Alteplase for the treatment of acute ischaemic stroke (review of technology appraisal 122)

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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

Sarah Davis acted as project lead on this assessment, critiqued the manufacturer's definition of the decision problem and their description of the underlying health problem and current service provision and contributed to the writing of the report. Michael Holmes acted as health economist on this assessment, critiqued the manufacturer's economic evaluation and contributed to the writing of the report. Emma Simpson acted as systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence, and contributed to the writing of the report. Anthea Sutton critiqued the searches included in the manufacturer's submission and contributed to the writing of the report.

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List of Abbreviations

AIC	Acute Ischaemic Stroke
ATLANTIS	Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke
BI	Barthel Index
CI	Confidence interval
CIC	Commercial in confidence
CT	Computed tomography
ECASS	European-Australasian Acute Stroke Study
ERG	Evidence Review Group
EVPI	Expected value of perfect information
HTA	Health Technology Appraisal
ICER	Incremental cost-effectiveness ratio
ITT	Intention to treat
mRS	modified Rankin Scale
MS	Manufacturer submission
NICE	National Institute for Health and Clinical Excellence
NIHSS	National Institutes of Health Stroke Scale
NINDS	National Institute of Neurological Disorders and Stroke
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RR	Relative risk
SICH	Symptomatic intracranial haemorrhage
SINAP	Stroke Improvement National Audit Programme
SPC	Summary of product characteristics
STA	Single Technology Appraisal

1. SUMMARY

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

The decision problem addressed in the manufacturer's submission (MS) is in-line with that specified within the scope. The submission compares treatment with alteplase in addition to standard care against standard care alone. This is appropriate given that no thrombolytic treatment other than alteplase is licensed in the UK for this purpose. As the most important therapy in acute ischaemic stroke (AIS) is restoration of the blood supply to the affected area of the brain,[1] other stroke treatment or prevention therapies, which function in different ways, would therefore not be relevant comparators. The population considered in the submission is in-line with the licensed indication. Prior to March 2012, the license for alteplase restricted treatment to those patients who could receive therapy within 3 hours of symptom onset. The license has recently been extended to patients who can receive therapy within 4.5 hours of symptom onset. The submission presents separate efficacy and cost-effectiveness estimates for the subgroup of patients who can receive treatment within 0 to 3 hours of symptom onset and the subgroup of patients who can receive treatment within 3 to 4.5 hours of symptom onset. This subgroup analysis was considered appropriate and was pre-specified in the scope.

The main outcomes addressed in detail within the submission were death, death or dependency and symptomatic intracranial haemorrhage (SICH). Dependency was defined as a score of less than 3 on the Modified Rankin Scale. The composite outcome of death or dependency is assumed to capture both the treatment effect of alteplase and the adverse impact of any treatment related SICH. It is the most important single measure of clinical benefit as the aim of treatment is not only to avoid death, but to increase the proportion of independent survivors[2]. It is also an economically relevant outcome as the ability to live independently is related to both health related quality of life[3] and to the subsequent costs of care provided by the NHS and personal social services.[4]

1.2 Summary of clinical effectiveness evidence submitted by the manufacturer

The MS identified 10 randomised controlled trials of alteplase in AIS, of which five provided relevant data and were included in either the main analyses or the sensitivity analyses. The time-frame for onset to treatment varied across the trials with no single trial providing a randomised comparison of treatment within 0 to 4.5 hours.

For the 0-3 hour treatment window, there were no additional trials identified to those included in the 2007 NICE STA of alteplase for the treatment of acute ischaemic stroke (TA122)[5,6].

The main trials providing evidence for the 0 to 3 hour treatment window were the NINDS trial, which examined treatment within 3 hours and the ECASS II trial, which stratified randomisation by onset to treatment time providing a pre-specified subgroup analysis for patients treated within 3 hours. The inclusion of further evidence from the ATLANTIS trials (which did not stratify randomisation by 0-3 hours) was explored in a sensitivity analysis although these estimates were informed by an ad-hoc subgroup analysis. Death or dependency at three months follow-up significantly favoured alteplase, relative risk (RR) 0.81 (95%CI 0.72-0.92) p=0.002, by random-effects meta-analysis of the two main trials which included 393 participants allocated to alteplase, and 389 to placebo. In terms of safety, there was no statistically significant difference in all cause mortality at 3 months in either the fixed or random effects meta-analysis. There was a significantly increased risk of SICH, RR 4.90 (1.90-12.61) p=0.001, by fixed effects meta-analysis, but the difference was not statistically significant by random effects meta-analysis, RR 3.94 (0.61-25.47) p=0.15. The results of the sensitivity analysis incorporating data from the ATLANTIS trials were similar although in this analysis the RR for SICH was significantly higher for both the fixed and random effects meta-analysis.

For the 3-4.5 hour treatment window, the main evidence used in the MS is the ECASS III RCT. This RCT included n=418 alteplase and n=403 placebo participants. In the ECASS III trial, death or dependency at three months follow-up did not show a statistically significant treatment effect, RR 0.87 (95%CI 0.73-1.05) p=0.14, although the midpoint favoured alteplase. In terms of safety, there was no statistically significant difference in all cause mortality at 3 month, but there was a significantly increased risk of SICH, RR 4.82 (1.06-21.87) p=0.04. The inclusion of further evidence from the ECASS II and ATLANTIS trials (which did not stratify randomisation by 3-4.5 hours) was explored in a sensitivity analysis, although this relied on ad-hoc subgroup analyses from these trials.

Sensitivity analysis using data from ECASS III and CIC data from an additional three studies (ECASS II, ATLANTIS A & B), alteplase n=694 placebo n=694, produced an RR which significantly favoured alteplase if analysed by fixed-effect methods RR 0.87 (0.78-0.99) p=0.03, showing a similar trend that failed to reach significance if analysed by random-effect methods 0.87 (0.74-1.04) p=0.12.

Considering the 0-4.5 hour treatment window, analysis of the two main trials of 0-3 hours, n=393 alteplase and n=389 placebo, and the main trial of 3-4.5 hours, n=418 alteplase and n=403 placebo, random-effects meta-analysis showed an RR for death or dependency of 0.83

(0.75-0.92) p=0.0006, significantly favouring alteplase. Again, there was no statistically significant increase in all cause mortality at 3 months, but there was a significantly increased risk of SICH. Heterogeneity between the three studies was low ($I^2 < 25\%$) for the outcomes of death and death or dependency, but higher for SICH ($I^2=42\%$). However, the heterogeneity across the three studies was lower than that seen when pooling data from the two trials examining 0-3 hours as the results of the ECASS III study were closer to those of the large NINDS study than the small subgroup analysis of the ECASS II study.

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

The ERG believes that all relevant RCTs were identified in the MS. The evidence submitted in the MS reflected the decision problem within the NICE final scope with all included trials providing relevant data. The analyses presented were restricted to participants for whom alteplase was administered within 4.5 hours of symptom onset, and so this accurately reflected the NICE scope. The RCTs included were generally of good quality with regard to randomisation and having blinded outcome assessors. However, both NINDS, one of the two main trials for 0-3 hours, and the trial contributing most participants for 0-3 hours, and the ECASS III RCT, providing the main evidence for 3-4.5 hours, had imbalances in baseline stroke severity favouring alteplase. There is disagreement in the literature, about the NINDS trial, as to whether this would significantly skew treatment effect outcomes. All of the RCTs used appropriate statistical techniques and conducted an intention-to-treat analysis. The meta-analysis approach was appropriate and both fixed and random effects analyses were provided. The ERG would agree with the exclusion of data derived from ad-hoc subgroup analyses from the base-case meta-analyses. With regard to the pooling of data across different treatment windows, a pooled analysis[7] of 3670 patients from 8 RCTs, which examined the interaction between treatment effect and onset to treatment time, found that there was a significant interaction for the outcomes of death and dependency (modified Rankin Scale (mRS) of greater than 1) and mortality, but not for SICH. (It should be noted that not all of the 8 RCTs included in the pooled analysis examined the use of alteplase in line with its UK marketing authorisation.) However, the adjusted odds ratios provided by the pooled analysis[7] supports the meta-analysis of the RCT data presented within the MS, in showing a significant treatment effect for dependency and a non-significant difference in mortality at three months for both the 0 to 3 and 3 to 4.5 hour onset to treatment windows.

1.4 Summary of cost-effectiveness evidence submitted by the manufacturer

The economic model submitted is an updated version of a published Health Technology Appraisal (HTA) which also formed the basis of Boehringer Ingelheim's submission to TA122. The model compares treatment with alteplase alongside standard care against a comparator of standard care alone. Estimates of cost-effectiveness have been provided for three treatment windows; 0 to 4.5 hours, 0 to 3 hours and 3 to 4.5 hours from symptom onset. The models for these three treatment windows use different estimates of treatment effect but are otherwise equivalent.

The efficacy estimates used in the basecase scenarios for the three treatment windows, were limited to the NINDS (0-3 hours), ECASS II (0-3 hours) and ECASS III (3-4.5 hours) trials as data were available from these trials for the required treatment windows using either the whole trial population or a pre-specified subgroup with randomisation stratified appropriately. Sensitivity analyses were conducted using alternative efficacy estimates which incorporated ad-hoc subgroup analyses of the ATLANTIS trials and ECASS II trials.

Treatment effect is captured by modelling the distribution of patients between the health states dependent, independent and dead at 6 months following treatment. This is based on efficacy outcomes from the trials at 3 months. The only trial providing longer-term follow-up, from a population meeting the licensed indication was NINDS, but results from this trial support the maintenance of benefits from 3 to 6 months and this was considered clinically reasonable. Dependency is defined as a score of less than 3 on the mRS. These outcomes are assumed to capture both the impact of alteplase on stroke severity and the impact of any SICH following alteplase. The probabilities of transitions between the health states beyond 6 months are assumed to be equivalent between the two treatment arms and were based on data from the Lothian Stroke Registry. After the first year, patients remain in the same health state until they either experience a recurrent stroke or die. Age-specific general population mortality risks are applied after the first year. These are adjusted to account for the higher risk of mortality following stroke. A fixed annual mortality risk is applied after recurrent stroke.

Costs and health-related quality of life estimates applied to the health states are based on published estimates from UK populations. The cost of alteplase varies from £300 to £600 depending on the dose required which is determined by the patient's weight. The cost of administration is estimated at £1,316. Costs and quality adjusted life years (QALYs) are estimated using a life-time horizon with future costs and benefits discounted at 3.5%. The

impact of parameter uncertainty was estimated in a probabilistic sensitivity analysis. Scenario analyses were run on key parameters.

The ICER (cost per QALY gained) for treatment within 0 to 4.5 hours from symptom onset was estimated at £2,296 when using the mean costs and QALYs from the probabilistic analysis. However, this cost-effectiveness estimate relies on combining efficacy estimates for treatment across two different time windows. When considering treatment within 3 hours, alteplase dominates standard care as the mean QALYs gained are greater and the mean cost is lower than for standard care. However, the ICER for treatment within of 3 to 4.5 hours of symptom onset was less favourable at £6,169 per QALY.

The cost-effectiveness results were generally robust under the sensitivity analyses conducted. The only factor having a significant impact was the lack of precision around the efficacy estimates. The relative risks for the outcomes of death and death or dependency were not statistically significant in the 3 to 4.5 hour onset to treatment window. Applying the upper and lower 95% confidence intervals for both these parameters as point estimates within the model resulted in a large variation in the ICER. The cost-effectiveness estimates for the 0 to 4.5 hour onset to treatment window were similarly sensitive to uncertainty in the efficacy estimates. All of the sensitivity analyses which examined the use of alternative efficacy estimates incorporating ad-hoc subgroup analyses from either the ATLANTIS trials (0 to 3 hour and 3 to 4.5 hour treatment window) or the ECASS II trial (3 to 4.5 hour treatment window) resulted in a decrease in both the QALYs gained and the costs accrued for alteplase compared to the basecase analysis, although none resulted in an ICER greater than £10,000 per QALY.

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

The economic model described in the MS is considered by the ERG to meet the NICE reference case.[8] The health states included in the model were considered to be appropriate to capture both the treatment effect of alteplase on stroke severity and the impact of SICH following thrombolytic therapy. The evidence used to populate the transition probabilities were considered to be relevant to the UK population. The data from the Lothian Stoke Registry which are used to determine the health state distribution in the standard care arm are now over 10 years old and may not reflect recent improvements in stroke outcomes following the introduction of specialist stroke units. However, any more recent source is likely to be confounded by improvements resulting from the use of alteplase and would therefore not be a suitable source of natural history data for the standard care arm. The costs and utility values

applied to the health states were considered to be appropriate and in-keeping with the reference case. The cost-effectiveness estimates were generally robust under the univariate sensitivity analyses conducted with the main cause of decision uncertainty relating to the precision around the efficacy estimates. The probabilistic sensitivity analysis samples independently from the relative risks for death and death or dependency, which ignores the correlation that is likely to exist between these two variables. This may mean that it doesn't provide an accurate description of the uncertainty around the mean costs and QALYs, although the ERG considers it unlikely that this would have a significant impact on the ICER. The ERG considers that it was appropriate to conduct separate analyses for the sub-population of patients who are eligible for treatment within 0 to 3 hours and for the sub-population who are eligible for treatment within 3 to 4.5 hours. The efficacy estimates for these two sub-populations suggest that the balance of risks and benefits may be slightly different and these differences in efficacy translate into differing cost-effectiveness estimates, even though the confidence intervals for the efficacy estimates are overlapping and there is no significant heterogeneity between the two treatment windows. Furthermore, neither sub-population has a central ICER estimate above £20,000 per QALY.

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

1.6.1 Strengths

The submission presents randomised and placebo controlled trial data from three studies for the extended treatment time window of 0 to 4.5 hours from symptom onset. As specified in the scope, separate efficacy and cost-effectiveness estimates are presented for the 0 to 3 hour time window and the 3 to 4.5 hour time window, alongside the combined analysis for 0 to 4.5 hours. The submitted economic model is similar to the model used to inform TA122 allowing the results to be compared and validated against those provided previously. The cost-effectiveness analysis meets the NICE reference case criteria. The cost-effectiveness results appear to be robust as the majority of the sensitivity analyses conducted did not increase the ICER beyond currently accepted threshold values.

1.6.2 Weaknesses and areas of uncertainty

The main area of uncertainty with regard to clinical effectiveness relates to differences in stroke severity at baseline, which potentially favour alteplase, in two of the three key trials. In the cost-effectiveness analysis the main driver of decision uncertainty is the lack of precision around the efficacy estimates. This is reflected in the fact that the global expected value of perfect information (EVPI) is much higher when considering the 0 to 3 hour and 3 to 4.5 hour

treatment windows separately, than when combining all data that is relevant to the 0 to 4.5 hour treatment window, as combining data from more trials reduces uncertainty in the efficacy estimates.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

None of the additional clinical and economic analysis undertaken by the ERG resulted in ICERs that varied from the results presented in the MS in any meaningful way.

The ERG conducted an exploratory sensitivity analysis using the trial outcomes from the standard care arm of the ECASS III trial at 3 months to populate the health state distribution for standard care within the economic model, as an alternative to the data from the Lothian Stroke Registry. Whilst the mortality risk within the ECASS III trial was lower than that seen in the Lothian Stroke Registry, the ICER was not significantly affected by altering the health state distribution in the standard care arm.

The ERG re-ran the PSA analysis for the 0 to 4.5 hour time window and found that whilst the distribution of marginal cost and QALYs were slightly different, giving a different cost-effectiveness acceptability curve (CEAC) from that presented in the MS, the mean incremental costs and QALYs were similar giving a mean ICER of £2,298 with a Jacknife 95% CI of £2,209 to £2,387.

2. BACKGROUND

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

The manufacturer's estimate of the incidence of first ever acute ischaemic strokes (AIS) in England and Wales for 2012 (62,023) is based on age specific incidence rates from a UK study (the Oxfordshire Vascular Study)[9] and population estimates from the Office of National Statistics. This is considered by the ERG to be an appropriate estimate of the incidence of first-ever AIS, but it excludes AIS in people who have experienced a prior stroke, some of whom may be eligible for treatment with alteplase. Applying the age-specific rates for all AIS, rather than first-ever AIS, from the Oxfordshire Vascular Study to the same population estimates gives an incidence of 84,477.

2.2 Critique of manufacturer's overview of current service provision

The manufacturer's description of current service provision is considered by the ERG to be broadly appropriate and relevant to the decision problem, although the ERG would question the estimate given for current usage of alteplase. The manufacturer assumes that 20% of patients having a first-ever AIS would receive alteplase within the original 0 to 3 hour onset to treatment window. This is based on sales figures for alteplase under the assumption that all sales of alteplase are used for the treatment of AIS. This figure is much higher than the thrombolysis rate of 8% achieved in the Stroke Improvement National Audit Programme (SINAP) audit[10]. Within the National Sentinel Audit of Stroke only 14% of patients were eligible for treatment with alteplase[11].

3. CRITIQUE OF MANUFACTURER'S DEFINITION OF DECISION PROBLEM

A summary of the decision problem addressed in the MS is shown in Table 1 [information has been modified from that presented in Table 6 of the MS to reflect the ERGs view of the decision problem addressed in the MS].

Table 1: Decision problem as issued by NICE and addressed by the MS

	Final scope issued by NICE	**Decision problem addressed in the submission**
Population	Adults with acute ischaemic stroke within 4.5 hours of symptom onset	Adults with acute ischaemic stroke within 4.5 hours of symptom onset
Intervention	Alteplase	Alteplase (administered as per the licensed dosage and technique detailed in the SPC)
Comparator(s)	Standard medical and supportive management that does not include alteplase	The standard medical care that does not include alteplase - there are no other drugs licensed for thrombolysis in this indication. Placebo is used as proxy for no treatment. Alteplase treatment is additive to current care
Outcomes	The outcome measures to be considered include: • Disability (Modified Rankin Scale) • Functional recovery • Neurological deficit • Change in mental health, including anxiety and depression • Mortality • Length of hospital stay • Adverse effects of treatment, including bleeding events • Health-related quality of life	The outcomes addressed are; • Disability (Modified Rankin Scale) • Functional recovery • Neurological deficit • Mortality • Length of hospital stay • Adverse effects of treatment, including bleeding events • Health-related quality of life Mental health outcomes are not addressed in the submission

Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	Cost-effectiveness has been expressed in terms of cost per QALY A life-time time horizon has been employed to capture the chronic nature of disability associated with stroke and any mortality differences Costs have been considered from an NHS and Personal Social Services perspective
Subgroups to be considered	If the evidence allows the following subgroup will be considered • Subgroup by time to treatment (0-3 hours and 3-4.5 hours) Guidance will only be issued in accordance with the marketing authorisation.	Both the 0-3 and 3-4.5 hour administration window have been considered.
Special considerations, including issues related to equity or equality	None specified in scope	Extension of the time frame for administration from 3 to 4.5 hours has the potential to broaden access, but it is unclear whether this will address any existing inequality in access

3.1 Population

The relevant patient population is defined as adults aged 18 to 80, with acute ischaemic stroke, without computed tomography (CT) evidence of intracranial haemorrhage, who can commence therapy within 4.5 hours of symptom onset. Alteplase is contraindicated in patients with severe stroke and in patients with minor neurological deficit or with symptoms which are rapidly improving. It is also contraindicated in patients with prior stroke in the previous 3 months and in patients with any history of prior stroke and concomitant diabetes. Further contraindications are given in the Summary of Product Characteristics within Appendix 9 of the MS. The populations included in the key clinical trials (ECASS II and III, NINDS,

ATLANTIC A and B) are representative of the patient population eligible for treatment in England and Wales except that the time window for onset to treatment varied across the trials with no single trial examining treatment within 0 to 4.5 hours. Two trials examined a treatment window of 0 to 3 hours either in their main analysis, or in a pre-specified subgroup analysis with randomisation stratified by onset to treatment time. A further trial examined a treatment window of 3 to 4.5 hours. Therefore the data allowed separate meta-analyses and cost-effectiveness analyses to be conducted for treatment within 0 to 3 hours and treatment within 3 to 4.5 hours.

