was refractory after 2 systemic chemotherapies ('chemo-refractory')
- whose disease had relapsed after an allogeneic stem cell transplant
- whose disease had relapsed after 2 or more systemic chemotherapies.

The clinical experts indicated that survival outcomes for these groups of people were poor and agreed that they could potentially benefit from tisagenlecleucel. The committee accepted that the company's 4 proposed positions for tisagenlecleucel were consistent with its marketing authorisation. It noted that the marketing authorisation did not specify treatment based on Philadelphia chromosome status: having discussed this, the committee agreed that the marketing authorisation included both people with and without the Philadelphia chromosome. It agreed that the treatment pathways for Philadelphia chromosome-negative and Philadelphia chromosome-positive B-cell acute lymphoblastic leukaemia should be considered in more detail.

Blinatumomab and salvage chemotherapy are both appropriate comparators and blinatumomab is the main comparator

3.3 The clinical experts stated that the treatment pathway for B-cell acute lymphoblastic leukaemia was evolving, and that NICE's technology appraisal guidance on [inotuzumab ozogamicin as an option for treating B-cell acute lymphoblastic leukaemia](#) may change the treatment pathway. The committee noted that this was not included in the scope of this appraisal because it was not established clinical practice in the NHS when the final scope was issued. Patients with primary refractory Philadelphia chromosome-negative B-cell acute lymphoblastic leukaemia would currently have blinatumomab or salvage chemotherapy, with the aim of bridging to an allogeneic stem cell transplant. Salvage chemotherapy

includes FLA(G)-IDA (fludarabine, cytarabine and idarubicin, with or without granulocyte-colony stimulating factor). For patients whose disease responds to initial therapy and then relapses, or who have a second or further relapse, the aim of treatment is a further remission which can then be consolidated with an allogeneic stem cell transplant. As for patients with primary refractory disease, treatment options are blinatumomab and salvage chemotherapy with FLA(G)-IDA. The clinical experts stated that treatment with blinatumomab was more likely to enable a subsequent stem cell transplant than treatment with salvage chemotherapy, so blinatumomab was the preferred treatment option providing it had not already been used (for example, after first relapse for adults). If blinatumomab cannot be offered then salvage chemotherapy would be offered. The clinical experts also stated that in their opinion inotuzumab ozogamicin was likely to replace blinatumomab as a treatment option after first relapse in the treatment pathway, with blinatumomab likely to become the preferred subsequent treatment option for patients who have a second relapse. However, the committee accepted that there are little data on the use of blinatumomab after inotuzumab ozogamicin, and it noted that this lack of evidence may affect the choice of treatment. The committee also accepted that there is no biologically plausible reason why blinatumomab should not be effective when used after inotuzumab ozogamicin. It agreed that blinatumomab was the main treatment option for relapsed or refractory Philadelphia chromosome-negative B-cell acute lymphoma, and that some people would be offered salvage chemotherapy. The committee concluded that blinatumomab and salvage chemotherapy were both appropriate comparators and that blinatumomab was the main comparator.

Patient numbers are too small to analyse the clinical and cost effectiveness of tisagenlecleucel for Philadelphia chromosome-positive disease separately

3.4 Philadelphia chromosome-positive disease accounts for around 3% of B-cell acute lymphoblastic leukaemia. It is associated with poor outcomes and is treated differently to Philadelphia chromosome-negative disease:

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Issue date: November 2018

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most people have at least 2 tyrosine kinase inhibitors (TKIs), before then having salvage chemotherapy or best supportive care. The clinical and patient experts explained that patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia whose disease relapses after treatment TKIs could benefit from tisagenlecleucel and that outcomes were expected to be similar to patients with Philadelphia chromosome-negative disease. The committee noted that although the company did not present a treatment pathway for Philadelphia chromosome-positive disease, it stated in its submission that in clinical studies, patients could only have tisagenlecleucel if their disease had already relapsed after 2 TKIs, or they had stopped taking them. The committee also noted that the company did not present a separate clinical- and cost-effectiveness analysis for Philadelphia chromosome-positive disease because of the small population size; the tisagenlecleucel clinical studies included only 5 patients with Philadelphia chromosome-positive disease, and there are expected to be only 1 or 2 patients per year in England. The committee concluded that the company's positioning of tisagenlecleucel for Philadelphia chromosome-positive disease based on clinical study eligibility was appropriate and acknowledged that patient numbers were too small for clinical- and cost-effectiveness in this population to be analysed separately.

Clinical evidence

Tisagenlecleucel is clinically effective but the lack of comparator data means the benefit compared with blinatumomab or salvage chemotherapy is unknown

3.5 The main evidence on the clinical effectiveness of tisagenlecleucel came from 3 single-arm studies:

- ELIANA, an international, multicentre, phase II study (n=97)
- ENSIGN, a US, multicentre, phase II study (n=73)

- B2101J, a US, single-centre, phase I/IIa study (n=66).

The company pooled results from all patients in the studies who had tisagenlecleucel (n=193). The clinical experts indicated that although patient numbers in the primary refractory and Philadelphia chromosome-positive populations were small, outcomes were expected to be similar to the overall pooled study population. Outcomes of each study included overall remission rate, overall survival, event-free survival and adverse events of treatment. The pooled analysis and full results from the ELIANA and B2101J studies are considered to be academic in confidence by the company and cannot be reported here. However, results from earlier analyses of the trials have been reported (ELIANA: Maude, Laetsch et al. 2018; B2101J: Maude, Grupp et al. 2018) so these results are reported here. Results from the individual studies showed that tisagenlecleucel was effective in inducing remission and improving survival for patients with B-cell acute lymphoblastic leukaemia (table 1). The committee heard from clinical experts that the results of the studies were generalisable to clinical practice, although the experts noted that clinicians were more likely to offer tisagenlecleucel to patients with a higher Karnofsky/Lansky performance status, who would be more likely to tolerate the bridging chemotherapy regimen and the potential adverse effects. The committee noted that there was no clinical evidence directly comparing tisagenlecleucel with blinatumomab or salvage chemotherapy because all 3 trials were single-arm studies. It concluded that tisagenlecleucel was clinically effective, but agreed that the lack of comparative data made the assessment of comparative effectiveness (and any cost-effectiveness analyses) more challenging.

Table 1 Efficacy outcomes for people who had tisagenlecleucel

	ELIANA n=75	ENSIGN n=58 (42 for overall remission rate)	B2101J n=59
Source	Maude, Laetsch et al. 2018*	Company submission	Maude, Grupp et al. 2018*
Overall remission rate: proportion of patients (95% CI)	81 (71 to 89)	69 (53 to 82)	93 (NR)
Median overall survival: months (95% CI)	NE	23.8 (9 to NE)	NR
Survival at 12 months: proportion of patients (95% CI)	76 (63 to 86)	63 (46 to 76)	79 (69 to 91)
Abbreviations: CI, confidence interval; NE, not estimable; NR, not recorded. * Data are from an earlier analysis than presented in the company submission and are not used in the economic modelling.			

Clinical evidence for tisagenlecleucel beyond 30 months is very uncertain because of small patient numbers and differences in the trial populations

3.6 The median follow-up in each study was less than 3 years, and after around 30 months survival estimates were based on less than 15 patients at risk, who were exclusively from the B2101J study. The committee noted that the patient population in B2101J was different to those in ELIANA and ENSIGN: patients in B2101J typically had a higher Karnofsky/Lansky performance status (that is, were in better health), were more likely to have already had an allogeneic stem cell transplant and were eligible for up to 3 infusions of tisagenlecleucel instead of 1. The committee concluded that because of the small patient numbers and the differences between study populations, the clinical evidence for tisagenlecleucel beyond 30 months was very uncertain.

There is no robust evidence that tisagenlecleucel has a curative effect

3.7 The clinical experts explained that tisagenlecleucel would be offered with the intent of curing relapsed or refractory B-cell acute lymphoblastic leukaemia. It was aware that a common assumption in oncology clinical trials of treatments given with curative intent is that people who survive for an arbitrary time period (typically 5 years) could be considered to be

long-term survivors, and effectively cured. The clinical experts considered that it may be appropriate to assume that patients in the population under consideration who survive for 3 years could be considered to be cured. Having acknowledged that survival estimates beyond 30 months were highly uncertain (see [section 3.6](#)) the committee concluded that with an assumed cure point of either 3 or 5 years, there was not robust evidence that tisagenlecleucel has a curative effect.

There is no clinical evidence on the efficacy of tisagenlecleucel after treatment with blinatumomab

3.8 The committee was aware that all 3 tisagenlecleucel studies excluded patients who had already had blinatumomab, and that in NHS clinical practice patients may have blinatumomab after first disease relapse (see [section 3.3](#)). The clinical experts explained that up to 20% of patients who relapse after having blinatumomab may become CD-19-negative, meaning they would be unlikely to benefit from tisagenlecleucel after second disease relapse. However, they noted that in clinical practice patients would have blinatumomab for up to 2 cycles: this means that CD-19-negative relapse would be unlikely, and so treatment with tisagenlecleucel after blinatumomab may be effective. The committee was aware that the [summary of product characteristics](#) states that tisagenlecleucel is not recommended if the disease has relapsed with CD-19-negative leukaemia after previous anti-CD-19 therapy (such as blinatumomab). The committee concluded that there was no clinical evidence to determine if tisagenlecleucel would be effective after treatment with blinatumomab, and that this added uncertainty around the generalisability of the results to clinical practice.

Despite limitations, the von Stackelberg et al. (2016) study is an appropriate source of data for the efficacy of blinatumomab

3.9 The evidence for the efficacy of blinatumomab came from a phase II trial in 70 patients aged under 18 years with relapsed or refractory B-cell acute lymphoblastic leukaemia (von Stackelberg et al. 2016). The study

population consisted of patients who were primary refractory, in first relapse after full salvage induction regimen, in second or later relapse or in any relapse after allogeneic stem cell transplantation. The patient population differed from that of the tisagenlecleucel studies: the tisagenlecleucel studies recruited patients up to the age of 25 years, whereas von Stackelberg et al. only recruited patients aged under 18 years. The committee noted that the 2 studies differed in several important prognostic factors, including the proportion of primary refractory patients, percentage of bone marrow blasts, number of previous treatments and time since last relapse. The committee acknowledged that patients in von Stackelberg et al. may therefore have had more progressive disease at baseline than patients in the tisagenlecleucel studies. The committee also noted that the median overall survival of 7.5 months in von Stackelberg et al. was lower than the overall survival of 9.9 months reported for patients aged 18 to 35 years (n=123) in the TOWER study of blinatumomab (the TOWER study was the main source of evidence used to inform NICE's technology appraisal guidance on [blinatumomab for previously treated Philadelphia chromosome-negative acute lymphoblastic leukaemia](#)). The committee acknowledged that this may indicate that patients in von Stackelberg et al. may have worse outcomes than would be expected for blinatumomab in clinical practice. It also noted that patients were followed up for 2 years and that no survival data were available beyond this point. Despite these limitations, the committee concluded that because neither the ERG nor the company presented a suitable alternative data source for the efficacy of blinatumomab, it was appropriate to consider von Stackelberg et al. in its decision-making.