3.2 Intervention

Alteplase is a recombinant human tissue-type plasminogen activator (in other words, an enzyme which causes blood clots to dissolve). It is therefore potentially of value in ischaemic stroke, in which the flow of blood to the brain has been interrupted, commonly by a clot blocking a blood vessel. However, its use in a stroke caused by intracerebral or subarachnoid haemorrhage is potentially disastrous. A UK licence for the use of alteplase within a 0-3hour administration time period from the onset of symptoms for the treatment of acute ischaemic stroke was granted in September 2002[12]. Boehringer Ingelheim received licence approval from the Medicines and Healthcare products Regulatory Agency (MHRA) for alteplase use to be extended to 4.5 hours from the onset of symptoms on 14th March 2012[13].

3.3 Comparators

The MS does not identify any active comparator for alteplase. This is appropriate because no thrombolytic agent other than alteplase is currently licensed within the EU for use in acute ischaemic stroke. As the most important therapy in acute ischaemic stroke is restoration of the blood supply to the affected area of the brain[1], other stroke treatment or prevention therapies, which function in different ways, would therefore not be relevant comparators.

3.4 Outcomes

The outcomes specified in the final scope were;

- disability (Modified Rankin Scale)
- functional recovery
- neurological deficit
- change in mental health, including anxiety & depression
- mortality

• length of hospital stay

• adverse effects of treatment, including bleeding events

• health-related quality of life

The outcomes addressed in detail within the submission are disability, death and adverse events including symptomatic intracranial haemorrhage. The composite outcome of 'death or dependence' is an important outcome measure within the submission as it used within the economic model to capture both the efficacy of treatment and the adverse effect of treatment related intracranial haemorrhages. Dependence is measured using the mRS which is a 7-point scale assessing overall function where a score of 0 indicates complete recovery and 6 is death (see Table 2). A score of 0-2 is considered to indicate functional independence while 3-5 indicates dependence.

Secondary outcomes reported for the ECASS III trial include neurological deficit, measured with the National Institutes of Health Stroke Scale (NIHSS), measures of functional recovery (Barthel Index (BI) and Glasgow Outcomes Scale(GOS)), and a global outcome measure combining the mRS, the NIHSS, the BI and the GOS. Secondary outcomes for the other trials including neurological deficit, functional recovery and length of hospital stay are described in appendix 9 of the MS, but are not tabulated in the main submission. Mental health outcomes, such as anxiety and depression, have not been addressed within the submission. However, health-related quality of life data, using the SF-36 instrument, are available from one RCT, and this instrument includes a mental health dimension.

Table 2: Modified Rankin Scale[14]

Grade	Description
0	No symptoms at all
1	No significant disability despite symptoms: able to carry out all usual duties and activities
2	Slight disability: unable to carry out all previous activities but able to look after own affairs without assistance
3	Moderate disability: requiring some help, but able to walk without assistance
4	Moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance
5	Severe disability: bedridden, incontinent, and requiring constant nursing care and attention
6	Dead

3.5 Other relevant factors

The MS states that there are equity issues surrounding both the incidence of stroke and subsequent access to health care, although no studies are cited which specifically show differential access to thrombolytic therapy within the UK. It states that the extended window for the administration of alteplase has the potential to broaden access. It is the opinion of the ERG that the only issue that is relevant to the UK setting is geographical. The distance between where a patient suffers the initial stroke and the nearest treatment centre will have a bearing on whether or not alteplase treatment can be administered within the recommended time frame. An extension of this time frame will increase the percentage of patients eligible for treatment, although it is unclear whether this will address any existing inequality.

4. CLINICAL EFFECTIVENESS

4.1 Critique of the methods used by the manufacturer to systematically review clinical effectiveness evidence

The review aimed to update the Cochrane review on thrombolysis[15] but restricting it to search for RCTs of alteplase (MS section 5.1).[13]

4.1.1 Searches

An existing search strategy from the Cochrane review "Thrombolysis for acute ischemic stroke" was adapted by excluding all thrombolytic drug terms other than those relating to alteplase. The search was limited to RCTs published from 2008 onwards as the Cochrane review searches were conducted in 2008.

The searches were conducted on the following databases via the OVID platform:

- Medline -R In-Process and Other Non-Indexed Citations
- Medline –R 1946-Present with Daily Update
- Embase
- All EBM reviews (Cochrane DSR, ACP Journal Club, DARE, CCTR, CMR, HTA, NHSEED
- Econlit

Searches were conducted on 14th February 2012. The specific date span for each database is not given. Additional searches were carried out on internal company databases, however this did not identify any extra studies.

The search strategy was appropriate and basing it on an existing published review ensured the population and intervention terms were comprehensive. However, the terms used to identify RCTs are different to those used in the Cochrane Review. It is not stated if a published search filter was used. Some of the terms used to find RCTs retrieved 0 results and therefore it is possible that alternative terms would have been more appropriate. For example:

Step 17: Randomised controlled trial.pt. should be randomized controlled trial.pt.

Step 18: Randomised controlled trials/ should be Randomized controlled trials/

Step 20: Controlled clinical trials/ should be Controlled Clinical Trial/

Step 35: Multicentre study.pt. should be Multicenter study.pt

By amending these search terms as above, an additional 9 references are found in the Medline search. However, 7 of these were found in the Embase search so were not missed. The 2 references that were not found in any of the searches are a comment on Lees 2010[7] and a letter commenting on Del Zoppo 2009.[16]

There are no additional comments about the Embase search strategy, as this used the same RCT terms as the original Cochrane Review.

The specific search strategies for EBM reviews and EconLit are not included so it is not possible to comment on these. The assumption is that the Medline or Embase strategies were used.

4.1.2 Inclusion/exclusion criteria used in the study selection.

The MS[13] described study selection in Section 5.2.1 and MS Table 8. The study selection process was based on the Cochrane review of thrombolysis,[15] but was adapted to restrict to use of alteplase within UK marketing authorisation. This was appropriate as it reflected the NICE scope.[17] The population was restricted to adults aged 18-80 with acute ischaemic stroke (AIS), without intracranial bleeding, confirmed by brain imaging. The intervention was alteplase in addition to standard medical and supportive management. The intervention was restricted to 0.9mg/kg alteplase (to a max. of 90mg, 10% as initial intravenous bolus, 90% as infusion over the subsequent 60 minutes) with treatment administration within the 0-4.5 hour time period. These inclusion criteria were appropriate as they conform with the licence for alteplase and the NICE scope.[17]

The MS section 2.6 states that the main comparator was placebo or standard medical and supportive management without thrombolysis. It was appropriate that there was no active comparator (section 2.6 MS), as alteplase is currently the only thrombolytic agent licensed in the UK for use in AIS.[18] The comparator used in study selection in the MS Table 8[13] was placebo. This was more restrictive than stipulated in the NICE scope[17] which stated "standard medical and supportive management that does not include alteplase". Placebo controlled trials may be considered less prone to bias than trials in which the comparator is no additional treatment, as the administration of placebo would allow blinding of patients and clinicians. In the case of alteplase, it is difficult to ensure that clinician blinding would be effective. As explained in the Cochrane review[15] and the MS section 5.10.2[13] the appearance of the drug would differ from placebo, as alteplase froths when shaken in solution with water or normal saline, and thus normal saline does not form an identical placebo. Also, the biological effect

of thrombolytic therapy may be apparent (for example, prolonged bleeding at venepuncture sites, easy bruising, gingival or conjunctival haemorrhages). In practice, the inclusion of non-placebo comparator at study selection would only allow the possibility of one additional trial, IST-3, and the results of this were not available at the time of MS.

The MS[13] states that the primary outcome measures were death or dependency (as defined by mRS score of 3-6) and mortality, however the study selection exclusion criteria did not exclude on the basis of outcomes, suggesting that other outcomes specified in the NICE scope[17] were considered. Study design was restricted to RCTs, MS section 5.1[13]. Given the known availability of RCTs on the topic, including RCTs and not lower quality studies was appropriate.

4.1.3 Studies included and excluded from the clinical effectiveness review

4.1.3.1 Identified studies

The MS section 5.2.2 presents a flow diagram of study selection. The ERG were initially concerned that some studies appeared to have been excluded because they included non-UK populations. Following clarification from the manufacturer, it was apparent that most discarded studies had more than one reason for exclusion, in particular many were not controlled trials.

In practice, most of the excluded studies were not RCTs, and no trials were excluded solely for the reason of having non-UK populations.

RCTs identified in the MS are shown in the Table below (Table 3).

For the 0-3 hour treatment window, there were no additional trials identified to those included in the 2007 NICE STA TA122.[5,6]

For the 3-4.5 hour treatment window, the main evidence used in the MS is the ECASS III RCT. Other trials with potentially relevant data for this time window were ATLANTIS A,[19] ATLANTIS B,[20] ECASS II,[21] EPITHET[22] and Wang *et al.*[23]

Wang *et al.*[23] was excluded from the MS section 5.2.1.1 for having "an unrepresentative population for the UK". The article for this study is in the Chinese language and the ERG has not reviewed this publication. However, details of the Wang *et al.* study are available in the Cochrane review[15]. As this was not a placebo-controlled study, the comparator being no thrombolytic therapy, this study would have been excluded from the MS study selection. The

study has two treatment groups with n=34 given the licensed dose, and n=33 given the unlicensed dose, of alteplase, and n=33 given no thrombolytic therapy. Data from this study published in the Cochrane review[15] were presented as one alteplase group combining both licensed and unlicensed doses, making these data outside the remit of the NICE Final Scope,[17] EPITHET was excluded from providing data in the MS section 5.2.1.2 for not having published data of the 3-4.5 hour time window (just 3-6 hours).

ATLANTIS A and B have relevant data, although the evidence provided is less applicable to the licensed population due to the time windows for treatment examined in these studies. Whilst subgroup analyses are available for patients falling within the time window for treatment specified in the license, these are considered to form less adequate evidence because randomisation was not stratified by time from symptom onset to treatment, meaning the groups of patients treated in 0-3 hours, and 3-4.5 or 3-6 hours, do not form true randomised comparisons, as acknowledged in the MS section 5.2.1.1.[13,5]

Similarly, ECASS II was stratified by 0-3 and 3-6 hours, and so provided randomised evidence for the 0-3 hour time window, and less adequate evidence for the 3-4.5 hour time window. CIC data for the 3-4.5 time window from ATLANTIS (A & B combined) and ECASS II were included in the MS in sensitivity analyses (MS sections 9.15.7 to 9.15.10).

Table 3 Identified RCTs in the MS

Study	Main reference	Intervention	0-3 hour treatment window	3-4.5 hour treatment window
ATLANTIS A	Clark *et al.* 2000[19]	Alteplase, at licensed dose, administered 0-6 hours after symptom onset	Included in TA122	Data published for 0-6, and 5-6 hours
ATLANTIS B	Clark *et al.* 1999[20]	Alteplase, at licensed dose, administered 0-5 (later part of study 3-5) hours after symptom onset	Included in TA122	Data published for 3-5 hours
ECASS I	Hacke *et al.*[24]	Alteplase, dose not licensed for UK use, administered 0-6 hours after symptom onset	Unlicensed dose	Unlicensed dose
ECASS II	Hacke *et al.* 1998[21]	Alteplase, at licensed dose, administered 0-6 hours after symptom onset	Included in TA122	Data published for 3-6 hours
ECASS III	Hacke *et al.* 2008[25]	Alteplase, at licensed dose, administered 3-4 hours (later part of study 3-4.5 hours) after symptom onset	NA	Data published for 3-4.5 hours
EPITHET	Davis *et al.* 2008[22]	Alteplase, at licensed dose, administered 3-6 hours after symptom onset	NA	Data published for 3-6 hours
Haley	Haley *et al.* 1993[26]	Alteplase, dose not licensed for UK use, administered 0-3 hours after symptom onset	Unlicensed dose	Unlicensed dose
IST-3	Sandercock 2011 [27]	Alteplase, at licensed dose, administered 0-6 hours after symptom onset	Data not available at time of MS	Data not available at time of MS
NINDS (NINDS I and NINDS II)	Marler *et al.* 1995[28]	Alteplase, at licensed dose, administered 0-3 hours after symptom onset	Included in TA122	NA
Wang	Wang *et al.* 2003[23]	Alteplase, two alteplase groups of which one at licensed dose, one dose not licensed for UK use, administered 0-6 hours after symptom onset	Excluded from MS	Excluded from MS

The IST-3 trial was mentioned in the MS, however data from this trial were not available at time of MS. MS section 1.6 considers that the trial was not placebo-controlled and so didn't meet the study selection criteria in the MS. The IST-3 trial was a randomised open-label blinded endpoint study[29] (see Appendix A for further details on IST-3).

For relevant non-RCT evidence, the MS section 5.8 describes one observational study, SITS-ISTR (Safe Implementation of Treatment in Stroke-International Stroke Thrombolysis Registry)[30]. This was an observational study specifically designed to assess alteplase

administered within 3-4.5 hours after onset of symptoms. The population eligibility criteria for this study conformed to the UK marketing authorisation.

4.1.3.2 Studies providing the main evidence

For the 0-3 hour treatment window, there were no additional trials identified to those included in the 2007 NICE STA TA122[6]. The main evidence was provided by the ECASS II and NINDS trials. Sensitivity analyses included the ATLANTIS A and ATLANTIS B trials which had relevant data for the 0-3 hour treatment window, but were of lower quality due to lack of stratification by time from onset to treatment. As the evidence for the 0-3 hour treatment window did not differ from TA122[6], the MS concentrates mainly on the 3-4.5 hour treatment window. However, data for the 0-3 hour treatment window is provided within the MS in Table 10, Appendix 14 and Appendix 15.

For the 3-4.5 hour treatment window, the main evidence was provided by the ECASS III trials. Sensitivity analyses included the ATLANTIS A and ATLANTIS B trials which had relevant data but were of lower quality due to lack of stratification by time periods, and the ECASS II trial which was stratified by the time periods 0-3 hours and 3-6 hours (not 3-4.5 hours).

This ERG report concentrates on the main evidence for the 3-4.5 hour treatment window, the ECASS III RCT, with data available from the MS, published ECASS III papers,[25,31] and the Cochrane review of thrombolysis.[15] Data from the other included studies, addressing 0-4.5 hours treatment after onset of symptoms, were available from the MS[13], the ERG report from NICE STA TA122,[5] and the Cochrane review,[15] as well as published trial papers.[19-21,25,28]

The main evidence for the 3-4.5 hour treatment window was the ECASS III RCT (Table 4). This RCT randomised patients, after brain imaging, to alteplase at its licensed dose or placebo. Treatment was delivered between 3 and 4.5 hours after onset of symptoms. The RCT was conducted across 130 sites in Europe, with a small proportion being from the UK (n=22 of 821). Population eligibility, described in section 5.3.3 of the MS, conformed to UK marketing authorisation.

Table 4 ECASS III Study details

Trial	Study design	Population eligibility	Outcomes
ECASS	RCT, multi-	Age 18-80	Primary outcome:

III (Hacke *et al.* 2008)[25]	centre, conducted 2003-2007 3-4 hour treatment window for first stage (n=228) 3-4.5 hour treatment window for remainder of trial (n=593)	Diagnosed with AIS causing a measurable neurological deficit (Ischaemic stroke defined as an event characterised by the sudden onset of an acute focal neurologic deficit due to cerebral ischaemia after CT scan excludes haemorrhage) Absence of intracranial haemorrhage confirmed by brain imaging Stroke symptoms apparent for at least 30 minutes, not significantly improved before treatment	disability mRS score at 90 days follow-up Secondary outcomes: Global outcome (composite measure using mRS, Glasgow Outcome Scale, NIHSS, Barthel Index) Disability (mRS and Barthel Index) Functional status NIHSS (at days 0, 1, 7) Safety: mortality, adverse events, ICH, SICH, symptomatic oedema

All included trials (ATLANTIS A, ATLANTIS B, ECASS II, ECASS III, NINDS I and II) were parallel-group RCTs (Table 5). All trials administered alteplase at the licensed dose of 0.9mg/kg to a maximum of 90mg, given as a 10% bolus followed by the remaining 90% as a 60-minute infusion. All included trials had participants administered alteplase within the licensed 0-4.5 hours, additionally three of the trials (ATLANTIS A, ATLANTIS B, ECASS II) included some participants with administration of alteplase outside of the licensed time window (4.5 to 6 hours).

Table 5 Included trials: 0-4.5 hour time window

Trial	Follow-up	Primary outcome measures	Location
ATLANTIS A	3 months	Clinical improvement defined as a decrease of ≥4 points on the NIHSS, or complete resolution of symptoms, from baseline to 24 hours and from baseline to 30 days Volume of cerebral infarct as measured by CT scan at 30 days	41 sites in North America
ATLANTIS B	3 months	Excellent neurological recovery at day 90 (defined as an NIHSS score of 0 or 1)	140 sites in North America
ECASS II	3 months	Favourable outcome (0-1) on the modified Rankin scale 90±14 days after treatment	108 sites in 14 European countries (including the UK), Australia, and New Zealand
ECASS III	3 months	Disability mRS score at 90 days follow-up	130 sites 19 European countries (including the UK)
NINDS 1	3 months (12-months for the combined NINDS I and II analysis)	Early improvement, defined as complete resolution of the neurological deficit, or improvement of 4 or more points from baseline NIHSS score, 24 hours after stroke onset	40 sites in USA
NINDS 2		Minimal or no neurological deficit at 3 months (a score of 0-1 on the NIHSS scale and mRS, 95 or 100 on the Barthel Index, and 1 on the Glasgow outcome scale)	

4.1.4 Relevant studies not discussed in the submission

The ERG believe that that there are no unidentified RCTs available meeting the inclusion criteria in the MS or NICE scope.