Jeha et al. (2006) and Kuhlen et al. (2017) should both be considered as sources of data for the efficacy of salvage chemotherapy

3.10 The company's systematic literature review did not identify any evidence for the efficacy of FLA(G)-IDA salvage chemotherapy. Instead, the company used clofarabine monotherapy as a proxy for salvage

chemotherapy. It provided evidence from a phase II study of clofarabine monotherapy in 61 patients aged under 21 years with relapsed or refractory B-cell acute lymphoblastic leukaemia (Jeha et al. 2006). The study reported an overall remission rate of 20% and median overall survival of 13 weeks. The clinical experts explained that clofarabine monotherapy was not used in clinical practice in the NHS because of concerns over increased toxicity compared with other treatment options. However, they noted that the efficacy of clofarabine was similar to that of FLA(G)-IDA, so it was plausible that data from Jeha et al. for clofarabine could be used as a proxy for salvage chemotherapy. The committee was aware of a submission from NHS England which stated that clinical practice had changed since the publication of Jeha et al., and that outcomes in the study were likely to be worse than in clinical practice because supportive care and the availability and speed of access to stem cell donors have since improved. The ERG identified 2 studies, published after the company's submission, which contained evidence on the efficacy of FLA-IDA. The most recent of these was a retrospective analysis of 242 UK children with B-cell acute lymphoblastic leukaemia in first relapse after allogeneic stem cell transplant (Kuhlen et al. 2017). The committee noted that the 3-year probability of overall survival reported in Kuhlen et al. was 20%. The committee also noted that the ERG considered that the much larger sample size and longer follow-up provided a more reliable and robust dataset compared with Jeha et al. However, the committee recalled that the ERG had highlighted several differences in prognostic factors between the tisagenlecleucel studies and Kuhlen et al. Factors which may underestimate survival for salvage chemotherapy compared with tisagenlecleucel include: a higher rate of previous allogeneic stem cell transplant; a higher rate of patients having only palliative care; and the inclusion of patients with T-cell acute lymphoblastic leukaemia or whose disease has relapsed less than 6 months after allogeneic stem cell transplant. Factors which may overestimate survival for salvage chemotherapy compared with tisagenlecleucel include: a higher

proportion of patients in first relapse and the inclusion of patients with extramedullary relapse. The committee accepted that both Jeha et al. and Kuhlen et al. had a number of limitations, but concluded that that it was appropriate to consider both studies in its decision-making.

The efficacy of tisagenlecleucel compared with blinatumomab and salvage chemotherapy is based on naive indirect comparisons which are uncertain

3.11 The company did a matching adjusted indirect treatment comparison to attempt to adjust prognostic factors in the pooled population of the 3 single-arm tisagenlecleucel studies to match those in the von Stackelberg et al. and Jeha et al. studies. Factors adjusted for were the number of previous relapses, median number of months since last relapse and proportion of patients with previous allogeneic stem cell transplant. The ERG highlighted that several other important prognostic factors could not be adjusted for, including median age, geographic region, genetic abnormalities and proportion of primary refractory patients. How adjusting these factors (had it been possible) may have affected the outcome of the matching adjusted treatment comparison was unclear. The results of the comparison are academic in confidence and cannot be reported here. However, the committee noted that the company did not use the data from the matching adjusted treatment comparison in its base-case economic analysis. The committee concluded that using a naive indirect treatment comparison was appropriate, but was subject to uncertainty as a result of the differences in the trial populations.

Subsequent stem cell transplant

The number of patients who would have an allogeneic stem cell transplant after having tisagenlecleucel is highly uncertain

3.12 The clinical experts explained that in current NHS practice, patients in first or second relapse have allogeneic stem cell transplants if they are considered eligible. The NHS England clinical commissioning expert confirmed that patients who have had a previous allogeneic stem cell

transplant and go on to relapse can be offered a second allogeneic stem cell transplant if they are in remission and their relapse occurred more than 1 year after their first transplant. NHS England estimated that the rate of allogeneic stem cell transplant was 15% to 20% after salvage chemotherapy and at least 24% after blinatumomab. Treatment with tisagenlecleucel is intended to be curative: that is, patients whose disease responds to treatment with tisagenlecleucel would not be expected to need a subsequent stem cell transplant. However, some patients in the tisagenlecleucel studies had subsequent allogeneic stem cell transplants; for example, interim analyses of the ELIANA study showed that of patients having tisagenlecleucel, 11% had a subsequent allogeneic stem cell transplant. The company provided an estimate of the rate of allogeneic stem cell transplant based on pooled data from the most recent data cuts of the tisagenlecleucel studies (the data are considered confidential and cannot be reported here), but this may not reflect clinical practice in the NHS. The committee concluded that the number of patients who would need an allogeneic stem cell transplant after tisagenlecleucel is highly uncertain.