There were potentially relevant data from the IST-3 and EPITHET trials, although data were not restricted to participants administered alteplase within the UK marketing authorisation in either trial. EPITHET did not present data for 3-4.5 hours and IST-3 included participants aged over 80. Whilst data from the IST-3 trial were not available at the time of MS, results have recently been published[32]. Further information on the EPITHET and IST-3 trials is provided in Appendix A

4.2 Summary and critique of submitted clinical effectiveness evidence

4.2.1 Summary of submitted clinical evidence for each relevant trial.

Table 6 Participants of included trials

Trial	**Number of patients randomised**	**Age in years, mean (± SD)**	**Baseline NIHSS score median (mean ± SD)**	**Time to treatment, median**
ATLANTIS A	Alteplase 71 Placebo 71	Alteplase 67±13 Placebo 65±12	Not reported. Mean: Alteplase 13±7 Placebo 13±6	Alteplase 4h 36m Placebo 4h 30 m
ATLANTIS B	Alteplase 307 Placebo 306	Alteplase 66±11 Placebo 65±11	Alteplase 10 (mean 11±6) Placebo 10 (mean 11±5)	Alteplase 4h 36m Placebo 4h 30 m
ECASS II	Alteplase 409 Placebo 391	Median age 68 in both groups	Alteplase 11 Placebo 11	Not reported
ECASS III	Alteplase 418 Placebo 403	Alteplase 64.9±12.2 Placebo 65.6±11.0	Alteplase 9 (mean 10.7±5.6) Placebo 10 (mean 11.6±5.9)	Alteplase 3h 59m Placebo 3h 58 m
NINDS 1	Alteplase 144 Placebo 147	Alteplase 67±10 Placebo 67±11	Alteplase 14 Placebo 14	0-90 min: Alteplase 89 min Placebo 88 min 91-180 min: Alteplase 156 min Placebo 151 min
NINDS 2	Alteplase 168 Placebo 165	Alteplase 69±12 Placebo 66±13	Alteplase 14 Placebo 15	

4.2.1.1 Key results

The main outcome utilised was the endpoint of death and dependency (mRS 3-6). This approach captures both functional recovery, and any death or disability caused by SICH. Other key outcomes were all-cause mortality and SICH. The SICH outcome included fatal and non-fatal SICH. Fatal SICH are also included in all-cause mortality. Most trials had follow-up of three months. NINDs data were available at twelve months follow-up.

Mortality

ECASS III mortality as reported by Hacke *et al.* 2008[25] are shown in Table 7.

Table 7 Cumulative mortality in ECASS III[25]

Follow-up	Mortality Alteplase group n (%)	Mortality Placebo group n (%)
Days 1-7	12 (2.9)	13 (3.2)
Days 8-30	22 (5.3)	21 (5.2)
Days 31-90	28 (6.7)	31 (7.7)
After day 90 (time not specified)	32 (7.7)	34 (8.4)

All included trials reported all-cause mortality (Table 8). The mortality rate in the placebo arm in the MS differs from the published ECASS III data at day 90 (31/403). This, and periods above as reported by ECASS III, are shown in Table 8.

Disability

For the ECASS III RCT, the primary outcome was mRS 0-1. This is reported in MS section 5.5.1. At three months follow-up, 52.4% (n=219) of the group assigned to alteplase treatment had an mRS score of 0 or 1, significantly (p=0.04) more than for the placebo group (45.2%, n=182). Adjusting for the baseline variable NIHSS score, smoking, hypertension on time between onset of symptoms and treatment, the MS section 5.5.1[13] reports an adjusted odds ratio from Bluhmki *et al.*[30] of 1.42 (95%CI 1.02-1.98) p=0.037 favouring alteplase.

For the definition of death or dependency (mRS 3-6), ECASS III at three months follow-up 33.5% (n=219) of the group assigned to alteplase treatment, and 38.5% (n=155) of the group assigned to placebo treatment were either dead or dependent. This did not differ significantly between treatment groups RR 0.87 (95%CI 0.73-1.05).

Disability as measured by the mRS was reported in all trials. Table 9 shows death or dependency (as defined by mRS score of 3-6).

Symptomatic intracranial haemorrhage

MS section 5.9.2 reports SICH in ECASS III according to different definitions (Table 10).

Symptomatic intracranial haemorrhage results from all included trials are shown in MS Table 8. The MS reports SICH rates as 10/418 for alteplase and 2/403 for placebo. The rate in the placebo arm differs from the published ECASS III data (1/403). This, and definitions above as reported by ECASS III, are shown in Table 11 SICH outcomes.

Table 8 All-cause mortality results from individual trials

Study	Time from symptom onset to treatment (hours)	Mortality Outcomes	Alteplase group	Placebo group	Relative risk (95% CI)	Absolute risk difference (alteplase vs. placebo group)
ATLANTIS A MS[13]	0-3	All-cause mortality at 3 months	3/10 (30%)	0/12 (0%)	8.27 (0.48-143.35)	+30%
ATLANTIS B MS[13]	0-3	All-cause mortality at 3 months	1/13 (7.7%)	2/26 (7.7%)	1.00 (0.10-10.04)	0%
ATLANTIS 3-4.5 [13]	3-4.5	All-cause mortality at 3 months	16/145 (11.0%)	10/157 (6.4%)	1.73 (0.81-3.69)	+4.6%
ECASS II MS[13]	**0-3**	All-cause mortality at 3 months	11/81 (13.6%)	6/77 (7.8%)	1.74 (0.68-4.48)	+5.8%
ECASS II 3-4.5 [13]	3-4.5	All-cause mortality at 3 months	9/131 (6.9%)	21/134 (15.7%)	0.44 (0.21-0.92)	-8.8%
ECASS III MS[13]	**3-4.5**	All-cause mortality [MS]	28/418 (6.7%)	33/403 (8.2%)	0.82 (0.50-1.33)	-1.5%
ECASS III Hacke *et al.* 2008[25]	**3-4.5**	All-cause mortality at 90 days from Hacke *et al.* 2008	28/418 (6.7%)	31/403 (7.7%)	0.87 (0.53-1.42)	-1.0%

Study	**Time from symptom onset to treatment (hours)**	**Mortality Outcomes**	**Alteplase group**	**Placebo group**	**Relative risk (95% CI)**	**Absolute risk difference (alteplase vs. placebo group)**
ECASS III Wardlaw *et al.* 2009[15] Hacke *et al.* 2008[25]	**3-4.5**	All cause mortality during follow-up (exceeds 90 days)	32/418 (7.7%)	34/403(8.4%)	0.91 (0.57-1.44)	-0.7%
NINDS I and II MS[13] Wardlaw *et al.* 2009[15]	0-3	All-cause mortality at 3 months	54/312 (17.3%)	64/312 (20.5%)	0.84 (0.61-1.17)	-3.2%
NINDS I and II Kwiatkowski *et al.* 1999[33]	0-3	All-cause mortality at 12 months	76/312 (24.4%)	87/312 (27.9%)	0.87 (0.67-1.14)	-3.5%

Table 9 Death or dependency results from individual trials

Study	Time from symptom onset to treatment (hours)	Death or dependency Outcomes	Alteplase group	Placebo group	Relative risk (95% CI)	Absolute risk difference (alteplase vs. placebo group)
ATLANTIS A MS[13]	0-3	Death or dependency at 3 months	7/10 (70.0%)	7/12 (58.3%)	1.20 (0.64-2.25)	+11.7%
ATLANTIS B MS[13]	0-3	Death or dependency at 3 months	3/13 (23.1%)	12/26 (46.2%)	0.50 (0.17-1.47)	-23.1%
ATLANTIS 3-4.5 [13]	3-4.5	Death or dependency at 3 months	75/145 (51.7%)	79/157 (50.3%)	1.03 (0.82-1.28)	+1.4%
ECASS II MS[13]	**0-3**	Death or dependency at 3 months	39/81 (48.1%)	44/77 (57.1%)	0.84 (0.63-1.13)	-8.4%
ECASS II 3-4.5[13]	3-4.5	Death or dependency at 3 months	61/131 (46.6%)	84/134 (62.7%)	0.74 (0.59-0.93)	-16.1%
ECASS III MS[13] Wardlaw *et al.* 2009[15]	**3-4.5**	Death or dependency at 3 months	140/418 (33.5%)	155/403 (38.4%)	0.87 (0.73-1.05)	-4.9%

Study	Time from symptom onset to treatment (hours)	Death or dependency Outcomes	Alteplase group	Placebo group	Relative risk (95% CI)	Absolute risk difference (alteplase vs. placebo group)
NINDS I and II MS[13] Wardlaw *et al.* 2009[15]	0-3	Death or dependency at 3 months	155/312 (49.7%)	192/312 (61.5%)	0.81 (0.70-0.93)	-11.8%

Table 10 Symptomatic intracranial haemorrhage (SICH) in ITT population of ECASS III[25]

Definition of SICH[25]	**Alteplase group n (%)**	**Placebo group n(%)**
ECASS III definition (any haemorrhage with neurologic deterioration, as indicated by an NIHSS score that was higher by 4 points or more than the value at baseline or the lowest value in the first 7 days, or any haemorrhage leading to death. In addition, the haemorrhage must have been identified as the predominant cause of the neurologic deterioration.)	10 (2.4)	1 (0.2)
ECASS II definition (blood at any site in the brain on the CT scan (as assessed by the CT reading panel, independently of the assessment by the investigator), documentation by the investigator of clinical deterioration, or AEs indicating clinical worsening (e.g. drowsiness, increase of hemiparesis) or causing a decrease in the NIHSS score of 4 or more points)	22 (5.3)	9 (2.2)
SITS-MOST definition (local or remote parenchymal hematoma type 2 on the imaging scan obtained 22 to 36 hours after treatment, plus neurologic deterioration, as indicated by a score on the NIHSS that was higher by 4 points or more than the baseline value or the lowest value between baseline and 24 hours, or haemorrhage leading to death)	8 (1.9)	1 (0.2)
NINDS definition (CT scans were required at 24 hours and 7-10 days after stroke onset, and whenever any clinical finding suggested haemorrhage. A haemorrhage was considered symptomatic if it had not been seen on a previous CT scan and there had been either a suspicion of a haemorrhage or any decline in neurological status.)	33 (7.9)	14 (3.5)

Table11 Symptomatic intracranial haemorrhage (SICH) results from individual trials

Study	Time from symptom onset to treatment (hours)	SICH Outcomes	Alteplase group	Placebo group	Relative risk (95% CI)	Absolute risk difference (alteplase vs. placebo group)
ATLANTIS A MS[13] Wardlaw *et al.* 2009[15]	0-3	SICH within 10 days	2/10 (20.0%)	0/12 (0%)	5.91 (0.32-110.47)	+20.0%
ATLANTIS B MS[13] Wardlaw *et al.* 2009[15]	0-3	SICH within 10 days	1/13 (7.7%)	0/26 (0%)	5.79 (0.25-132.98)	+7.7%
ECASS II MS[13] Wardlaw *et al.* 2009[15]	**0-3**	SICH within 10 days	5/81 (6.2%)	3/77 (3.9%)	1.58 (0.39-6.41)	+2.3%
ECASS III MS[13]	**3-4.5**	SICH within 10 days	10/418 (2.4%)	2/403 (0.5%)	4.82 (1.06-21.87)	+1.9%

Study	Time from symptom onset to treatment (hours)	SICH Outcomes	Alteplase group	Placebo group	Relative risk (95% CI)	Absolute risk difference (alteplase vs. placebo group)
ECASS III Hacke *et al.* 2008[25] Wardlaw *et al.* 2009[15]	**3-4.5**	SICH within 10 days (ECASS III definition from Hacke *et al.* 2008)	10/418 (2.4%)	1/403 (0.2%)	9.64 (1.24-74.97)	+2.2%
ECASS III Hacke *et al*. 2008[25]	**3-4.5**	SICH within 10 days (ECASS II definition from Hacke *et al*. 2008)	22 (5.3%)	9 (2.2%)	2.36 (1.01-50.6)	+3.0%
ECASS III Hacke *et al*. 2008[25]	**3-4.5**	SICH within 10 days (SITS-MOST definition from Hacke *et al*. 2008)	8 (1.9%)	1 (0.2%)	7.71 (0.97-61.39)	+1.7%
ECASS III Hacke *et al*. 2008[25]	**3-4.5**	SICH within 10 days (NINDS definition from Hacke *et al*. 2008)	33 (7.9%)	14 (3.5%)	2.27 (1.23-4.18)	+4.4%

Study	Time from symptom onset to treatment (hours)	SICH Outcomes	Alteplase group	Placebo group	Relative risk (95% CI)	Absolute risk difference (alteplase vs. placebo group)
NINDS I and II MS[13] Wardlaw *et al*. 2009[15]	0-3	SICH within 10 days	20/312 (6.4%)	2/312 (0.6%)	10.00 (2.36-42.42)	+5.8%
NINDS I and II NINDS study group 1995 [28]	0-3	SICH at 3 months	23/312 (7.4%)	4/312 (1.3%)	5.75 (2.01-16.43)	+6.1%
NINDS I and II Kwiatkowski *et al*. 1999 [33]	0-3	SICH at 12 months	25/312 (8.0%)	5/312 (1.6%)	5.00 (1.94-12.89)	+6.4%

4.2.1.2 Other outcomes

Functional recovery or neurological deficit

ECASS III reported a Global outcome measure, combining the 90-day outcome of a score of 0-1 on the mRS, a score of 1 on the Glasgow Outcome Scale, and a score of 0-1 on the NIHSS. MS section 5.5.1 reports an odds ratio of 1.28 (95%CI 1.00-1.65) from Hacke *et al.* 2008[25] in favour of alteplase for this outcome. In ATLANTIS B and ECASS II,[13] NIHSS from baseline to 30 days showed a statistically significant difference favouring alteplase, whereas other secondary endpoints in these trials did not show significant treatment effects.

Adverse effects of treatment

Table 15 and section 5.9 of the MS summarise adverse events in ECASS III in the ITT population. Investigator-defined drug-related AEs were reported for 23.9% (n=100/418) of the group assigned to alteplase, and 6.9% (n=28/403) of the placebo group. For the group assigned to alteplase 25.1% (n=105/418) had a serious AE. For the group assigned to placebo 24.6% (n=99/403) had a serious AE. Fatal AEs were reported for 7.7% (n=32/418) of the group assigned to alteplase, and 8.4% (n=34/403) of the placebo group. SICH are reported above. Any ICH was reported in 27.0% (n=113/418) alteplase group and 17.6% (n=71/403) of the placebo group.

Health-related quality of life

Health-related quality of life was only reported by one of the included studies, ECASS II.[34] The results reported were for patients treated 0-6 hours after symptom onset, and so some of the participants would fall outside UK marketing authorisation. This RCT found no significant treatment effect for either the physical (p=0.284) or the mental (p=0.183) components of SF-36.[21] This was based on median scores of 49.8 for alteplase and 48.1 for placebo on the mental health component, and for the physical component median scores of 38.4 and 36.7 respectively.[21] It should be noted that there was also no significant difference in this trial's primary outcome when considering all patients treated in the timeframe of 0-6 hours after symptom onset[21].

Length of hospital stay

Length of hospital stay is defined as a secondary outcome for ECASS II (section 5.3.5 of MS) and ECASS III (Table A20 of MS) within the MS,[13] although no results are presented. Length of stay data are described in MS Appendix 9 for ECASS I, but this study is not considered relevant due to the use of a dose outside of the UK marketing authorisation.

Mental health outcomes

Mental health outcomes including anxiety and depression were specified in the scope of the appraisal, but no data are presented for these outcomes within the submission.

4.2.1.3 Non-RCT evidence

For relevant non-RCT evidence, the MS section 5.8 describes one observational study, SITS-ISTR [30]. This was a large, un-controlled study of alteplase. At three month follow-up, 57% (10,531 of 18,317) of patients treated within 0-3 hours of symptom onset were functionally independent. For patients treated within the 3-4.5 hour treatment window, 60% (1,075 of 1,784) were functionally independent. Mortality rates were 12% for both 0-3 and 3-4.5 hour treatment windows at three months follow-up, and SICH rates were 2% for both the 0-3 hour and the 3-4.5 hour treatment windows.

4.2.2 Quality assessment

The MS page 183 has the quality assessment for the ECASS III trial. The criteria chosen for validity assessment of the included RCT, based on CRD guidance,[7,35] were appropriate.

With regard to question 1 from Table A2 of the MS, "Was randomisation carried out appropriately?" The MS describes random assignment, in blocks of four at each centre. With regard to question 2 from Table A2, "Was the concealment of treatment allocation adequate?" The MS has interpreted the question as referring to blinding. Concealment of treatment allocation, when used in quality assessment of randomised trials, indicates that the treatment group that will be allocated cannot be known in advance of assignment.[7,35] Treatment allocation needs to be concealed to prevent selection bias, as explained in CRD guidance, so that investigators cannot predict the treatment group to which the next patient will be allocated.[7,35] The concealment of treatment allocation in ECASS III was achieved by central randomisation using a voice-randomisation system (as specified in the MS in answer to question 1 in Table A2), thus there was adequate concealment of treatment allocation.

With regard to question 3 from Table A2, "Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?" The MS concludes that any differences between the treatment groups were unlikely to have a significant effect on results. The MS (page 184) points out that there was a difference between treatment groups in history of stroke, with fewer patients in the alteplase treatment group (7.7%) having a history of stroke than in the placebo group (14.1%). Although not mentioned in Table A2, Table 12 of

the MS also describes a statistically significant difference in severity of stroke at baseline, with the mean NIHSS score being 10.7 for the alteplase treatment group and 11.6 for the placebo group.

With regard to question 4 from Table A2, "Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?" The MS describes that patients, clinicians and outcome assessors were blinded. The MS has discussed the problem of blinding clinicians to treatment group (p184 MS), however the trial had blinded outcome assessors which should address the potential bias.

With regard to question 5 from Table A2 "Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?" The MS states there was no imbalance in drop-outs between groups. With regard to question 6 from Table A2 "Is there any evidence to suggest that the authors measured more outcomes than they reported?" The MS states that there isn't. With regard to question 7 from Table A2 "Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?" The MS states that there was an ITT analysis with missing data replaced by worst possible primary endpoint.

Quality assessment of all included trials are shown in the tables below (adapted from Lloyd-Jones *et al*.[5]). Trials were generally of good quality in terms of the generation, allocation and concealment, of randomisation, although none of the trials stratified randomisation by stroke severity. Blinding of clinicians was problematic as noted earlier (section 4.1.2), however trials attempted to blind outcome assessors by employing assessors not involved in administering treatment.