Adverse events

The most common adverse reaction is cytokine release syndrome

3.13 The company provided an analysis of the adverse events for each of the 3 tisagenlecleucel studies. The analyses were considered to be academic in confidence by the company and cannot be reported here, but the [summary of product characteristics](#) includes details of some adverse events. The most common non-haematological adverse reactions were cytokine release syndrome (77%), infections (65%), hypogammaglobulinaemia (47%), pyrexia (40%) and decreased appetite (39%). Grade 3 and 4 adverse reactions were reported in 88% of patients. The most common grade 3 and 4 non-haematological adverse reaction was cytokine release syndrome (47%). NHS England's clinical lead for the Cancer Drugs Fund explained that cytokine release syndrome occurs

soon after treatment with tisagenlecleucel. Mild or moderate cytokine release syndrome needs considerable observation and supportive care but more severe cytokine release syndrome needs full intensive care and treatment with tocilizumab and steroids. It noted that treatment strategies for these side effects are described in tisagenlecleucel's [summary of product characteristics](#) and in the risk management plan that is part of the marketing authorisation. The committee was also aware that tocilizumab has a marketing authorisation for treating CAR T-cell-induced severe or life-threatening cytokine release syndrome in people aged 2 years and older. NHS England's clinical lead for the Cancer Drugs Fund explained that there is great need for staff training because the symptoms of cytokine release syndrome are so diverse and unexpected. The committee concluded that cytokine release syndrome is a common toxicity associated with tisagenlecleucel and the costs associated with managing and treating it should be reflected in the cost-effectiveness modelling.

It is unknown how many patients will need intravenous immunoglobulin treatment for B-cell aplasia and for how long

3.14 The committee noted that most people having tisagenlecleucel in clinical trials would have B-cell aplasia. The clinical experts noted that current practice in clinical trials was for prophylactic treatment with intravenous immunoglobulin (IVIG) for B-cell aplasia, but that the clinical effectiveness of this approach had not been studied. Long-term treatment for B-cell aplasia with IVIG would only be considered for patients with concurrent infections, but there are not enough data on the rate of infections to determine how often long-term treatment is needed. The clinical experts indicated that an assumption of 50% of patients having IVIG over 1 to 2 years as proposed by NHS England was reasonable, but was based on current practice rather than clinical evidence. One expert suggested that treatment may only last for 3 to 12 months. The committee concluded that it was unknown how many patients would need IVIG treatment for B-cell aplasia and for how long.

The company's economic model

The structure of the company's model is appropriate for decision-making

3.15 The company used a partitioned-survival economic model for all treatments that included 3 states: event-free, progressed disease and death. Before entering the partitioned-survival part of the model, patients having tisagenlecleucel also progressed through a decision tree to capture outcomes for patients who discontinued treatment or died before having tisagenlecleucel. The model contained a structural assumption that after 5 years, general population health-related quality-of-life and costs were applied. The committee concluded that the structure of the company's model was appropriate for its decision-making.

Blinatumomab is the main comparator to consider in the economic modelling

3.16 The committee recalled that blinatumomab and salvage chemotherapy were both appropriate comparators and that blinatumomab is preferred to salvage chemotherapy for treating relapsed or refractory B-cell acute lymphoblastic leukaemia (see [section 3.3](#)). The committee therefore concluded that blinatumomab and salvage chemotherapy should both be considered as comparators in the economic model and that blinatumomab was the main comparator.

Survival modelling in the economic model

The extrapolation of overall survival for tisagenlecleucel is an important source of uncertainty in the economic model

3.17 The company stated in its submission that using simple parametric survival curves or spline models to model overall survival for tisagenlecleucel produced curves with poor statistical and visual fit. The committee considered the company's preferred extrapolation of overall survival for tisagenlecleucel. It noted the use of a mixture cure model with the exponential distribution to estimate a cure fraction (that is, the proportion of patients cured). After infusion, the cured patients were

immediately restored to the age- and gender-matched mortality of the general UK population adjusted for increased mortality in the acute lymphoblastic leukaemia population using a multiplier of 9.05 from MacArthur et al. (2007). Uncured patients followed the parametric survival curve from the time of infusion. The committee noted that the cure fraction for overall survival was a major driver of the cost-effectiveness estimates, and that it varied by approximately 35% in the company's exploratory analyses (the cure fractions are considered confidential and cannot be reported here). The committee was aware that the ERG used the log-logistic distribution in its base case, because the cure fraction for overall survival estimated by the exponential function exceeded the percentage of event-free survival events in the tisagenlecleucel trials and was therefore a less plausible assumption. It also noted that when the ERG did a scenario analysis using the log-normal distribution, which estimated the lowest cure fraction, the incremental cost-effectiveness ratio (ICER) compared with the ERG's deterministic base-case results increased by £16,567 per quality-adjusted life year (QALY) gained for the comparison with blinatumomab and £28,925 for the comparison with salvage chemotherapy. The committee noted that the variance in cure fraction reflected the lack of long-term survival data (see [section 3.6](#)). It also recalled that there was no robust evidence to support the underlying assumption of tisagenlecleucel having a curative effect (see [section 3.7](#)). It concluded that the extrapolation of overall survival for tisagenlecleucel is an important source of uncertainty in the economic model.

Estimates of long-term survival with blinatumomab are subject to uncertainty

3.18 The company also used the mixture cure method to extrapolate the overall survival curve for blinatumomab, and chose a log-normal distribution in its analysis. The ERG noted that, as with tisagenlecleucel (see [section 3.17](#)), modelling overall survival using this approach is subject to uncertainty and produced cure fractions ranging from 4% to 22%. It preferred the log-logistic distribution because this more closely matched the survival curve in the appraisal of [blinatumomab](#). The

committee was also aware that a naive comparison of the blinatumomab curve with the tisagenlecleucel curve was subject to uncertainty because of differences between the trial populations (see [section 3.11](#)). The committee accepted the ERG's approach but concluded that estimates of long-term survival with blinatumomab are subject to uncertainty.