Table 12 Quality assessment of included trials (adapted from Lloyd-Jones *et al.*[5])

Trial	What randomisation technique was used?	How was the allocation sequence concealed until interventions were assigned?	Was a justification of the sample size provided?
ATLANTIS A Clark *et al.* 2000[19]	Blocked randomisation stratified by clinical centre	Numbered treatment packs, the code for which was held by the co-ordinating centre.	Yes. However, enrolment was stopped prematurely because of concerns about safety in patients receiving alteplase 5-6 hours after symptom onset.
ATLANTIS B Clark *et al.* 1999[20]	Blocked randomisation stratified by clinical centre	Numbered treatment packs, the code for which was held by the co-ordinating centre.	Yes. However, enrolment was stopped prematurely following an interim analysis which indicated that treatment was unlikely to prove beneficial.
ECASS II Hacke *et al.* 1998[21]	Blocked randomisation stratified by centre for time since symptom onset (0-3 or 3-6 hours)	Sequentially numbered packs. The randomisation schedule was known only to the Clinical Trial Support Unit at Boehringer Ingelheim and to one member of the External Safety Committee. However, in emergencies, investigators had access to sealed opaque envelopes containing treatment allocation.	Yes
ECASS III Hacke *et al.* 2008[25]	Blocked randomisation stratified by centre	Centralised randomisation using a voice-randomisation system	Yes
NINDS I and II Marler et al 1995[28]	Permuted-block design with blocks of various sizes, with patients stratified according to clinical centre and time from stroke onset to start of treatment (0-90 or 91-180 minutes)	The Central Coordinating Centre received blind-labelled vials prepared by Genentech, plus a code list for the vial contents, and established a patient ID number which was then attached to the vial. These numbers were randomly ordered and randomly assigned to alteplase or placebo, with blocking by the 9 local clinical centres, not the 40 treatment centres. The 2 time strata were randomised separately. All treatment sites within each clinical centre's administration received an identically labelled supply of blinded vials, and a list indicating the order in which the patient numbers were to be utilised (ID numbers were random, not sequential). As each treatment site had the same list of numbers, when a patient was enrolled at one site, all sites were notified to mark off that number.	Yes

Table 13 Quality assessment of included trials (continued) (adapted from Lloyd-Jones *et al.*[5])

Trial	Were outcome assessors blinded to study allocation?	Were the study groups comparable at baseline?	Was an ITT analysis undertaken?
ATLANTIS A Clark *et al.* 2000[19]	The clinical exams at 30 and 90 days were performed by an individual who was not present during study drug administration and did not see the patient in the first 24 hours. Also, all patients who died and had any type of ICH were reviewed by the blinded independent data safety monitoring board.	Mostly, but a significantly higher percentage of patients in the placebo group were diabetic.	Yes, using "last observation carried forward" method, with death as the worst outcome score on all measures.
ATLANTIS B Clark *et al.* 1999[20]	The clinical exams at 30 and 90 days were performed by an individual who was not present during study drug administration and did not see the patient in the first 24 hours. Also, the records all patients who died and had any type of ICH were reviewed by the blinded independent data safety monitoring board.	Mostly, but a significantly higher percentage of patients in the alteplase group were diabetic.	Yes, using "last observation carried forward" method, with death as the worst outcome score on all measures.
ECASS II Hacke *et al.* 1998[21]	Follow-up at 90 days was carried out at each local centre by one of the local investigators. Measures were taken to reduce the risk that the examiner would be able to identify the treatment received (e.g. they did not receive the results of coagulation tests).	Said to be so by the investigators. However, the placebo group had a higher proportion of women, people on aspirin therapy, people receiving subcutaneous heparin, people with atrial fibrillation, but fewer people with previous MI.	Yes. For missing values, the last observation was carried forward. For the mRS and the BI, a worst-case imputation (mRS=5, BI=0) was made for missing values at day 90.
ECASS III Hacke *et al.* 2008[25]	Patients were assessed by an examiner who was unaware of the treatment assignment. Members of the safety outcome adjudication committee, who were unaware of the treatment assignments, reviewed all CT or MRI scans, and classified the findings.	Mostly, apart from severity of stroke and history of stroke	Yes, with worst possible outcome for missing data
NINDS I Marler et al 1995 [28]	Each CT scan was reviewed for evidence of haemorrhage by a neuroradiologist blinded to clinical information. (When reviewing the submitted	Said by the investigators to be well matched in all respects except weight; there also seem to be discrepancies in terms of aspirin therapy and	Yes. Patients who were not assessed by NIHSS at 24 hours were considered to have had no improvement.

Trial	Were outcome assessors blinded to study allocation?	Were the study groups comparable at baseline?	Was an ITT analysis undertaken?
	scans, this neuroradiologist was aware of symptomatic and asymptomatic ICHs reported by the treatment centres, and would confirm or reject the finding. Outcomes were determined by certified examiners who had neither performed the baseline examination nor been present during the initial treatment. To prevent premature extrapolation of the results of NINDS I to NINDS II, investigators remained unaware of the results of NINDS I until the completion of NINDS II.	previous TIA. The FDA also draws attention to the fact that patients in the alteplase group have slightly less severe strokes than those in the placebo group	
NINDS II Marler et al 1995[28]		Said by the investigators to be well matched in all respects except aspirin use; however, there also seems to be as much of a weight discrepancy as in NINDS I, where the investigators comment on it. The FDA also draws attention to a small but statistically significant difference in age, the alteplase group being older; they are also lighter and have slightly less severe strokes	Yes. Patients who died before the 3-month assessment were given the worst possible score for all outcomes. For surviving patients with missing data, if no outcome data were available at 3 months, data from the measurement closest in time, but at least 7 days after randomisation, were used; otherwise, the worst possible score was assigned.

The NINDS study had an excess of patients with the mildest strokes (baseline NIHSS 2-6) in the alteplase group, and the FDA noted that this had the potential to bias the study, especially for dichotomised endpoints where such patients need only improve slightly to meet the criteria for success.[5,36] An HTA report[37] suggested that the NINDS trial should be excluded from sensitivity analyses, whereas the Cochrane review[15] suggested the imbalance probably caused about a 3% overestimate of the effect of alteplase on death or dependency leaving the treatment effect to be clinically worthwhile.[5] The ECASS III trial had an imbalance in baseline characteristics in terms of the alteplase group having fewer patients with a history of stroke, and lower severity of stroke, than the placebo group. Unlike NINDS, ECASS III restricted to NIHSS score>25 at baseline. Hacke *et al.*[25] presented an adjusted analysis of the primary outcome measure of ECASS III, adjusted by baseline NIHSS, smoking status, time from onset of symptoms to treatment and prior hypertension, and reported that the primary outcome measure still had a statistically significant treatment effect following adjustment.

4.2.3 Statistical approach

Section 5.3.6 of the MS describes the statistical approach used by ECASS III. ECASS III was adequately powered to detect between group differences for the primary outcome of mRS score 0-1. Analysis was by ITT, with missing outcome data assigned the worst possible outcome. Missing baseline NIHSS score data were assigned the best possible score. Section 5.3.7 of the MS lists the sub-group analyses carried out, and points out that all subgroup analyses were not adequately powered. Figures 3 to 5 in the MS present both pre-specified and post-hoc subgroup analyses from Bluhmki *et al.* 2009.[31] All RCTs used appropriate statistical techniques. All RCTs presented ITT analyses (see section 4.2.2).

4.2.4 Outcome selection

The ERG judged outcome selection in the MS to be an appropriate approach, reflecting the outcomes in the final scope provided by NICE. The main outcome utilised was the endpoint of death and dependency (mRS 3-6). This approach captures both functional recovery, and any death or disability caused by SICH, and was the approach used in the 2007 NICE STA of alteplase 0-3 hours.[5,6] It was also the approach used in the Cochrane review of thrombolysis.[15]

4.2.5 Relevance to scope

All trials included in the analyses in the MS provided outcome data relevant to the NICE final scope.[17] All trials were placebo controlled which fits within (being slightly more restrictive than) the scope set out by NICE.[17]

Contraindications for alteplase comprise: age under 18 or over 80; where minor neurological deficit is present or symptoms are rapidly improving; where a patient has suffered a severe stroke as assessed clinically (e.g. NIHSS>25) and/or by appropriate imaging techniques; where a patient suffers a seizure at onset of the stroke; where there is evidence of intracranial haemorrhage (ICH) on the CT-scan or symptoms suggestive of a of subarachnoid haemorrhage; patients who have received heparin in the previous 48 hours if the aPTT is elevated, or who have a platelet count <100,000/mm3 or who have suffered a stroke in the previous 6 months or who have a history of prior stroke and diabetes; patients with blood glucose levels < 50 mg/dl or >400 mg/dl at baseline and patients with systolic blood pressure > 185 or diastolic BP > 110 mm Hg. All trials included adult patients diagnosed with AIS eligible for treatment with alteplase (Table 14), although some included other patients. NINDS included 42 patients aged over 80. ECASS III was the only trial to explicitly exclude patients with NIHSS>25 at baseline. NINDS differed from ECASS III in that ECASS III

restricted to age under 80 and baseline NIHSS<25, and excluded diabetics with prior stroke, or any heparin use.

All trials administered alteplase at the licensed dose of 0.9mg/kg alteplase to a maximum of 90mg (10% as initial intravenous bolus, 90% as infusion over the subsequent 60 minutes). All included trials had participants administered alteplase within the licensed 0-4.5 hours, additionally three of the trials (ATLANTIS A, ATLANTIS B, ECASS II) included some participants with administration of alteplase outside of the licensed time window (4.5 to 6 hours). However, analyses were restricted to participants for whom alteplase was administered within 4.5 hours of symptom onset, and so this accurately reflected the NICE scope.

Table 14 Trial population and protocol violations

Trial	Number of patients randomised	Randomised patients treated within 4.5 hours after symptom onset	Population eligibility criteria	Trial protocol violations
ATLANTIS A 0-6 hours[13,19]	Alteplase 71 Placebo 71	ATLANTIS A and B Alteplase 168 Placebo 195	Inclusion: Age 18-79 Clinical diagnosis of ischaemic stroke causing a measurable neurological deficit Onset of symptom of ischaemic stroke within 6 hours of the time to initiation of treatment with the study drug (if not known - e.g. patient wakes up with new symptoms - the time the patient was last observed to be neurologically intact is taken as the time of onset) Exclusion: Coma, severe obfundation, fixed eye deviation, or complete hemiplegia Minor stroke symptoms only (i.e. <4 points on the NIHSS and normal speech and visual fields), or major symptoms that are rapidly improving by time of randomisation Cerebral CT scan with evidence of high-density lesion consistent with haemorrhage of any degree, or significant mass effect with midline shift, or subarachnoid haemorrhage History of stroke within the previous 6 weeks Known active seizure disorder, or first seizure within the 6 hours immediately before administration of study drug Previous known intracranial haemorrhage, neoplasm, subarachnoid haemorrhage, arteriovenous malformation, or aneurysm Clinical presentation of subarachnoid haemorrhage, even if CT scan normal Hypertension: SBP >185 or DBP >110 on repeated measures before study entry, or requiring aggressive (e.g. intravenous) treatment to reduce BP to within these limits Presumed septic embolus Presumed pericarditis or presence of ventricular thrombus or aneurysm related to recent acute MI Recent (within 30 days) surgery or biopsy of a parenchymal organ Recent (within 30 days) trauma, with internal injuries or ulcerative wounds Recent (within 90 days) head trauma Any active or recent (within 30 days) haemorrhage Known hereditary or acquired haemorrhagic diathesis, e.g. activated partial thromboplastin time or	No protocol violations were reported

Trial	Number of patients randomised	Randomised patients treated within 4.5 hours after symptom onset	Population eligibility criteria	Trial protocol violations
			prothrombin time greater than normal, unsupported coagulation factor deficiency, or oral anticoagulant therapy with the prothrombin time greater than normal Pregnancy, lactation, or parturition within the previous 30 days Baseline lab values: glucose <50 or >400, platelets <100,000, haematocrit <25 Other, serious, advanced, or terminal illness Any other condition which the investigator feels would pose a significant hazard to the patient if rTPA therapy were initiated Current participation in another research drug protocol	
ATLANTIS B 0-5 hours[13,20]	Alteplase 307 Placebo 306		Inclusion: Age 18-79 Clinical diagnosis of ischaemic stroke causing a measurable neurological deficit Onset of symptom of ischaemic stroke within 3-5 hours of initiation of treatment with the study drug (if not known - e.g. patient wakes up with new symptoms - the time the patient was last observed to be neurologically intact is taken as the time of onset) Exclusion: Coma, severe obfundation, fixed eye deviation, or complete hemiplegia Minor stroke symptoms only (i.e. <4 points on the NIHSS and normal speech and visual fields), or major symptoms that are rapidly improving by time of randomisation Cerebral CT scan with evidence of high-density lesion consistent with haemorrhage of any degree, or significant mass effect with midline shift, subarachnoid haemorrhage, or parenchymal hypodensity, loss of gray/white matter distinction, and/or effacement of cerebral sulci in >33% of the middle cerebral artery territory History of stroke within the previous 6 weeks Known active seizure disorder, or first seizure within the 6 hours immediately before administration of study drug Previous known intracranial haemorrhage, neoplasm, subarachnoid haemorrhage, arteriovenous malformation, or aneurysm Clinical presentation suggestive of subarachnoid haemorrhage, even if initial CT scan is normal	Alteplase 27 (8.9%) of which 11 did not receive treatment (2 no treatment, 9 placebo) 2 before 3 hours 14 after 5 hours Placebo 21 (6.9%) of which 1 no treatment 4 given alteplase 6 before 3 hours 10 after 5 hours

Trial	Number of patients randomised	Randomised patients treated within 4.5 hours after symptom onset	Population eligibility criteria	Trial protocol violations
			Hypertension: SBP >185 or DBP >110 on repeated measures before study entry, or requiring aggressive (e.g. intravenous) treatment to reduce BP to within these limits Presumed septic embolus Presumed pericarditis or presence of ventricular thrombus or aneurysm related to recent acute MI Recent (within 30 days) surgery or biopsy of a parenchymal organ Recent (within 30 days) trauma, with internal injuries or ulcerative wounds Recent (within 90 days) head trauma Any active or recent (within 30 days) haemorrhage Known hereditary or acquired haemorrhagic diathesis, e.g. activated partial thromboplastin time or prothrombin time greater than normal, unsupported coagulation factor deficiency, or oral anticoagulant therapy with the prothrombin time greater than normal Pregnancy, lactation, or parturition within the previous 30 days Baseline lab values: glucose <50 mg/dL or >400 mg/dL, platelets <100,000/L, haematocrit <25 Other, serious, advanced, or terminal illness Any other condition which the investigator feels would pose a significant hazard to the patient if rTPA therapy were initiated Current participation in another research drug protocol	

Trial	Number of patients randomised	Randomised patients treated within 4.5 hours after symptom onset	Population eligibility criteria	Trial protocol violations
ECASS II 0-6 hours[13,21]	Alteplase 409 Placebo 391	Alteplase 212 Placebo 211	Inclusion: Age 18-80 Clinical diagnosis of moderate to severe ischaemic hemispheric stroke Onset of symptom of ischaemic stroke within 6 hours of the time to initiation of treatment with the study drug No or only minor early signs of infarction on the initial CT scan Could be followed up for the 90-day study period Exclusion: Signs of intracerebral haemorrhage or parenchymal hypoattenuation exceeding a third of the middle-cerebral-artery territory Brain swelling exceeding 33% of the middle-cerebral-artery territory Subarachnoid haemorrhage Time of stroke onset not exactly known (e.g. waking with stroke symptoms) Coma or stupor Hemiplegia plus fixed eye deviation Minor stroke symptoms only (i.e. >50 of the maximum 58 points on the Scandinavian stroke scale (SSS) before randomisation, or rapid improvement of symptoms Hypertension at time of randomisation: SBP >185 or DBP >110 Any traumatic brain injury within the previous 14 days Recent (within 3 months) surgery on the central nervous system Haemorrhage of the GI or urinary tract Current therapy with iv or subcutaneous heparin to raise the clotting time Known hereditary or acquired haemorrhagic diathesis (e.g. activated partial thromboplastin time or prothrombin time greater than normal, uncorrected coagulation factor deficiency, oral anticoagulant therapy, or haemorrhagic retinopathy) Pregnancy, lactation, or parturition within the previous 30 days Lack of a medically approved method of contraception in women of childbearing age Baseline blood glucose <2.75 mmol/L(50 mg/dL) or >22.0 mmol/L (400 mg/dL) Baseline platelet counts <100 x 109 Packed cell values <25% Current or recent (within 3 months) participation in another trial of an investigational drug	Alteplase 34 (8.3%) of which 2 did not receive treatment Placebo 38 (9.7%) of which 5 did not receive treatment (Most protocol violations were violations of the CT criteria.)