Long-term overall survival with salvage chemotherapy is underestimated by the company's approach and overestimated by the ERG's approach

3.19 The company's extrapolation of overall survival used a standard parametric model with a generalised gamma distribution based on data from Jeha et al. (2006). The ERG preferred to base its extrapolation on data from Kuhlen et al. (2017; see [section 3.10](#)). It also preferred to use a mixture cure model because this was consistent with the method of extrapolation used for tisagenlecleucel and blinatumomab. The ERG chose the log-normal distribution as the best fitting distribution. When the ERG did a scenario analysis using the log-normal distribution and incorporating adverse event and allogeneic stem cell transplant rates from Kuhlen et al. (2017), the ICER compared with the company's deterministic base-case result for salvage chemotherapy increased by £8,758 per QALY gained. The clinical experts and the Cancer Drugs Fund clinical lead both indicated that the estimated long-term survival would likely be between the values predicted by the base-case modelling assumptions of the company and ERG. The committee concluded that there was a substantial degree of uncertainty in the extrapolation of overall survival for salvage chemotherapy and that it was underestimated by the company's approach and overestimated by the ERG's approach. It agreed that the most plausible estimate for long-term overall survival would be somewhere between the values predicted by the 2 models.

The ERG's correction to the company's approach to modelling long-term mortality in the mixture cure model is appropriate

3.20 The ERG noted an apparent error in the company's model whereby the modelled overall survival could not deviate from the curve predicted by the

mixture cure model. This implied that the long-term mortality of patients was lower than that of the general population and lower than observed in epidemiological studies of long-term survivors of acute lymphoblastic leukaemia in some periods of the model. In a small number of scenarios it also led the model to make inconsistent predictions; for example, patients would come back to life. The company stated that its approach was intended and that it reflected the most appropriate estimates of survival in both the cured and uncured fractions. The committee considered that the long-term mortality curve predicted by the ERG's model was more plausible and therefore concluded that the ERG's correction to the company's model was appropriate.

Costs in the economic model

It is appropriate to assume that patients would have 2 cycles of blinatumomab

3.21 The company's model included the assumption that patients could have up to 5 cycles of blinatumomab. However, clinical advice to the ERG indicated that in clinical practice, patients would only have 2 cycles of blinatumomab and the ERG preferred to incorporate this assumption into its model. The committee recalled that it too had heard expert advice that patients would usually only have 2 cycles of blinatumomab (see [section 3.8](#)). It concluded that it was appropriate to assume patients would have 2 cycles of blinatumomab.

The rate of allogeneic stem cell transplant after tisagenlecleucel has a substantial effect on the cost-effectiveness estimates

3.22 The rate of subsequent allogeneic stem cell transplant in the company's base-case model was taken from pooled results of the tisagenlecleucel studies (see [section 3.12](#)). The company considered that this may be higher than the rate in NHS clinical practice. The committee recalled its previous conclusions that the rate of allogeneic stem cell transplant in clinical practice is highly uncertain and would depend on whether tisagenlecleucel was a curative therapy. It noted that an ERG scenario

analysis decreased the ICERs for tisagenlecleucel in the ERG's deterministic base-case compared with both blinatumomab and salvage chemotherapy by around £4,000 per QALY gained when it was assumed that no patients had a subsequent allogeneic stem cell transplant. It also noted that if tisagenlecleucel were considered as a bridge to allogeneic stem cell transplant (that is, assuming that all patients have a subsequent allogeneic stem cell transplant), the ICERs increased by around £20,000 per QALY gained. The committee was aware that this represented the maximum possible increase in the ICER based on rate of subsequent stem cell transplant and that any increase could be substantially lower. Based on this, it concluded that the rate potentially has a substantial effect on the cost-effectiveness estimates.

The cost of intravenous immunoglobulin treatment for B-cell aplasia is uncertain

3.23 The company's economic model assumed that patients having IVIG for B-cell aplasia would have treatment for around 1 year. The ERG considered that this was an overestimate, because not all patients with B-cell aplasia would have IVIG. It also considered that patients may be treated for longer than 1 year. Therefore, the ERG's base-case assumed that a smaller proportion of patients (that is, only those with hypogammaglobulinaemia) had IVIG. It also examined different lengths of treatment in scenario analyses, with ICERs increasing by around £3,000 per QALY gained for a treatment length of 3 years. The committee also considered a scenario analysis in which all patients in the event-free survival state in the model with hypogammaglobulinaemia had IVIG treatment indefinitely, which increased the ICERs by around £13,000 per QALY gained. It agreed that this scenario was likely to overestimate the costs of IVIG treatment because it resulted in a mean treatment length of 6.5 years, which was longer than that anticipated by both NHS England and the clinical experts. The committee noted that the ERG's base case was more closely aligned with assumptions proposed by NHS England and concluded that the ERG's assumptions were more plausible than the

company's. It also recalled its previous conclusion that the extent of IVIG treatment in NHS clinical practice was unknown (see [section 3.14](#)). It therefore concluded that the cost of IVIG treatment for B-cell aplasia after tisagenlecleucel was uncertain, but that it would affect the cost-effectiveness estimates.

Cost-effectiveness estimate

The assumptions in the ERG's base case are more appropriate than those in the company's

3.24 The committee noted that the ERG's base-case model was more closely aligned with several of its preferred assumptions, specifically:

- choosing an overall survival extrapolation for tisagenlecleucel in which the cure fraction in the mixture cure model did not exceed the probability of event-free survival from the clinical trials (see [section 3.17](#))
- incorporating the ERG's correction to the long-term mortality rate (see [section 3.20](#))
- assuming that patients have 2 cycles of blinatumomab (see [section 3.21](#))
- assuming that IVIG treatment for B-cell aplasia is only given to patients with hypogammaglobulinaemia (see [section 3.23](#)).

The committee concluded that the ERG's base case was more appropriate for its decision-making than the company's.

The most plausible ICERs compared with blinatumomab are above £30,000 per QALY gained

3.25 The committee recalled that there was a high degree in uncertainty in the estimates of overall survival for tisagenlecleucel and blinatumomab because of the length of follow-up in the tisagenlecleucel studies (see [sections 3.6](#) and [3.7](#)), use of a naive indirect treatment comparison (see [section 3.11](#)) and choice of overall survival extrapolations for both

tisagenlecleucel and blinatumomab (see [sections 3.17](#) and [3.18](#)). It also recalled that it preferred the ERG's base case for decision-making (see [section 3.24](#)). The committee noted that the ERG's probabilistic base-case ICER for tisagenlecleucel (incorporating the patient access scheme) compared with blinatumomab was £29,501 per QALY gained, whereas the company's probabilistic base-case ICER was £20,046 per QALY gained. The committee recalled that the extrapolation of overall survival for tisagenlecleucel was an important source of uncertainty in the model (see [section 3.17](#)). It agreed that the ERG's exploratory scenario analysis which used a log-normal cure model for overall survival for tisagenlecleucel was plausible, and noted that the deterministic ICER for tisagenlecleucel increased to £44,299 per QALY gained in this scenario. It was also aware that the ICER was likely to increase by around £2,000 per QALY gained if a probabilistic analysis was used. It noted that all ICERs increased when the commercial arrangements for blinatumomab (the comparator) and tocilizumab (used to treat cytokine release syndrome) were taken into account. These ICERs cannot be reported as the simple discounts on the list price of blinatumomab and tocilizumab are commercial in confidence. The committee concluded the most plausible ICERs for tisagenlecleucel compared with blinatumomab when taking into account all the patient access scheme discounts were over £30,000 per QALY gained.

The most plausible ICERs compared with salvage chemotherapy are above £45,000 per QALY gained

3.26 The committee recalled that there was a high degree in uncertainty in the estimates of overall survival for tisagenlecleucel and salvage chemotherapy because of the length of follow-up in the tisagenlecleucel studies, use of a naive indirect treatment comparison and choice of overall survival extrapolations for both tisagenlecleucel and salvage chemotherapy (see section 3.25). It recalled that it preferred the ERG's base case and in particular its preference for use of a mixture cure model for consistency with the modelling of the other comparators (see [section](#)

[3.20](#)). It therefore only considered alternative extrapolations using the mixture cure model. The committee noted that the ERG's probabilistic base-case ICER for tisagenlecleucel (incorporating the patient access scheme) compared with salvage chemotherapy was £48,265 per QALY gained and that this was higher than the company's probabilistic base case of £27,066 per QALY gained. The committee recalled that the extrapolation of overall survival for tisagenlecleucel was an important source of uncertainty in the model (see [section 3.17](#)). The committee agreed that the ERG's exploratory scenario analysis which used a log-normal cure model for overall survival for tisagenlecleucel was plausible and noted that the deterministic ICER for tisagenlecleucel increased to £74,322 per QALY gained in this scenario. It was also aware that the ICER was likely to increase by around £3,000 per QALY gained if a probabilistic analysis was used. It noted that the ICERs slightly decreased when the commercial arrangement for tocilizumab (used to treat cytokine release syndrome) was taken into account. These ICERs cannot be reported as the simple discount on the list price of tocilizumab is commercial in confidence. The committee concluded that the most plausible ICERs for tisagenlecleucel compared with salvage chemotherapy, when taking into account all patient access scheme discounts, were over £45,000 per QALY gained.

Costs of subsequent allogeneic stem cell transplant and treatment for B-cell aplasia are uncertain and may have a substantial impact on cost-effectiveness estimates

3.27 The committee recalled that the likely costs of subsequent allogeneic stem cell transplants and B-cell aplasia after treatment with tisagenlecleucel were both uncertain (see [sections 3.22](#) and [3.23](#)). It noted that changes to the assumptions that underpin these costs could have a substantial effect on the ICERs. The committee concluded that in addition to survival estimates, the costs of subsequent allogeneic stem cell transplant and treatment for B-cell aplasia were important sources of uncertainty in the model.

Innovation

Tisagenlecleucel is innovative but there are no additional benefits that have not been captured in the analysis

3.28 The committee considered tisagenlecleucel to be innovative because it represents a step-change in the treatment of relapsed or refractory B-cell acute lymphoblastic leukaemia. The company's submission stated that substantial positive effects for patients and caregivers, such as allowing return to work or employment, had not been captured in the economic analysis. The committee was mindful that the effect of tisagenlecleucel on employment were outside NICE's reference case, which specifies that the costs and benefits of a technology should be considered from the perspective of the NHS and personal social services. It noted that tisagenlecleucel was granted eligibility as a priority medicine through the European Medicines Agency's PRIME scheme. The committee concluded that there are no additional benefits that had not been captured in the economic analysis.

Discount rate

A discount rate of 3.5% should be applied for costs and benefits

3.29 The committee discussed the use of the alternative discount rate. A discount rate of 1.5% for costs and benefits may be considered by the committee when treatment effects are both substantial in restoring health and sustained over a very long period (normally at least 30 years), and if the committee is satisfied that the introduction of the technology does not commit the NHS to substantial irrecoverable costs. The committee noted that tisagenlecleucel appeared clinically effective, but recalled its previous conclusion that there was no robust evidence that tisagenlecleucel was a curative therapy (see [section 3.7](#)). The committee concluded that the reference case should use a discount rate of 3.5% for both costs and benefits.