Trial	Number of patients randomised	Randomised patients treated within 4.5 hours after symptom onset	Population eligibility criteria	Trial protocol violations
ECASS III 3-4.5 hours[13,25]	Alteplase 418 Placebo 403	Alteplase 418 Placebo 403	Inclusion Criteria: Female or male inpatients Age: 18 - 80 years. Clinical diagnosis of ischemic stroke causing a measurable neurological deficit defined as impairment of language, motor function, cognition and/or gaze, vision or neglect. Ischemic stroke is defined as an event characterized by the sudden onset of an acute focal neurologic deficit presumed to be due to cerebral ischemia after CT scan excludes haemorrhage. Onset of symptoms between 3 and 4 hours prior to initiation of administration of study drug. (3-4.5hrs following protocol amendment). Stroke symptoms are to be present for at least 30 minutes and have not significantly improved before treatment. Symptoms must be distinguishable from an episode of generalized ischemia (i.e. syncope), seizure, or migraine disorder. Exclusion criteria: Evidence of intracranial haemorrhage (ICH) on the CT-scan. Symptoms of ischaemic attack began more than 4 hours and 30 minutes prior to infusion start or when time of symptom onset is unknown. Minor neurological deficit or symptoms rapidly improving before start of infusion. Severe stroke as assessed clinically (e.g. NIHSS>25) and/or by appropriate imaging techniques. Epileptic seizure at onset of stroke Symptoms suggestive of subarachnoid haemorrhage, even if the CT-scan is normal. Administration of heparin within the previous 48 hours and a thromboplastin time exceeding the upper limit of normal for laboratory History of prior stroke and concomitant diabetes. Prior stroke within the last 3 months Platelet below 100,000/mm3. Systolic blood pressure >185 mmHg or diastolic blood pressure >110 mmHg, or aggressive management (IV medication) necessary to reduce BP to these limits. Blood glucose <50 or > 400 mg/dl (< 2.77 or > 22.15 mmol / l). Known haemorrhagic diathesis Patients receiving oral anticoagulants Manifest or recent severe or dangerous bleeding Known history of or suspected intracranial haemorrhage Suspected subarachnoid haemorrhage or condition after subarachnoid haemorrhage from aneurysm History of central nervous system damage (i.e. neoplasm, aneurysm, intracranial or spinal surgery) Haemorrhagic retinopathy, e.g. in diabetes (vision disturbances may indicate haemorrhagic retinopathy)	Alteplase 43 (10.3%) of which 12 Did not receive treatment 4 Had uncontrolled hyper-tension 10 Did not meet age criterion 10 Did not meet CT criteria 1 Received treatment outside 3-4.5hr window 6 Had other reason. Placebo 48 (11.9%) of which 13 Did not receive treatment 13 Had uncontrolled hyper-tension 6 Did not meet age criterion 7 Did not meet CT criteria 7 Received treatment outside 3-4.5hr window 2 Had other reason

Trial	Number of patients randomised	Randomised patients treated within 4.5 hours after symptom onset	Population eligibility criteria	Trial protocol violations
NINDS 0-3 hours[13,36,38]	NINDS I Alteplase 144 Placebo 147	NINDS I Alteplase 144 Placebo 147	Inclusion: Ischaemic stroke with clearly defined time of onset and deficit measurable on the NIHSS No evidence of intracranial haemorrhage on the initial CT scan Age >18 (at start of study upper age limit of 80, but this limit was removed) Clinical Centre administering the specific treatment site has a sufficient balance of patients between strata (enrolment into 91-180 min stratum permitted only if number of patients in that stratum not more than 2 greater than in the 0-90 stratum) Exclusion: evidence of intracranial haemorrhage on the initial CT scan Another stroke or serious head trauma within the previous 3 months Major surgery in the last 14 days History of intracranial haemorrhage Systolic BP >185 or diastolic BP >100 mm Hg, or aggressive treatment required to reduce BP to those limits Rapidly improving or minor symptoms Symptoms suggestive of subarachnoid haemorrhage GI or urinary tract haemorrhage within previous 21 days Arterial puncture at a non-compressible site within the previous 7 days Seizure at stroke onset Taking anticoagulants, or had received heparin within the 48 hours preceding stroke onset and with an elevated partial-thromboplastin time Prothrombin time >15 seconds, platelet counts <100,000/mm3, or glucose concentrations <50 mg/dl (2.7 mmol/L) or > 400 mg/dl (22.2 mmol/L) Female and lactating or pregnant serious medical illness that would interfere with trial clinical presentation consistent with MI or post-MI pericarditis	Alteplase 29 (9.1%) Placebo 25 (8.0%) The most common protocol violation involved the BP criteria.
	NINDS II Alteplase 168 Placebo 165	NINDS II Alteplase 168 Placebo 165		

4.2.6 Evidence synthesis

The MS presents meta-analyses using the Mantel–Haenszel method to calculate relative risks (RR). This was an appropriate method. The Cochrane handbook recommends presenting RR data as they are more easily interpretable than odds ratios, and the Mantel–Haenszel method is reliable even when few trials are available for analysis.[39] Meta-analyses are presented for both fixed and random effects, as recommended by Cochrane[39].

There were no additional trials identified to those included in the 2007 NICE STA TA122[6]. The main evidence was provided by meta-analysis of the ECASS II and NINDS trials. Sensitivity analyses included the ATLANTIS A and ATLANTIS B trials. For the 3-4.5 hour treatment window, the main evidence was provided by the ECASS III trials. Sensitivity analyses included CIC data from the ATLANTIS A, ATLANTIS B and the ECASS II trials in meta-analyses[13]. Table 15 shows RRs generated by meta-analyses. Study results of ECASS III are shown in the Table, alongside meta-analyses. The death or dependency outcome uses the definition mRS 3-6.

For the 0-3 hour treatment window, there was no statistically significant difference in all cause mortality at 3 months in either the fixed or random effects meta-analysis. There was an increased risk of SICH, RR 4.90 (1.90-12.61) p=0.001 significant by fixed meta-analysis, but failing to reach significance by random effects meta-analysis. The results of the sensitivity analysis incorporating data from the ATLANTIS trial were similar although in this analysis the RR for SICH was significantly higher for both fixed and random effects meta-analysis.

Death or dependency at three months follow-up significantly favoured alteplase, RR 0.81 (95%CI 0.72-0.92) p=0.002, by the meta-analysis of the two main trials which included 393 participants allocated to alteplase, and 389 to placebo. Similarly, by the sensitivity analysis including n=416 alteplase, and n=427 placebo participants, RR 0.82 (95%CI 0.72-0.93) p=0.002, death or dependency at three months follow-up significantly favoured alteplase.

For the 3-4.5 hour treatment window, the main evidence used in the MS is the ECASS III RCT. This RCT included n=418 alteplase and n=403 placebo participants. In the ECASS III trial, death or dependency at three months follow-up did not show a statistically significant treatment effect RR (for alteplase with reference to placebo) 0.87 (95%CI 0.73-1.05) p=0.14. Sensitivity analysis using CIC data from an additional three studies, alteplase n=694 placebo n=694, produced an RR which significantly favoured alteplase if analysed by fixed-effect

methods RR 0.87 (0.78-0.99) p=0.03, showing a similar trend that failed to reach significance if analysed by random-effect methods 0.87 (0.74-1.04) p=0.12. As can be seen, the RR values were similar, and this difference can be attributed to the more conservative estimates produced by random-effect analyses than by fixed-effect analyses. For the 3-4.5 hour treatment window, there was no statistically significant difference in all cause mortality at 3 month, but there was a significantly increased risk of SICH, RR 4.82 (1.06-21.87) p=0.04.

Considering the 0-4.5 hour treatment window, analysis of the two main trials of 0-3 hours, n=393 alteplase and n=389 placebo, and the main trial of 3-4.5 hours, n=418 alteplase and n=403 placebo, random-effects meta-analysis showed an RR 0.83 (0.75-0.92) p=0.0006, significantly favouring alteplase. Again, there was no statistically significant increase in all cause mortality at 3 months, but there was a significantly increased risk of SICH. Heterogeneity between the three studies was low ($I^2 < 25\%$) for the outcomes of death and death or dependency, but moderate for SICH ($I^2=42\%$). However, the heterogeneity across the three studies, examining two different treatment windows, was lower than that seen when pooling data from the two trials examining 0 to 3 hours as the results of the ECASS III study were closer to those of the large NINDS study than the small subgroup analysis of the ECASS II study. A pooled analysis of 3670 patients from 8 RCTs[7] which examined the interaction between treatment effect and onset to treatment time, found that there is a significant interaction for the outcomes of death and dependency (mRS of greater than 1) and mortality, but not for SICH. (It should be noted that not all of the 8 RCTs included in the pooled analysis examined the use of alteplase in line with its UK marketing authorisation.) However, the adjusted odds ratios provided by the pooled analysis[7] support the meta-analysis of the RCT data presented within the MS, in showing a significant treatment effect for dependency and a non-significant difference in mortality for both the 0 to 3 and 3 to 4.5 hour onset to treatment windows.

Table 15 Meta-analyses: All-cause mortality at three months follow-up

Treatment window	Trials	Number of events: Alteplase	Participants in analysis: Alteplase	Number of events: Placebo	Participants in analysis: Placebo	Relative Risk (fixed effects model) (95% CI)	Relative Risk (random effects model) (95% CI)
0-3 hours	ECASS II, NINDS	65	393	70	389	0.92 (0.68-1.25) p=0.61	1.05 (0.55-2.03) p=0.88
0-3 hours	ATLANTIS A and B, ECASS II, NINDS	69	416	72	427	0.97 (0.72-1.31) p=0.85	1.15 (0.62-2.16) p=0.65
3-4.5 hours	ECASS III	28	418	33	403	0.82 (0.50-1.33) p=0.42	
3-4.5 hours	ATLANTIS A and B, ECASS II, ECASS III	53	694	64	694	0.83 (0.59-1.18) p=0.30	0.85 (0.43-1.67) p=0.63
0-4.5 hours	ECASS II (0-3) ECASS III (3-4.5) NINDS (0-3)	93	811	103	792	0.89 (0.69-1.15 p=0.37	0.89 (0.67-1.18) p=0.41
0-4.5 hours	ATLANTIS A and B (0-3 and 3-4.5) ECASS II (0-3 and 3-4.5) ECASS III (3-4.5) NINDS (0-3)	122	1110	136	1121	0.91 (0.72-1.14) p=0.39	0.96 (0.65-1.41) p=0.83

Table 16 Meta-analyses: Death or dependency at three months follow-up

Treatment window	Trials	Outcome measure	Number of events: Alteplase	Participants in analysis: Alteplase	Number of events: Placebo	Participants in analysis: Placebo	Relative Risk (fixed effects model) (95% CI)	Relative Risk (random effects model) (95% CI)
0-3 hours	ECASS II, NINDS	Death or dependency at 3 months	194	393	236	389	0.81 (0.72-0.93) p=0.002	0.81 (0.72-0.92) p=0.002
0-3 hours	ATLANTIS A and B, ECASS II, NINDS	Death or dependency at 3 months	204	416	255	427	0.81 (0.72-0.92) p=0.001	0.82 (0.72-0.93) p=0.002
3-4.5 hours	ECASS III	Death or dependency at 3 months	140	418	155	403	0.87 (0.73-1.05) p=0.14	
3-4.5 hours	ATLANTIS A and B, ECASS II, ECASS III	Death or dependency at 3 months	276	694	318	694	0.87 (0.78-0.99) p=0.03	0.87 (0.74-1.04) p=0.12
0-4.5 hours	ECASS II (0-3) ECASS III (3-4.5) NINDS (0-3)	Death or dependency at 3 months	334	811	391	792	0.84 (0.75-0.93) p=0.001	0.83 (0.75-0.92) p=0.0006)
0-4.5 hours	ATLANTIS A and B (0-3 and 3-4.5) ECASS II (0-3 and 3-4.5) ECASS III (3-4.5) NINDS (0-3)	Death or dependency at 3 months	480	1110	573	1121	0.85 (0.78-0.93) p=0.0002	0.85 (0.77-0.94) p=0.001

Table 17 Meta-analyses: Symptomatic intracranial haemorrhage (SICH)

Treatment window	Trials	Outcome measure	Number of events: Alteplase	Participants in analysis: Alteplase	Number of events: Placebo	Participants in analysis: Placebo	Relative Risk (fixed effects model) (95% CI)	Relative Risk (random effects model) (95% CI)
0-3 hours	ECASS II, NINDS	SICH within 10 days	25	393	5	389	4.90 (1.90-12.61) p=0.001	3.94 (0.61-25.47) p=0.15
0-3 hours	ATLANTIS A and B, ECASS II, NINDS	SICH within 10 days	28	416	5	427	5.03 (2.12-11.95) p=0.0003	4.24 (1.52-11.83) p=0.006
3-4.5 hours	ECASS III	SICH within 10 days	10	418	2	403	4.82 (1.06-21.87) p=0.04	
0-4.5 hours	ECASS II (0-3) ECASS III (3-4.5) NINDS (0-3)	SICH within 10 days	35	811	7	792	4.88 (2.19-10.87) p=0.0001	4.18 (1.39-12.53) p=0.01

4.2.7 Additional clinical work conducted by the ERG

No additional work was carried out by the ERG.

4.3 Conclusions

The ERG believes that all relevant RCTs were identified in the MS. The submitted evidence in the MS reflected the decision problem within the NICE final scope.

RCTs included were generally of good quality with regard to randomisation and having blinded outcome assessors. However, both NINDS, one of the two main trials for 0-3 hours, and the trial contributing most participants for 0-3 hours, and the ECASS III RCT, providing the main evidence for 3-4.5 hours, had imbalances in baseline stroke severity favouring alteplase. There is disagreement in the literature as to whether the imbalance in the NINDS trial would significantly skew treatment effect outcomes.[37] [15]

Risk of mortality at three months follow-up was not significantly different for alteplase than for placebo, for either 0-3 or 3-4.5 hour treatment windows. Risk of SICH was significantly higher for alteplase than for placebo for both treatment windows. The main outcome was death or dependency.

For the 0-3 hour treatment window, there were no additional trials identified to those included in the 2007 NICE STA TA122[5,6]. Death or dependency at three months follow-up significantly favoured alteplase, RR 0.81 (95%CI 0.72-0.92) p=0.002, by random-effects meta-analysis of the two main trials which included 393 participants allocated to alteplase, and 389 to placebo. Similarly, by the sensitivity analysis including ATLANTIS A and B, n=416 alteplase, and n=427 placebo participants, RR 0.82 (95%CI 0.72-0.93) p=0.002, death or dependency at three months follow-up significantly favoured alteplase.

For the 3-4.5 hour treatment window, the main evidence used in the MS is the ECASS III RCT. This RCT included n=418 alteplase and n=403 placebo participants. In the ECASS III trial, death or dependency at three months follow-up did not show a statistically significant treatment effect RR (for alteplase with reference to placebo) 0.87 (95%CI 0.73-1.05) p=0.14, although the midpoint favoured alteplase. Sensitivity analysis using CIC data from an additional three studies (ATLANTIS A and B, and ECASS II), alteplase n=694 placebo n=694, significantly favoured alteplase for the outcome of death or dependency if analysed by fixed-effect methods RR 0.87 (0.78-0.99) p=0.03, showing a similar trend that failed to reach significance if analysed by random-effect methods 0.87 (0.74-1.04) p=0.12.

Considering the 0-4.5 hour treatment window, analysis of the two main trials of 0-3 hours, n=393 alteplase and n=389 placebo, and the main trial of 3-4.5 hours, n=418 alteplase and n=403 placebo, random-effects meta-analysis showed an RR 0.83 (0.75-0.92) p=0.0006, significantly favouring alteplase. There is some evidence from a pooled analysis of 8 RCTs[7] to support an interaction between treatment efficacy and time from onset to treatment. However, none of the meta-analyses which combined data from the three main studies across the two treatment windows showed heterogeneity that was large or statistically significant.

5. COST EFFECTIVENESS

5.1 ERG comment on manufacturer's review of cost-effectiveness evidence

5.1.1 Objective of cost-effectiveness review.

The MS does not explicitly state the objectives of the cost-effectiveness review. The cost-effectiveness search was conducted in December 2011 on the following databases:

EMBASE via Ovid (1988-present)
MEDLINE via Ovid (1948-present)
NHS EED via Metaxis (1990-present)
MEDLINE In-Process via Ovid (1948-present)
EconLit via Ovid (1961-present)

The search strategy was appropriate, and standard cost-effectiveness terms were used to identify economic evaluations, although it is not stated whether this was using a published methodological search filter or not. There is a slight error in the presentation of the Embase search strategy, step 28 is not included in the combination of terms, however this would not have affected the search results. In addition, the MEDLINE In-Process strategy is unclear as it appears to also include MEDLINE (1948-present) as MeSH headings are not available in the MEDLINE In-Process database. This is a minor point which again would not affect the results of the search.

5.1.2 Inclusion and exclusion criteria

The MS does not explicitly state the inclusion criteria. However, under the search strategy heading in Appendix 10 of the MS they provide the following table which can be considered as de facto inclusion criteria. The MS does not state the exclusion criteria.

Table 18 Inclusion criteria for cost-effectiveness review

Study Design	**Cost-effectiveness analysis, cost-utility analysis, cost-benefit analysis, cost-consequence analysis**
Setting	Any Location
Population	Acute stroke patients
Intervention	Actilyse®, Alteplase rt-PA, rtPA
Comparator(s)	Any
Outcome(s)	Cost per QALY and/or cost per unit of effect
Time Period	No restriction

5.1.3 Included and excluded studies

Of the 24 full text articles assessed in the MS, 9 studies were included in the review and 15 were excluded. The reasons for exclusion were as follows:

- Cost only studies (2)
- Not acute ischemic stroke (1)
- Not English Lang (2)
- Literature/Clinical Reviews (6)
- Abstract only (n=4)

Table 19 is taken from the MS and provides a description of the 9 included studies. The most relevant study identified is the Sandercock *et al*. study[37] as it is the only one that is conducted from the perspective of the UK.

Table 19: Studies included in the cost-effectiveness review

Study	Year	Country(ies) where study was performed	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention,comparator)	ICER (per QALY gained)
Fagan *et al.*	1998	USA	Markov Model using data from NINDS rt-PA stroke trial. 30 year time horizon. 1000 patient cohort Treatment initiated within 3 hrs of symptoms	67 (assumed age of cohort)	Placebo: 3183 rt-PA: 3934	Total costs not clearly stated- $4.3million dollar saving over 30 years reported	rt-PA dominant
Sinclair *et al.*	2001	Canada	Markov Model using data from NINDS rt-PA stroke trial. 30 year time horizon. 1000 patient cohort Treatment initiated within 3 hrs of symptoms	67 (assumed age of cohort)	no t-PA arm: 9670 t-PA arm 13130	no t-PA arm: $CAN 10690000 t-PA arm: $CAN 103100000	t-PA dominant
Chambers *et al.*	2002	US / Europe	Decision Tree (Acute care)- 3month time horizon Markov model with 3 month cycle over 25 years (Long-term care) 3-6 hours of onset of symptoms 1000 patient cohort	Not stated	No early therapy:1834 rt-PA: 1989	No early therapy: £25.41M rt- PA: £23.08M	rt-PA dominant
Stahl *et al.*	2003	US	Discrete Event Simulation Model Current practice compared to NINDS compliant practice. Lifetime Horizon	Not stated	Current practice: 3.63 NINDS-compliant: 3.64	Current practice: $69539 NINDS-compliant: $69105 (Average per patient)	rt-PA dominant
Sandercock *et al.*	2002/ 4	UK	Decision Tree to determine patient treated with rt-PA and short-term outcomes Markov model, annual cycle 1 year time horizon and Lifetime horizon Treated within 6 hours of onset	69- model populated with data from the Lothian Stroke Register.	1 Year- Standard: 40.24 rt-PA: 41.05 Lifetime- Standard: 223.38 rt-PA: 227.01	1 Year- Standard £614 964 rt-PA: £625965 Lifetime- Standard:£2971394 rt-PA: £2620862	£13 581 rt-PA dominant

					(per 100 patients)	(per 100 patients)	
Moodie *et al.*	2004	Australia	MORUCOS model (Model of Resource Utilization, Costs and Outcomes for Stroke) - details of model structure not stated. Lifetime horizon	Not stated- Model populated with data from NEMESIS-community based stroke incidence study	**Note: Results reported as DALYs** Current Practice: 198164 DALYs lost rt-PA: 198009 DALYs lost	Current practice: A$ 814 014 721 rt-PA: A$ 813 631 856	rt-PA dominant
Mar *et al.*	2004	Spain	Markov model Annual cycle Lifetime horizon Treatment within 3hrs of symptoms	Sample of 540 Mean age of 70.9	(Men and women reported separately) Untreated: 4.616 Thrombolysis: 5.144 (men)	Untreated: €10509 Thrombolysis: €12537	€3841
Ehlers *et al.*	2006	Denmark	Decision Tree and Markov model Time horizon of 1,2,3 and 30 years Treated within 3hrs of onse	68 yrs	Conservative Treatment: 2.64 rt-PA: 3.07	Conservative Treatment: $112337 rt-PA: $97922	rt-PA dominant
Araujo *et al.*	2010	Brazil	Markov Model with annual cycle Treatment within 3 hours	Adults over the age of 18.	Only reported incrementally 0.41 (Men and women reported separately)	Only reported incrementally - R$ 15103	rt-PA dominant
ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life year(s)							

5.1.4 Conclusions of the review

The review concludes that no previous cost-effectiveness studies were identified that were of relevance to this submission. In the previous alteplase MS (TA 122) the manufacturers correctly identified that the Chambers *et al.* and Sandercock *et al.*[37,40] studies were the only studies relevant to the submission. It is the opinion of the ERG that these studies remain the only ones of relevance. However, a de novo economic model is still necessary as the economic models in the Chambers *et al.* and Sandercock *et al.* studies do not fulfil the licensing requirements for alteplase.