End of life

Tisagenlecleucel does not meet both criteria to be considered a life-extending treatment at the end of life because the life expectancy evidence is uncertain

3.30 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's [Cancer Drugs Fund technology appraisal process and methods](#). The committee considered whether the life expectancy of people having standard care for relapsed or refractory B-cell acute lymphoblastic leukaemia was less than 24 months. It recalled that treatment was offered with the expectation that some patients would have a subsequent allogeneic stem cell transplant and potentially be cured. The median overall survival for this patient population was 7.5 months in the study of blinatumomab (von Stackelberg et al. 2016) and 13 weeks in the study used as a proxy for salvage chemotherapy (Jeha et al. 2006). It noted the company's and ERG's base-case results for undiscounted mean overall survival (results are considered commercial in confidence by the company and cannot be reported here). The committee was aware that the mean survival estimates from the economic model were driven by the proportion of long-term survivors (that is, patients alive after 5 years in the model). The clinical experts explained that the life expectancy of people who were not long-term survivors after having blinatumomab or salvage chemotherapy would be close to the median life expectancy from the clinical studies. The committee noted that around 15% of patients having blinatumomab were long-term survivors in both the company's and ERG's base-case analyses. For salvage chemotherapy, the proportions of long-term survivors were 16% in the ERG's model and 8% in the company's model. Both the company's and the ERG's models predicted a mean overall survival of much longer than 24 months for blinatumomab. The committee noted that the company's model predicted a mean overall survival of less than 24 months for people having salvage chemotherapy, whereas the ERG model predicted a mean overall survival of much longer than 24

months. The committee agreed that there was a high degree of uncertainty around the overall survival extrapolations for both blinatumomab and salvage chemotherapy (see [sections 3.17](#) and [3.18](#)). It also recalled further uncertainties around the short survival follow-up for blinatumomab and the choice of data source for the efficacy of salvage chemotherapy (see [sections 3.9](#) and [3.10](#)). Taking into account the undiscounted mean overall survival estimates, the high degree of uncertainty around the estimates and its conclusion that most patients would have blinatumomab, the committee concluded that the life expectancy criterion was not met but acknowledged that there was considerable uncertainty around this estimate. The committee then considered if tisagenlecleucel met the criterion for providing an extension to life of more than 3 months. It noted that the median overall survival for tisagenlecleucel was over 23 months in all 3 tisagenlecleucel trials. Furthermore, both the company's and the ERG's modelling suggested that tisagenlecleucel was associated with a gain in overall survival of over 8 years compared with both blinatumomab and salvage chemotherapy (irrespective of the choice of salvage chemotherapy data). The committee concluded that although tisagenlecleucel met this criterion, it did not meet both of NICE's criteria to be considered a life-extending treatment at the end of life when compared with blinatumomab and salvage chemotherapy.

Conclusion

Tisagenlecleucel is not recommended for routine use for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years

3.31 The committee recalled that although the precise life expectancy of people with relapsed or refractory B-cell acute lymphoblastic leukaemia was uncertain, tisagenlecleucel did not meet the end-of-life criteria (see [section 3.30](#)). It also recalled that the size of the clinical benefit compared with blinatumomab or salvage chemotherapy was uncertain (see [section 3.5](#)) and that it is not yet known whether tisagenlecleucel is a curative

therapy (see [section 3.7](#)). The most plausible ICERs for tisagenlecleucel compared with both blinatumomab and salvage chemotherapy were above £30,000 per QALY gained (see [sections 3.25](#) and [3.26](#)). The committee therefore concluded that it could not recommend tisagenlecleucel for routine use in the NHS to treat relapsed or refractory B-cell acute lymphoblastic leukaemia.

Cancer Drugs Fund

Further data collection could address uncertainties in the clinical and cost-effectiveness evidence

3.32 Having concluded that tisagenlecleucel could not be recommended for routine use, the committee then considered if it could be recommended for treating relapsed or refractory B-cell acute lymphoblastic leukaemia within the Cancer Drugs Fund. The committee discussed the arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting the [addendum to the NICE process and methods guides](#). The committee recognised that tisagenlecleucel is an innovative treatment and therefore it considered whether clinical uncertainty associated with tisagenlecleucel could be addressed through collecting more data. The committee was aware that more data from ELIANA, ENSIGN and B2101J will become available for tisagenlecleucel over time. It agreed that:

- Further data on overall survival would be a valuable addition to the clinical evidence base and would likely resolve uncertainties around length of overall survival and if tisagenlecleucel could be considered a curative treatment.
- With further evidence, it may be possible to gain a more complete understanding of the costs of subsequent allogeneic stem cell transplant and treatment for B-cell aplasia.

- Using tisagenlecleucel in the NHS would allow data to be collected which more accurately reflect the costs and benefits of its use in clinical practice.

Tisagenlecleucel meets the criteria for use in the Cancer Drugs Fund for this indication in people who would have blinatumomab

3.33 Having acknowledged that blinatumomab was the most common treatment option for relapsed or refractory B-cell acute lymphoblastic leukaemia, the committee first considered if tisagenlecleucel met the criteria to be considered for inclusion in the Cancer Drugs Fund when compared with blinatumomab. It noted that the most plausible ICER for tisagenlecleucel compared with blinatumomab was over £30,000 per QALY gained. The committee acknowledged that all the ICERs for tisagenlecleucel compared with blinatumomab were associated with a high degree of uncertainty, and concluded that tisagenlecleucel had the plausible potential to satisfy the criteria for routine use if this uncertainty could be reduced. The committee recognised that more long-term survival data for tisagenlecleucel and further data on the rate of subsequent allogeneic stem cell transplants would allow for a more robust cost-effectiveness estimate. It noted that if the rate of allogeneic stem cell transplant was lower in clinical practice then the ICERs would decrease. The committee agreed that tisagenlecleucel met the criteria to be included in the Cancer Drugs Fund for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years who would have blinatumomab.

The use of salvage chemotherapy is likely to decline so a recommendation in patients who would currently have salvage chemotherapy is not needed

3.34 The committee considered whether tisagenlecleucel met the criteria to be considered for inclusion in the Cancer Drugs Fund when compared with salvage chemotherapy. It recalled that the most plausible ICERs for tisagenlecleucel compared with salvage chemotherapy were above £45,000 per QALY gained. The committee acknowledged that all the

ICERs for tisagenlecleucel compared with salvage chemotherapy were associated with a high degree of uncertainty, and concluded that tisagenlecleucel did not have the plausible potential to satisfy the criteria for routine use. The committee recalled that inotuzumab ozogamicin will likely replace blinatumomab after first disease relapse, and that blinatumomab will replace salvage chemotherapy after second disease relapse (see [section 3.3](#)). The committee therefore agreed that it would not make a distinction between people who would currently have blinatumomab or salvage chemotherapy in its recommendations, because the use of salvage chemotherapy as a treatment for relapsed or refractory disease was likely to decline over time.

It is reasonable to include people with Philadelphia chromosome-positive disease from the recommendations

3.35 The committee recalled that the company did not present a separate cost-effectiveness analysis for tisagenlecleucel's use for Philadelphia chromosome-positive disease (see [section 3.4](#)). The committee was aware that the proportion of patients with Philadelphia chromosome-positive disease within the population specified in the marketing authorisation is very small, and there will likely only be 1 or 2 patients per year in England. It was also aware that for these patients, treatment options are limited and prognosis is poor. The committee accepted that excluding this population from its recommendation would leave an unmet need and recalled that treatment benefits with tisagenlecleucel were expected to be similar regardless of Philadelphia chromosome status. The committee agreed that more uncertainty was acceptable given the very small size of the patient population. It considered it reasonable to include people with Philadelphia chromosome-negative disease, and therefore agreed that it would not make a distinction based on Philadelphia chromosome status in its recommendations.

Tisagenlecleucel is recommended for use in the Cancer Drugs Fund for relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25

3.36 Based on its considerations for all populations covered by the marketing authorisation (see [sections 3.33](#) to [3.35](#)), the committee concluded that it could recommend tisagenlecleucel for use as an option within the Cancer Drugs Fund to treat relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years, only if the conditions in the managed access agreement are followed.

Other factors

Tisagenlecleucel use in the NHS

3.37 The committee was aware of statements from clinical experts and NHS England that introducing CAR T-cell therapies to the NHS needs the provision of a new service. Infrastructure for transporting and storing the treatment, accreditation to administer the treatment, training of staff and access to intensive care units to manage adverse events all need to be included. The committee also noted that NHS England and the company consider a cautious approach is needed because these technologies are associated with severe side effects such as cytokine release syndrome (see [section 3.13](#)). Working collaboratively, NHS England and the company aim to manage the risks associated with introducing tisagenlecleucel by adopting a cautious approach to treatment planning, particularly concerning the management of adverse events (for further information see the [summary of product characteristics](#)). NHS England and the company agreed that phased implementation to the NHS is necessary to deliver this treatment.

Potential equalities issue

3.38 The committee noted a potential equality issue raised during the scoping process that blood support or haematopoietic stem cell transplant are not acceptable to some religious groups such as Jehovah's witnesses. These

patients would normally instead have best supportive care. The committee agreed that if tisagenlecleucel does become an available treatment option, people can choose whether or not they wish to have it. Accordingly, this is not viewed as an equality issue.

4 Implementation

- 4.1 When NICE recommends a treatment as an option for use within the Cancer Drugs Fund, NHS England will make it available according to the conditions and implementation arrangements in the managed access agreement (which for tisagenlecleucel, will require that the necessary infrastructure and safety measures are in place for the treatment to be available). This means that, if a patient has relapsed or refractory B-cell acute lymphoblastic leukaemia and the doctor responsible for their care thinks that tisagenlecleucel is the right treatment, it should be available for use, in line with NICE's recommendations and the Cancer Drugs Fund criteria in the managed access agreement. Further information can be found in NHS England's [Appraisal and funding of cancer drugs from July 2016 \(including the new Cancer Drugs Fund\) – A new deal for patients, taxpayers and industry](#).
- 4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance when the drug or treatment, or other technology, is approved for use within the Cancer Drugs Fund. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, for use within the Cancer Drugs Fund, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document or agreement of a managed access agreement by the NHS in Wales, whichever is the latter.

5 Review of guidance

- 5.1 The data collection period is expected to end in June 2023 when the follow-up of the final patient in the ELIANA study will be completed. At this point the process for exiting the Cancer Drugs Fund will begin and the review of the NICE guidance will start.
- 5.2 As part of the managed access agreement, tisagenlecleucel will continue to be available through the Cancer Drugs Fund after the data collection period has ended and while the guidance is being reviewed. This assumes that the data collection period ends as planned and the review of guidance follows the standard timelines described in NICE's [Cancer Drugs Fund methods guide \(addendum\)](#).

Professor Peter Selby
Chair, Appraisal Committee
November 2018

6 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee C](#).

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The [minutes](#) of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Alan Lamb

Technical Lead

Nicola Hay

Technical Adviser

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Project Manager

ISBN: [to be added at publication]