5.2 Summary and critique of manufacturer's submitted economic evaluation by the ERG

5.2.1 NICE reference case checklist

Table 20: NICE reference case checklist

Element of health technology assessment	**Reference case**	**Does the submission adequately address the reference case?**
Defining the decision problem	The scope developed by the Institute	Yes
Comparator	Therapies routinely used in the NHS, including technologies regarded as current best practice	Yes
Perspective on costs	NHS and PSS	Yes
Perspective on outcomes	All health effects on individuals	Yes
Type of economic evaluation	Cost-effectiveness analysis	Yes
Synthesis of evidence on outcomes	Based on a systematic review	Yes
Measure of health effects	QALYs	Yes
Source of data for measurement of HRQL	Reported directly by patients and/or carers	Yes
Source of preference data for valuation of changes in HRQL	Representative sample of the public	Yes
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes

5.2.2 Model structure

The economic model is an extension of the economic model constructed and published as part of the HTA of thombolytic therapy by Sandercock *et al.*[37] The model has been replicated using the same structure and inputs described in the text of the published appraisal, with parameters revised using up-to-date data on costs and effects where possible. The economic evaluation extends the Sandercock *et al.* analysis further by incorporating the efficacy evidence for the 3-4.5 hour treatment window sub-group as reported in ECASS III. Use of the relative risks for this treatment window enables the effectiveness estimate to reflect the extended product licence.

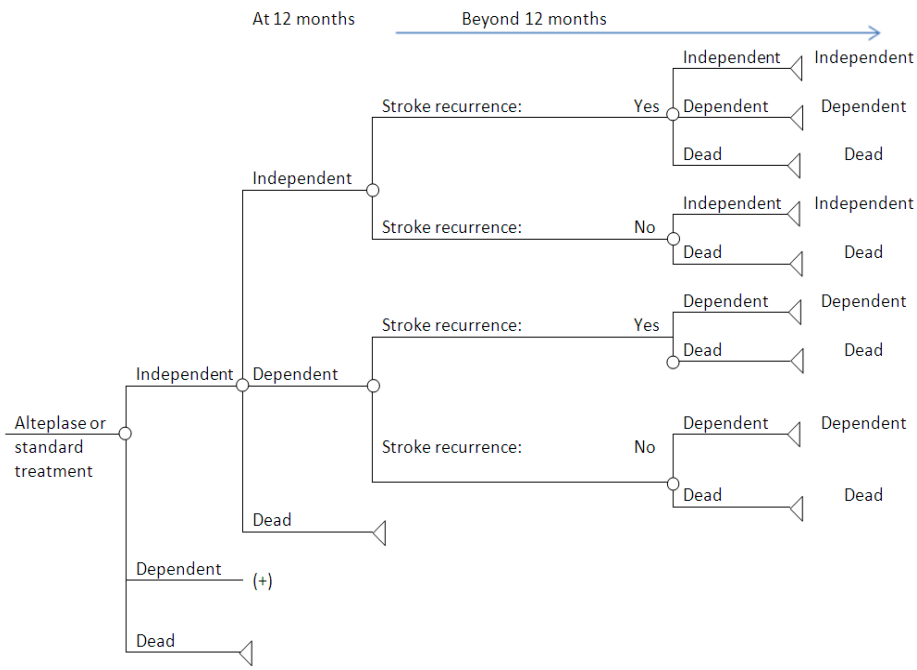
The model is split into 3 phases:

- Phase 1: Patients enter phase I with AIS with confirmed eligibility for alteplase treatment. It is during this phase that the treatment effect of alteplase is applied.
- Phase II. Patients enter phase II at 6 months. No treatment effect is applied here.
- Phase III: Patients enter phase III at 12 months. During phase III a 12 month cycle length is applied for the rest of the lifetime model.

A 6 month initial cycle length (for the first 2 cycles only) was utilised since the most appropriate data identified to represent this population in England and Wales were 6 and 12 months after a stroke. These data, from the Lothian Stroke Registry (LSR)[41], provided information on the proportion of in the independent and dependent post-stroke health states and the proportion who are dead at 6 months, in the absence of alteplase treatment, and transition probabilities between health states from 6 to 12 months. Beyond 12 months, patients could experience a recurrent stroke following which they could be in three health states: dead, dependent or independent. Beyond 12 months patients who did not experience a recurrent stroke either stayed in the same health state or died.

The model has a Markov structure, a diagram of the model, provided in the MS, is shown in Figure 1, below.

Figure 1: Model schematic



The key model assumptions are:

- The SITS-MOST[42] patient cohort is representative of those who would receive the treatment in England and Wales in clinical practice.
- Patients in the dependent state at 12 months and beyond were assumed to be unable to move to an independent state.
- Patients in the independent state at 12 months and beyond were unable to move to a dependent state unless they survived a recurrent stroke.
- Alteplase treatment effect was complete at 90 days and maintained at 6 months
- There is no treatment effect beyond 6 months and the transition probabilities are assumed equivalent for both arms.
- The independent state is defined as mRS 0-2
- The dependent state is defined as mRS 3-5
- The independent state represents either a ‘mild’ or ‘moderate’ stroke.
- The dependent state represents a ‘severe stroke’.
- The rate of recurrent stroke and stroke death is the same in both arms and is independent of stroke severity
- HRQL associated with the three health states remains constant over time

5.2.3 Population

The model has the potential to reflect the use of alteplase across its full licence. The model has been used to estimate incremental cost-effectiveness ratios (ICERs) for the 0-4.5 hour window of use for alteplase and for the subgroups represented by the 0-3 hours and 3-4.5 hours windows of use. In the model the age and gender proportions are set to reflect demographics amongst this patient group in England and Wales. The demographics are the same for all three scenarios. The model was populated with patients likely to receive alteplase for AIS (based on SITS-MOST[42], 39.8% female, median age 68). The assumption made that, due to SITS-MOST being a European based observational study of patients receiving alteplase, the baseline characteristics and demographics of this cohort would be representative of those who would receive the treatment in England and Wales in clinical practice. The median age of patients receiving alteplase within the SINAP audit was higher at 72 years, but this difference may reflect the off-label use of alteplase in patients aged over 80, who made up 22% of those receiving thrombolysis in SINAP[10]. The SITS-MOST study restricted participation to patients meeting the license criteria for alteplase and therefore excluded patients aged over 80 which is reflected in the lower median age for the cohort[42]. The proportion of females is fixed over time despite the fact that general population mortality rates differ by gender, however this is likely to have a minor impact on the results.

5.2.4 Interventions and comparators

The ERG considers that the intervention described in the MS matches the intervention described in the final scope. A UK licence for the use of alteplase within a 0-3hour administration time period from the onset of symptoms for the treatment of acute ischaemic stroke was granted in September 2002. Boehringer Ingelheim received licence approval from the MHRA for alteplase use to be extended to 4.5 hours from the onset of symptoms on 14th March 2012[13].

The MS does not identify any active comparator for alteplase. This is appropriate because no thrombolytic agent other than alteplase is currently licensed within the EU for use in acute ischaemic stroke. As it has recently been noted that the most important therapy in acute ischaemic stroke is restoration of the blood supply to the affected area of the brain,[1] other stroke treatment or prevention therapies, which function in different ways, would therefore not be relevant comparators.

5.2.5 Perspective, time horizon and discounting

The economic perspective is the National Health Service (NHS) and the Personal Social Services (PSS) in accordance with the NICE reference case. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. The manufacturer's model uses a life-

time time horizon to capture the chronic nature of disability associated with stroke, in accordance with the NICE reference case. A discount rate of 3.5% is used in the model as per the NICE reference case.

5.2.6 Treatment effectiveness

The following studies were identified in the MS as being relevant to the decision problem:

- Pooled Analysis of ECASS II (n=158) and NINDS (n=624) – 0 to 3 hour window
- ECASS III (n=821) – 3 to 4.5 hour window of use
- Pooled analysis of ECASS III, ECASS II and NINDs – 0 to 4.5 hour window of use.

The above studies were used to generate efficacy parameter values for inclusion in the basecase cost-effectiveness analyses. In addition, the inclusion of subgroups of patients from ATLANTIS A and B to generate efficacy parameters formed part of the sensitivity analysis for both the 0-3 hour (n=61) window and the 0-4.5 hour window (n=302) cost-effectiveness analysis. These efficacy estimates, as previously identified by the ERG in TA 122, are subgroup analyses in which stratification was not pre-specified prior to randomisation and hence were problematic in terms of inclusion in the base-case analysis. This was also true of an ad hoc subgroup analysis of 3-4.5 hour window of use data set from ECASS II (n=265) which was included in the sensitivity analysis.

Fifty one percent of the 0-4.5 hour data set in the base-case pooled analysis of ECASS II, ECASS III, and NINDS consisted of patients using alteplase 3-4.5 hours after symptom onset which is a higher than the estimated 24% proportion in actual clinical practice (See MS Section 7.1. for estimation of 24%). An alternative method of estimating the relative risk for the 0-4.5 window of use analysis was employed in the sensitivity analysis to correct for this; a proportionate weighting based on an estimated actual clinical practice proportionate split between 0-3 hour and 3-4.5 hour use was applied to the separate relative risks for the 0-3 and 3-4.5 hour usage to estimate a conflated 0-4.5 hour relative risk. This weighting was based on a study by Rudd *et al.*(2011)[11] which is outlined in more detail in Section 7.1 where it is used in the resource use estimates of the impact of extending alteplase window of use from 0-3 hours to 0-4.5 hours. The weighting used assumed a 76:24 split between 0-3 hours and 0-4.5 hour use.

In line with recommendations from the ERG in TA122, relative risks were considered the appropriate relative efficacy parameter for inclusion in the model. Relative risks were generated for the following for alteplase compared to placebo (in line with TA122):

- Relative risk of death
- Relative risk of dependency or death

Dependency in the cost-effectiveness model is defined as a score on the modified Rankin Scale of 3-5 and this definition was used as the basis of the relative risk calculations. The relative risks used in the base-case and sensitivity analysis are outlined in Tables 21 to 24 below. These tables follow from the meta-analyses described in section 4.2.6 above. The MS states that in all pooled analyses applied within the cost-effectiveness model, a random effects model of meta-analysis was applied. The ERG noted that this was true, with the exception of one of the sensitivity analyses for the 0 to 4.5 hour time window where the RR for death or dependency cited is based on a fixed effects meta-analysis.

Table21: Relative risks of death used in the base-case analysis.

Relevant Time Window	Analysis in which used	Method to generate parameter value	Studies used	Mean estimate	Lower CI	Upper CI
0-3 hours	**Base-case**	Meta-analysis	ECASS II (0-3) + NINDs	1.05	0.55	2.03
3-4.5 hours	**Base-case**	Single study data analysis	ECASS III	0.82	0.5	1.33
0-4.5 hours	**Base-case**	Meta-analysis	ECASS II (0-3) + NINDs + ECASS III	0.89	0.67	1.18

Table 22: Relative risks of death used in the sensitivity analysis.

Relevant Time Window	Analysis in which used	Method to generate parameter value	Studies used	Mean estimate	Lower CI	Upper CI
0-3 hours	Sensitivity analysis	Meta analysis	ECASS II (0-3) + NINDs + ATLANTIS A & B (0-3)	1.15	0.62	2.16
3-4.5 hours	Sensitivity analysis	Meta analysis	ECASS III + ECASS II (3-4.5) + ATLANTIS (3-4.5)	0.85	0.43	1.67
0-4.5 hours	Sensitivity analysis	Meta analysis	ECASS II (0-3) + NINDs + ATLANTIS A & B (0-3) + ECASS III	0.93	0.68	1.26
0-4.5 hours	Sensitivity analysis	Apply 76:24 weighting (Rudd *et al.* 2011): see above in this section	ECASS II + NINDs (0-3 hours) ECASS III (3-4.5 hours)	0.99	Not available	Not available
0-4.5 hours	Sensitivity analysis	Meta analysis	ECASS II (0-3) + NINDs + ATLANTIS A & B (0-3) + ECASS III + ECASS II (3-4.5) + ATLANTIS (3-4.5)	0.96	0.65	1.41

Table 23: Relative risks of death or dependency used in the base-case analysis.

Relevant Time Window	Analysis used in	Method to generate parameter value	Studies used	Mean estimate	Lower CI	Upper CI
0-3 hours	Base-case	Meta analysis	ECASS II (0-3) + NINDs	0.81	0.72	0.92
3-4.5 hours	Base-case	Single study data analysis	ECASS III	0.87	0.72	1.04
0-4.5 hours	Base-case	Meta analysis	ECASS II (0-3) + NINDs + ECASS III	0.83	0.75	0.92

Table 24: Relative risks of death or dependency used in the sensitivity analysis.

Relevant Time Window	Analysis used in	Method to generate parameter value	Studies used	Mean estimate	Lower CI	Upper CI
0-3 hours	Sensitivity analysis	Meta analysis	ECASS II (0-3) + NINDs + ATLANTIS A & B (0-3)	0.82	0.72	0.93
3-4.5 hours	Sensitivity analysis	Meta analysis	ECASS III + ECASS II (3-4.5) + ATLANTIS (3-4.5)	0.87	0.74	1.04
0-4.5 hours	Sensitivity analysis	Meta analysis	ECASS II (0-3) + NINDs + ATLANTIS A & B (0-3) + ECASS III	0.84	0.75	0.93
0-4.5 hours	Sensitivity analysis	Apply 76:24 weighting (Rudd *et al.* 2011): see above in this section	ECASS II + NINDs (0-3 hours) ECASS III (3-4.5 hours)	0.82	Not available	Not available
0-4.5 hours	Sensitivity analysis	Meta analysis	ECASS II (0-3) + NINDs + ATLANTIS A & B (0-3) + ECASS III + ECASS II (3-4.5) + ATLANTIS (3-4.5)	0.85	0.77	0.94

5.2.7 Natural history

The distribution of patients between the health states of independent, dependent and death in the standard treatment arm of the model at 6 months was based upon data identified in a systematic literature review as being most appropriate to represent the distribution that would be anticipated amongst the population of England and Wales (details of this literature review are shown in Appendix 16 of the MS). The study used to populate this parameter value was the LSR, (Wardlaw *et al.*1998)[41], a registry of 1,779 prospectively identified patients who required inpatient care due to suspected or confirmed stroke between September 1989 and June 2000 in Lothian, Scotland. The manufacturer also provided the distribution of health states found in the ECASS III trial at 3 months. The mortality rate is lower and the independent health states outcome is higher than those observed in the LSR study. These differences could be due to improvements over time or may be due to differences in the population, for example the ECASS III trial excluded patients over 80 years of age. The parameter values from the LSR, which were used in the model and the distribution of outcomes observed in ECASS III are shown in the Table 25 below. The ERG ran the deterministic model with the health

state outcomes from ECASS III to examine the difference this makes. The results are presented in section 5.3.

Table 25: Six month health state distributions for the no treatment arm

	Independent	Dependent	Dead
Lothian Stroke Register	0.3953	0.3256	0.2791
ECASS III	0.6154	0.3027	0.0819

Outcomes of those experiencing disability or death due to symptomatic intracranial haemorrhage (SICH) or AIS are conflated in the model as they are in the studies used to estimate death and dependency relative risks i.e. they are assumed to be captured in the overall distribution of patients between the states independent, dependent, and dead, which in turn capture relevant utility valuations. In those patients experiencing a SICH an additional CT scan was attributed to the treatment process, with an associated additional cost. No additional costs were added to those who experienced an asymptomatic ICH. The proportion of patients experiencing a SICH (being an ICH with 4 or more points on the NIHSS score increase – ECASS III definition) in the no treatment arm in the model was taken from ECASS III[25] and was 0.25% (1/403). Estimates for the proportion of patients experiencing a symptomatic ICH in the alteplase arm were generated using the relevant relative risks estimated from the relevant studies as outlined in Table 26. The rate of SICH in ECASS III was lower than those seen in other trials, leading to lower rates in the model. However, the ERG considers that this is unlikely to significantly bias the results as the main impact of SICH is captured through the outcomes of death and dependency. There were some discrepancies noted by the ERG between the RRs for SICH reported in Table 21 of the MS and those actually applied in the model. Table 26 below shows the rates actually applied in the submitted model. As the model is not sensitive to variation in the SICH rate, these discrepancies are unlikely to have a significant impact on the ICER.

Table 26: Relative Risk of symptomatic intracranial haemorrhage (ICH) [Adapated from Table 21 of MS with corrections by ERG]

Relevant Time Window	Analysis used in	Method to generate parameter value	Studies used	Mean estimate	Lower CI	Upper CI
0-3 hours	Base-case	Meta-analysis	ECASS II + NINDs	3.94	0.61	25.47
0-3 hours	Sensitivity analysis	Meta-analysis	ECASS II + NINDs + ATLANTIS A & B	4.24	1.52	11.83
3-4.5 hours	Base-case	Single study data analysis	ECASS III	9.64	4.63	17.57
0-4.5 hours	Base-case	Meta-analysis	ECASS II + NINDs + ECASS III	4.18	1.39	12.63
0-4.5 hours	Sensitivity analysis	Meta-analysis	ECASS II + NINDs + ATLANTIS A & B	4.24	1.52	11.83
0-4.5 hours	Sensitivity analysis	Apply 76:24 weighting (Rudd *et al.* 2011): see above in this section	ECASS II + NINDs (0-3 hours) ECASS III (3-4.5 hours)	5.87	Not available	Not available

5.2.8 Implementation of clinical data in Phase I (6-12 months)

Patients entered the post-treatment phase at 6 months and departed at 12 months. In this period it was possible to transition from any state to another (with the exception of transitioning from the absorbing 'dead' state) with an equal probability in each model arm. Transition probabilities were taken from the LSR [37,41] (as identified as most appropriate on systematic literature review). The parameter values used in the model are shown below in Table 27. These parameter values were fixed in the PSA.

Table 27: Phase 2 (6 to 12 month) transition probabilities (extracted from LSR[37,41])

	From Independent	From Dependent	From Dead
To Independent	0.8750	0.1111	0
To Dependent	0.0938	0.7407	0
To Dead	0.0313	0.1481	1

5.2.9 Implementation of clinical data in Phase III (12 month cycles beyond the first 12 months)

Each cycle was 12 months in length. In each cycle of Phase III a patient could suffer a recurrent stroke. The rate of recurrent stroke was based on the LSR[41] which was identified by the manufacturer as the most appropriate source following a systematic literature review The rate was assumed the same for the alteplase and no treatment arms. The likelihood of a fatal event given a recurrent stroke was taken from the LSR[41].The parameter values used in the model to estimate the annual transition probability of experiencing a recurrent stroke and the subsequent probability of death are shown in the Table 28 below.

Table 28: Annual risk of stroke recurrence and the associated risk of mortality

Parameter	Value	Source
Annual risk of stroke recurrence at 1 year	0.05	Wardlaw *et al.* (1998)[41]
Annual stroke mortality among patients with recurrent stroke	0.25	Wardlaw *et al.* (1998)[41]

The transition probabilities of moving from independent and from dependent to recurrent stroke are assumed to be the same as are the ensuing recurrent stroke mortality rates.

Those who are in the dependent state at 12 months and beyond are assumed to be unable to move to the independent state. Those who were in the independent state at 12 months and beyond were unable to move to the dependent state unless they survived a recurrent stroke in which case they had an equal likelihood of entering each of the living health states. The systematic literature review outlined in Appendix 16 of the MS identified no source data for these parameter values. These assumptions were also made in the NICE STA for alteplase (0-3hours), Sandercock *et al.*[37] and Fagan *et al.*1998.[43]

Patients in Phase III who did not transition into the recurrent stroke state had a probability of moving into the death state. This transition probability was based upon an age and gender specific mortality rates (constructed using 2007-2009 ONS life tables for England and Wales)[44]. Gender weighted was according to the population of the SITS-MOST study[42]. The mortality rates were adjusted using a multiplier factor to reflect the higher death rate amongst patients who have had a stroke compared to the general population. The history of stroke multiplier of 2.3 was taken from the Perth stroke study[45]. No uncertainty was included in the manufacturer's model for this estimate.

5.2.10 Calculation of transition probabilities

The relative risks of death and of death dependency from Tables 21 to 24 were used to modify the 6 month baseline distribution of those not receiving thrombolytic treatment to reflect the treatment

effect of alteplase. The proportion in the death state is estimated first, and then the proportion that is dead or dependent is estimated using the relative risk for death or dependency, allowing the proportion in the dependency state to be calculated as the difference between these two figures.

5.2.11 Variation of Transition Probabilities with Time

It was assumed that the alteplase treatment effect was complete at 90 days and maintained at 6 months (rendering all transition probabilities post phase I equal in both the alteplase and standard treatment arms). This assumption is based upon follow-up of the NINDS[33] and Cologne trials[46] (studies of alteplase with a 0-3 onset to treatment window). The authors reported that, when the 12 month data (with the 6 month results being very similar) were compared to the 3 month outcomes, the rate of agreement for those patients having a favourable result was 91% on the mRs and GOS and 88% on the BI, suggesting fair stability within outcomes over a 12 month period. There are instances where stroke severity may move from severe at onset to moderate during recovery. This possible change in disability status has been incorporated through the use of the LSR transition rates within the 6-12 month period in which the outcome will stabilise. Maintenance of treatment effect from 3 to 6 months is further supported by recent data from the IST-3 trial in which the proportional effects on death and disability seen at 6 months were comparable with those seen at 3 months in previous trials[32]. Complete stability is assumed to be reached with disability status at the 12 month post-stroke point, where patients cannot change in non-morbidity disability status (independent and dependent) unless a subsequent stroke is experienced.

5.2.12 Health related quality of life

The manufacturer conducted a literature review to identify QoL studies. Appropriate sources were searched. These were MEDLINE, MEDLINE In-Process, EMBASE, NHS EED and EconLit. However, the exact purpose of the search is unclear. The search strategy suggests that for the MEDLINE/MEDLINE In-Process/NHS EED/EconLit search, the aim was to retrieve studies using only EQ-5D, whereas the EMBASE search strategy would retrieve other measures excluding the EQ-5D measure. It is unclear to the ERG whether or not further studies would have been identified if the search strategies were designed to find studies including EQ-5D or SF 36 (or variants of SF 36) measures.

The MS states that no data was found in this review to populate the health economic model's utility values for dependent and independent stroke health states, other than those previously identified in the TA 122 submission. These were from Dorman *et al.*[3] Given the above search strategy restrictions, the ERG are unable to judge if this is a reasonable finding.

Utility scores for the dependent and independent states are based on the responses to the EuroQoL quality of life questionnaire of a sample of 147 LSR patients as described in Sandercock *et al.*[37] and the Health Technology Appraisal of clopidogrel and dipyridamole.[47] The classification of dependence used in the LSR study has been validated against the modified Rankin Scale where a mRS score of 3-5 defined dependency.[48] The ERG is satisfied that the source data for QALY measures followed a similar dependence classification to that used in the economic model. It appears reasonable that the manufacturer has used the LSR study utilities as these values were elicited from a UK population, and were measured and valued using the EuroQol as per the NICE reference case. In the model these utility values stay fixed over the lifetime of the patient unless a recurrent stroke causes transition from the independent to dependent health state. Fixing the utilities over time may overestimate the lifetime QALYs accrued by patients in the independent state following stroke as it doesn't allow for any deterioration in the HRQoL over time. This may favour alteplase over standard care, but as the model isn't particularly sensitive to the utility values applied, the effect is likely to be small. Table 29 shows the utility values used in the manufacturer's model.

Table 29: Utility values used in the manufacturer model

Utility values		**95% CI**	
Independence	0.74	0.69	0.79
Dependence	0.38	0.29	0.47

5.2.13 Resources and costs

5.2.13.1 Independent, dependent and death health state costs

The manufacturer conducted a literature review to identify studies that would provide costs for the health states of independent, dependent and death. Existing searches were utilised, followed by an updated search to identify publications after 2010. Appropriate sources were searched (MEDLINE, MEDLINE In-Process, EMBASE, NHS EED, EconLit), and the search strategies used were appropriate. The MS states that no studies were found that were considered more relevant than the Youman *et al.* study[4] used in the previous TA 122 assessment.

The Youman *et al.*[4] study applied national unit costs to resource-use data from a large, randomised, prospective trial[49] of stroke care in the UK to calculate the 3-month cost of acute events and long-term care. Stroke was divided into mild, moderate and severe events, defined by the Barthel Index. For the purpose of the model, it is assumed that mild and moderate strokes described the costs of independent stroke survivors, and that severe stroke described the cost of dependent stroke survivors. It is the opinion of the ERG's clinical advisors that the Youman *et al.*[4] study remains the best available evidence for the cost of stroke in the UK.

The MS has assumed that those in the independent state experienced either a 'mild' or 'moderate' stroke whilst those in the dependent state experienced a 'severe stroke'. The proportion of those in the independent state who had experienced a moderate compared to a mild stroke was taken from Youman *et al.*[4] In the first year of care the MS has assumed that patients were hospitalised for the initial 3 months irrespective of health state. The ERG considers these to be reasonable assumptions. The cost of a fatal stroke event was taken from Youman *et al.* 4 The calculations of annual cost of stroke care (as reported in Youman *et al.*), used in the manufacturer's model are shown in Table 30, below.

Table 30: Calculation of annual cost of stroke care [as reported in Youman *et al.* 2003[4] inflated to 2012/13 prices with the PSSRU HCHS inflation index.]

Parameter	Mean Value	CI	
Costs of ongoing care			
3-month cost of ongoing care at home (including accommodation)	£445	£266	£623
3-month cost of ongoing care in an institution (including accommodation)	£5,280	£5,003	£6,634
Mild Stroke			
3-month cost of acute event	£6,953	£6,216	£7,686
Proportion discharged home	1.000		
Proportion discharged to an institution	0.000		
Proportion dead	0.000		
Moderate Stroke			
3-month cost of acute event	£6,567	£6,008	£7,125
Proportion discharged home	0.959		
Proportion discharged to an institution	0.008		
Proportion dead	0.033		
Severe Stoke			
3-month cost of acute event	£14,394	£13,057	£15,730
Proportion discharged home	0.732		
Proportion discharged to an institution	0.172		
Proportion dead	0.096		
Distribution of stroke severity within independent state			
Proportion of mild strokes amongst independent stroke patients	0.413		
Proportion of moderate strokes amongst independent stroke patients	0.587		
Annual costs of health states			
Cost of independent stroke year 1	£8,131	£6,961	£9,314
Cost of independent stroke post-year 1	£1,872	£1,156	£2,610
Cost of dependent stroke year 1	£18,487	£16,559	£21,031
Cost of dependent stroke post-year 1	£5,458	£4,669	£7,068
Costs of events			
Cost of acute event fatal stroke	£9,247	£7,424	£13,461
CT Scan following sICH	£110	£55	£220

5.2.13.2 Cost of alteplase

The cost of alteplase is dependent on the body weight of the patient. The manufacturer has assumed that the mean body weight of patients in the SITS-MOST[42] study is representative of the average stroke patient in UK clinical practice. The mean body-weight of subjects in the 3-4.5h cohort from the SITS-MOST[42] trial (76kg) was thus used to calculate the cost of alteplase.

Based on this data, the dose received by a patient with the average weight is 68.4mg (76kg * 0.9mg/kg). The cost of 68.4mg alteplase is based on a 50mg pack (£300) plus a 20mg pack (£180) and is thus estimated to be £480. The cost can range from £300 to £600 depending on the individual's weight and the average cost is likely to be higher than £480 as any patient weighing over 78kgs would require two 50mg packs. However, a univariate sensitivity analysis covering this range of cost has been conducted by the MS. The source of the price of the packs is not referenced in the MS but the prices cited are consistent with those given in the BNF.[18]

5.2.13.3 Administration Costs

The administration costs incurred though the use of alteplase were based upon the resource use figures described by Sandercock *et al.*[37] and are adjusted to the current year using the Personal Social Services Research Unit (PSSRU) Pay & Prices index. The estimates of administration costs used in the manufacturer's model are shown in Table 31, below. These estimates of extra staffing requirements associated with administering alteplase were considered reasonable by the ERG's clinical advisors, although they felt that these administration costs may not reflect the real costs of running a comprehensive 24 hour thrombolysis service. In the previous appraisal of alteplase (TA122) it was noted by the committee that there would be costs associated with re-organising stroke services to enable the wide use of alteplase in accordance with its marketing authorisation, such as the need for 24 hour access to computed tomography scanning and physicians with a specialist interest in stroke care. However, the Committee decided that it would not be appropriate to include the costs incurred in optimising services to a level that allows alteplase to be given in line with its marketing authorisation.

Table 31: Administration costs as reported in the MS

Extra staffing requirements	Cost per hour	Unit cost	Source /comments	Unit cost[#] (adjusted to 2012/13 levels)
5 min additional nurse time	£97*	£8.08	PSSRU 2011 (staff nurse 24hr ward)	£8.31
190 min registrar time	£87*	£275.50	PSSRU 2011 (registrar group)	£283.09
50 min consultant time	£162*	£135	PSSRU 2011 (medical consultant costs)	£138.72
5 min routine observation by senior nurse in place of more junior nurse	£25/ hour (£122*-£97*)	£2.08	It has been assumed that observations are carried out by a senior nurse, and that each observation takes 5 minutes PSSRU 2011 (ward manager 24hr ward and staff nurse 24hr ward)	£2.14
12 additional sets of observations at 5 min each	£142*	£142	It has been assumed that routine observations take 5 minutes to be carried out PSSRU 2011 (ward manager 24hr ward)	£145.91
5 hours 1:1 senior nurse care	£142*	£710	PSSRU 2011 (ward manager 24hr ward)	£729.56
10 min overnight junior staff review	£50*	£8.33	PSSRU 2011 (foundation house officer 1)	£8.56
Total drug administration cost				**£1,316.29**

* Costs used reflect, where available, the hourly wage based on the shortest working week and include the cost of training.
[#] As PSSRU 2012 has not been published, unit costs from PSSRU 2011 were adjusted to 2012/13 levels by using an inflation rate of 3% (based on the Pay & Prices index from PSSRU 2011)

5.2.13.4Other costs

Clinicians are required to exclude the possibility of ICH by CT scan before giving alteplase therapy. However, the Royal College of Physicians recommends that all suspected stroke patients are CT scanned as soon as possible irrespective of the intention to use thrombolytic therapy. The MS has therefore not included an additional cost of a CT scan to the alteplase arm of the model. The ERG considers this to be reasonable.

For patients experiencing a SICH an additional CT scan would be undertaken. The MS has included this cost (£100) to those patients experiencing a SICH. The MS has assumed that all other costs are

captured in the 6 month health states for patients as the costs of care are related to the dependency level of the patient regardless of whether they have had an ischaemic stroke or a SICH. The cost of surgery for SICH is not included in the model as it is contraindicated. The ERG considers these assumptions regarding the costs following SICH to be reasonable.

The MS has not included the cost of aspirin due to the low procurement cost. The ERG does not consider that the exclusion of the cost of aspirin will affect the model results.

5.2.14 Sensitivity analyses

The manufacturer conducted univariate, probabilistic and additional sensitivity analysis.

5.2.14.1Univariate sensitivity analysis

Table 32, below, shows the mean values, the range of these values and the source or rational for these values that were used in the base-case deterministic analysis and the deterministic sensitivity analysis. The RRs for death and death or dependency were included simultaneously in the univariate sensitivity analysis under the assumption that they are linked.

Table 32: Values used in deterministic sensitivity analysis (0-4.5 hour window of use – basecase model)

Variable	Deterministic Value	Range		Source / Rationale
		Low	High	
Patient Characteristics				
Starting Age	68	59	75	SIT-MOST[42] reported range (2007)
Resource Use and Discounts				
Discount Rate- Costs	3.50%	0%	6%	NICE Reference case
Discount Rate- Outcomes	3.50%	0%	6%	NICE Reference case
Cost of Alteplase	£480	£300	£600	Maximum dose (SPC- 90mg) and 50% of max dose
Administration cost of Alteplase	£1,281	£896.70	£1,665	+/- 30%
Cost of independent stroke (Year 1)	£8,131	£6,961	£9,314	Youman *et al* [4] (reported range)
Cost of dependent stroke (Year 1)	£18,487	£16,559	£21,031	Youman *et al* [4] (reported range)
Cost of independent stroke (post Year 1)	£1,872	£1,156	£2,610	Youman *et al* [4] (reported range)
Cost of dependent stroke (post Year 1)	£5,458	£4,669	£7,068	Youman *et al* [4] (reported range)
Cost of acute event- fatal stroke	£9,247	£7,424	£13,461	Youman *et al* [4] (reported range)
Mortality				
Stroke patient mortality multiplier	2.3	1.15	4.6	100% increase, 50% decrease
Mortality rate following recurrent stroke	0.25	0.125	0.5	100% increase, 50% decrease
Annual Risk of Stroke Recurrence	0.05	0.025	0.1	100% increase, 50% decrease
Alteplase Efficacy				
SICH risk- Alteplase	2.39%	1.15%	4.36%	Hacke *et al.* 2008[25]
Relative risk- Death or Dependency	0.830	0.750	0.920	Meta-Analysis (95% CI)
Relative risk- Death	0.890	0.670	1.180	Meta-Analysis (95% CI)
Relative risk- Death or Dependency	0.830	0.790	0.871	Meta-analysis (+/- 1 sd)
Relative risk- Death	0.890	0.793	0.987	Meta-analysis(+/- 1 sd)
Utility Values				
Utility- Independent	0.74	0.69	0.79	Dorman *et al* [3]
Utilty- Dependent	0.38	0.29	0.47	Dorman *et al* [3]

5.2.14.2 Probabilistic sensitivity analysis

Table 33, below, summarises the variables included in the probabilistic sensitivity analysis (PSA) along with the distributions assigned to each variable. The following variables were fixed in the PSA;

- Health state distribution at 6 months
- Transition probabilities between 6 and 12 months
- Stroke recurrence risk
- Mortality risk following recurrent stroke.
- Mortality multiplier for stroke versus the general population.

The ERG did not think that it was reasonable to include uncertainty around the cost of alteplase as the distribution applied reflects heterogeneity in the dose required by individual patients rather than uncertainty in the estimate of the mean cost. Therefore, the PSA may overestimate uncertainty in the cost of alteplase. No justification was given for the distribution applied around the administration cost of alteplase. Different parameters from those cited in the MS are used within the model to describe the probabilistic distribution for SICH in the models for 0 to 3 hours and 0 to 4.5 hours. However, this is not anticipated to have any significant impact on the cost-effectiveness. The relative risks for death and death or dependency are sampled independently within the PSA which ignores the correlation that is likely to exist between these two outcomes, and allows for the possibility of a negative number of patients within the dependent health state. The ERG explored the potential impact of this assumption and do not expect it to have a large impact on the central ICER.

Table 33: Values and distributions used in the probabilistic sensitivity analysis (PSA)

Variable	Deterministic Value	Range		Distribution
		Low	High	
Resource Use and Discounts				
Cost of Alteplase	£480	£300	£600	Gamma distribution derived from reported range
Administration cost of Alteplase	£1316	£658	£2633	Gamma distribution derived from reported range
Cost of independent stroke (Year 1)	£8131	£6961	£9314	Gamma distribution derived from reported range
Cost of dependent stroke (Year 1)	£18487	£16559	£21031	Gamma distribution derived from reported range
Cost of independent stroke (post Year 1)	£1872	£1156	£2610	Gamma distribution derived from reported range
Cost of dependent stroke (post Year 1)	£5458	£4669	£7068	Gamma distribution derived from reported range
Cost of acute event- fatal stroke	£9247	£7424	£13461	Gamma distribution derived from reported range
Mortality				
Annual Age-Specific Mortality	Various	N/A	N/A	Beta distribution derived from 100000 patient cohort and ONS life table data
Alteplase Efficacy				
SICH risk- Alteplase	2.39%	1.15%	4.36%	Beta distribution, derived from Hacke *et al.*[25]
Relative risk- Death	0.818	0.504	1.32	Lognormal distribution, derived from Hacke *et al.*[25]
Relative risk- Dependency	0.885	0.776	1.198	Lognormal distribution, derived from Hacke *et al.*[25]
Utility Values				
Utility- Independent	0.74	0.69	0.79	Beta distribution, derived from reported range
Utilty- Dependent	0.38	0.29	0.47	Beta distribution, derived from reported range

5.2.14.3 Additional deterministic sensitivity analysis

The manufacturer conducted 3 additional deterministic sensitivity analyses.

1. ATLANTIS A and B were added to ECAS II (0-3Hr), NINDS and ECAS III in the pooled meta-analysis.

2. Fifty one percent of the 0-4.5 hour data set in the base-case pooled analysis of ECASS II, ECASS III, and NINDS consisted of patients using alteplase 3-4.5 hours after symptom onset which is a higher than the estimated 24% proportion in actual clinical practice (See section 7 of the MS). A sensitivity analysis was conducted using a weighted pooled analysis to calculate the relative risk for the 0-4.5 window. A proportionate weighting based on the proportional split between treatment within 0 to 3 hours and treatment within 3 to 4.5 hours in actual clinical was applied to the separate relative risks for the 0-3 and 3-4.5 hour treatment windows to estimate a conflated 0-4.5 hour relative risk. This weighting was based on a study by Rudd *et al.*[11] which is described in section 7.1 of the MS. The weighting used assumed a 76:24 split between 0-3 hours and 0-4.5 hour use.
3. An ad hoc data set of 3-4.5 hour data from ECASS II and ATLANTIS was obtained (see section 5.2.1.2 of the MS). This was included in a pooled analysis of ECASS III, ECASS II (0-3), NINDS, ATLANTIS A & B (0-3 hours) to identify the impact that its inclusion had upon the ICER. Relative risks for SICH based on a pooled analysis of ECASS III, ECASS II (0-3 hours), NINDS, ATLANTIS A & B (0-3 hours) were used in the model since they were not sourced for ECASS II (3-4.5 hours) and ATLANTIS (3-4.5 hours).

5.2.14.4 Subgroup analyses

Two subgroup analyses were carried out as stipulated in the scope. These were based on the window for use of alteplase from the onset of symptoms:

- 0-3 hour window of use (Licensed use of alteplase since 2002; formed basis of TA122)
- 3-4.5 hour window of use (Recent extension to existing licence confirmed by the MHRA on 14th of March 2012)

5.2.15 Cost-effectiveness results

Table 34 shows the results of the base-case deterministic analysis. Alteplase gains 0.333 QALYs at an additional cost of £811 compared to no treatment resulting in an ICER of £2,441.

Table 34: Base-case results (0-4.5 hour window of use) – deterministic model

	Independent life years (ILY)	**Life years**	**QALYs**	**Cost**	**ICER**
Standard care	2.812	6.460	2.975	£28,519	
Alteplase in addition to standard care	4.255	6.826	3.308	£29,330	
Incremental	1.443	0.366	0.333	£811	£2,441

Sensitivity analyses

5.2.15.1 Univariate sensitivity analysis

The results of this analysis showed that the only parameters that had a conspicuous influence on the ICER were the RRs of death and death or dependency. Using the higher 95% CI for the RRs of death and death or dependency, the no treatment arm gained more QALYs with an increased cost compared to alteplase resulting in an ICER of £44,342 for no treatment versus alteplase. Using one sd above the mean value for the RRs of death and death or dependency, the ICER for alteplase versus no treatment was £1,478, (mistakenly reported as £1,261 in the MS). This ICER is lower than the base-case ICER of £2,441 which would appear to be counter intuitive as it appears that the ICER improves when the mortality risk for alteplase is higher. The base-case has a lower RR for death and death or dependency and intuitively we would expect the ICER to be more favourable to alteplase than when a higher RR is used. However, the model shows that with a RR of death and death or dependency one sd above the mean, compared to the base-case, there are less QALYs gained but at a lower cost. This is explained by the fact that there are more patients dying but also fewer patients in the dependent state as fewer patients are alive. The cost saving for fewer dependent patients outweighs the additional QALYs gained in the base-case, resulting in a lower ICER. This is being driven by the fact that the confidence interval on the RR of death is wider than the confidence interval around the RR for death and dependency.

5.2.15.2 Probabilistic sensitivity analysis

For the 0 to 4.5 hour window of use the ICER for alteplase versus no treatment is £2,296 as shown in Table 35. (These results were provided by the manufacturers in response to a request for clarification from the ERG after an error in their result sheet within the model was noted by the ERG and corrected by the manufacturer[34] and therefore differ from those in Table 44 of the original MS)

Table 35: Base-case results for 0 to 4.5 hour window of use - probabilistic model

	Standard care			**Alteplase in addition to standard care**			
	Average	**Lower 95%CI**	**Upper 95% CI**	**Average**	**Lower 95%CI**	**Upper 95% CI**	**ICER**
QALYS	2.919	2.670	3.170	3.236	2.905	3.581	
Costs	£28,148	£25,227	£31,358	£28,876	£24,732	£33,206	£2,296
ILY	2.757	2.747	2.767	4.152	3.780	4.499	
Life years	6.313	6.287	6.340	6.647	6.003	7.172	

Figures 2 and 3 show the cost-effectiveness plane and cost-effectiveness acceptability curve (CEAC) for the base-case probabilistic results. The CEAC and cost-effectiveness plane obtained by running the model provided by the manufacturer were slightly different and are provided in section 5.3

Figure 2: Cost-effectiveness plane (0-4.5 hour window of use)

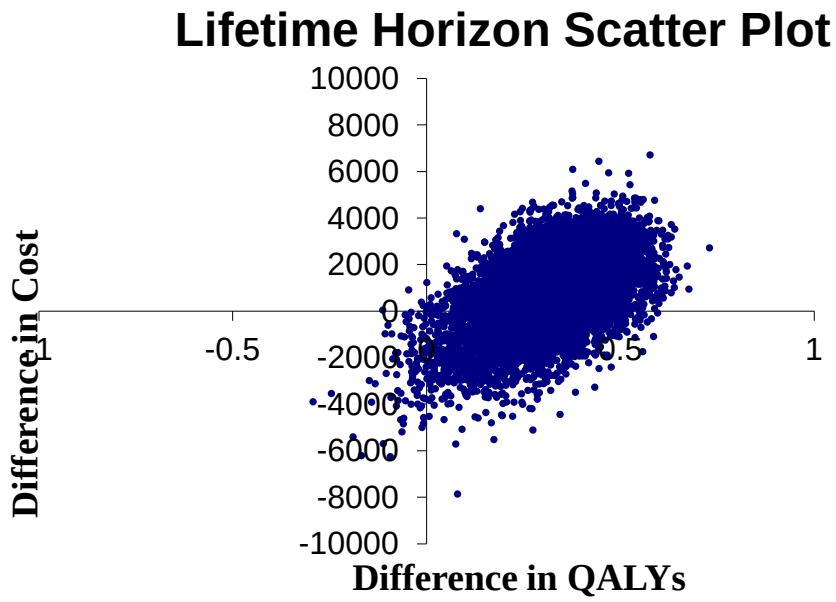
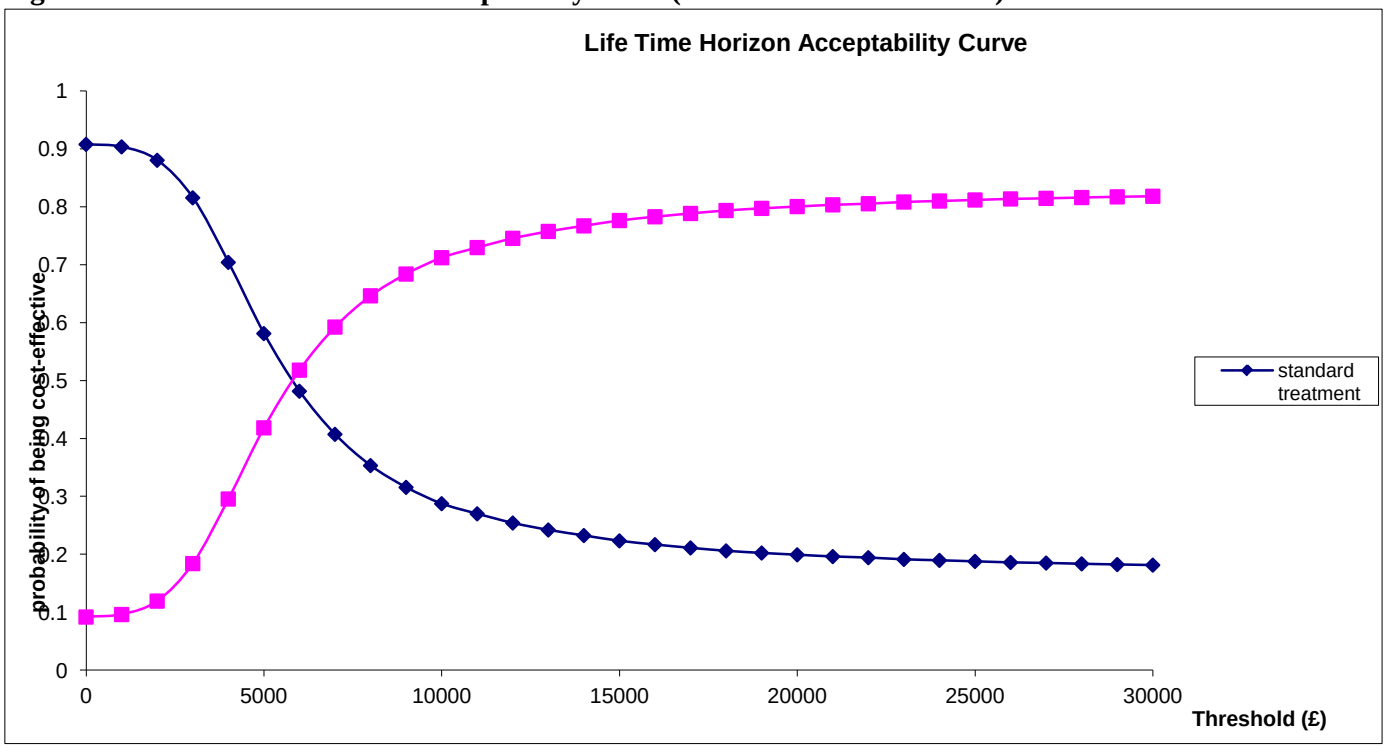


Figure 3: Cost-effectiveness acceptability curve (0-4.5 hour window of use)



5.2.15.3 Additional deterministic analysis results

For the 3 additional sensitivity analyses described in section 5.2.14.3, above, alteplase either dominated or the ICER was less than £2,000.

5.2.15.4 Subgroup analyses results, 0-3 hour window of use

No new studies were identified by the manufacturer relating to the use of alteplase in the 0-3 hour therapeutic window that were not considered as part of TA122. Given this, the manufacturer presented a limited analysis of the cost-effectiveness of this subgroup. The results are shown in Table 36, below. These results are slightly different from those presented in the previous TA 122 assessment, shown in Table 37, below. No explanation was given by the manufacturer for these differences, although the differences do not appear unreasonable given that various parameters have been updated.

Table 36: Base-case results (0-3 hour window of use) – deterministic model

	Independent life years (ILY)	life years	QALYs	Cost	ICER
Standard care	2.812	6.460	2.975	£28,519	alteplase dominant
Alteplase in addition to standard care	4.299	6.464	3.211	£27,401	

Table 37: Results of the base-case deterministic analysis from previous TA 122 assessment

	Cost	Life Years	Independent Life years	QALYs	ICER
Alteplase in addition to standard care	£22,173	6.528	4.220	3.215	**Alteplase dominant**
Standard care	£22,700	6.364	2.777	2.938	
Incremental	-£527	0.164	1.443	0.277	

The results of the 0-3 hour window of use PSA analysis are shown below in Table 38 (provided following a clarification request by ERG)[34]. These are reasonably consistent with the deterministic base-case results.

Table 38: Base-case results 0-3 hours window of use – probabilistic model

	Standard care			Alteplase in addition to standard care			
	Average	Lower 95%CI	Upper 95% CI	Average	Lower 95%CI	Upper 95% CI	ICER
QALYS	2.916	2.667	3.162	3.096	2.358	3.631	alteplase dominant
Costs	£28,113	£25,123	£31,307	£26,445	£16,724	£33,548	
ILY	2.757	2.747	2.767	4.177	3.697	4.621	
Life years	6.313	6.286	6.339	6.174	4.096	7.441	

In the previous TA 122 assessment, the ERG commented that "arguably the ATLANTIS studies should also be excluded because they did not stratify randomisation by time to treatment, and therefore the subgroups of patients treated within 3 hours do not form true randomised comparisons". However, for completeness, the manufacturer included an analysis based on the inclusion of ATLANTIS A and B. Results shown in Table 39.

Table 39: Sensitivity analysis on the inclusion of ATLANTIS A & B for the 0-3 hour window of use – deterministic model

	Independent life years (ILY)	Life years	QALYs	Cost	ICER
Standard care	2.812	6.460	2.975	£28,519	alteplase dominant
Alteplase in addition to standard care	4.230	6.224	3.118	£26,470	

5.2.15.5 Subgroup analyses results, 3-4.5 hours window of use

Given that use of alteplase in a 3-4.5 hour therapeutic window was not considered as part of TA122, a full set of cost-effectiveness results and associated sensitivity analysis were presented by the manufacturer. The results of the base-case deterministic analysis are shown in Table 40, below.

Table 40: Base-case results (3-4.5 hour window of use) – deterministic model

	Independent life years (ILY)	life years	QALYs	Cost	ICER
Standard care	2.812	6.460	2.975	£28,519	
Alteplase in addition to standard care	4.097	6.968	3.305	£30,587	£6,272

Table 41, and figures 4 and 5, below, shows the results of the PSA. The ICER from the PSA is reasonably consistent with the deterministic analysis.

Table 41: Base-case results (3-4.5 hour window of use) – probabalistic model

	Standard care			Alteplase in addition to standard care			
	Average	Lower 95%CI	Upper 95% CI	Average	Lower 95%CI	Upper 95% CI	ICER
QALYS	2.921	2.676	3.170	3.221	2.729	3.664	£6,169
Costs	£28,079	£25,129	£31,286	£29,934	£23,969	£35,530	
ILY	2.757	2.747	2.767	3.984	3.240	4.621	
Life years	6.313	6.286	6.340	6.752	5.648	7.530	

Figure 4: **Cost-effectiveness plane (3-4.5 hour window of use)**

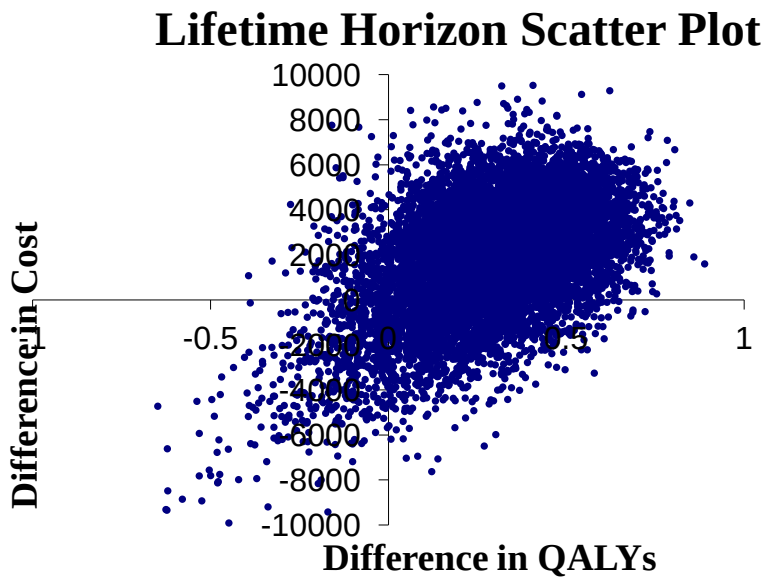
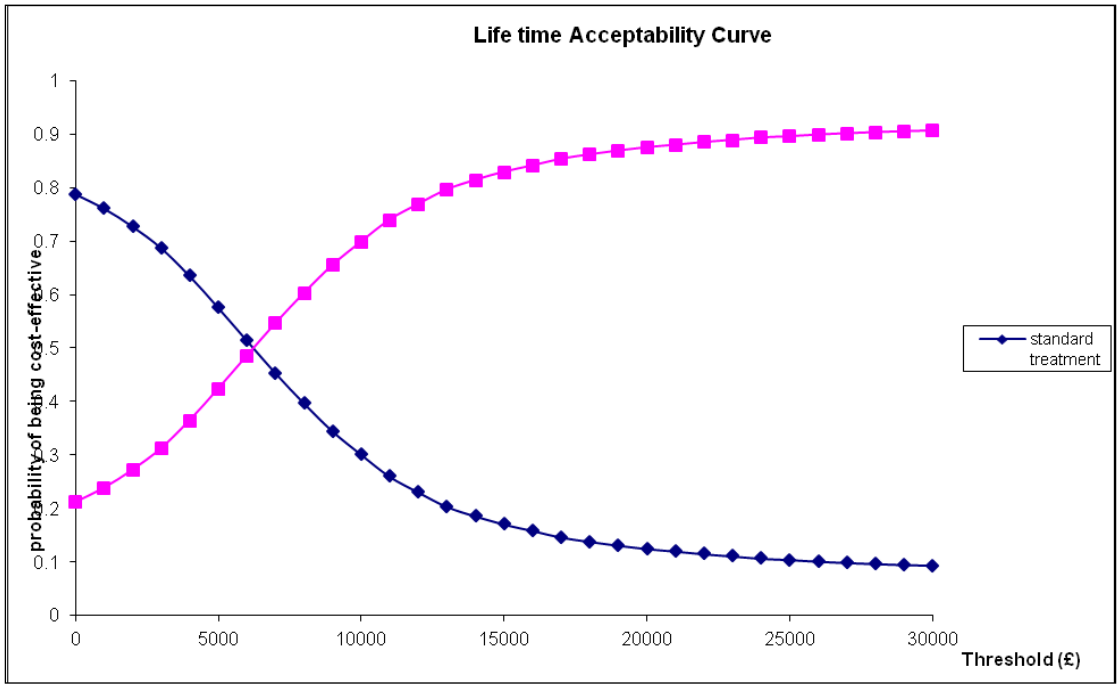


Figure 5: **Cost-effectiveness acceptability curve (3-4.5 hour window of use)**



The manufacturer conducted a univariate sensitivity analysis for the 3 – 4.5 hours window of use, using the same values as used in the 0 – 4 hours base-case analysis. A table of these values is shown in section 5.2.14.1, Table 32. The results of this analysis are shown in Table 42, below.

Table 42: Univariate sensitivity analysis (3-4.5 hour window of use)

Variable	Parameter range		ICER for lifetime horizon	
	Low	High	Low	High
Starting Age	59	75	£5,354	£7,634
Discount Rate- Costs	0%	6%	£6,701	£6,053
Discount Rate- Outcomes	0%	6%	£5,037	£7,193
Cost of Alteplase	£300	£600	£5,000	£7,330
Administration cost of Alteplase	£896.70	£1,665	£4,277	£10,263
Cost of independent stroke (Year 1)	£6,961	£9,314	£6,013	£6,534
Cost of dependent stroke (Year 1)	£16,559	£21,031	£6,320	£6,208
Cost of independent stroke (post Year 1)	£1,156	£2,610	£5,440	£7,129
Cost of dependent stroke (post Year 1)	£4,669	£7,068	£6,466	£5,877
Cost of acute event- fatal stroke	£7,424	£13,461	£6,539	£5,655
Stroke patient mortality multiplier	1.15	4.6	£5,523	£7,502
Mortality rate following recurrent stroke	0.125	0.5	£6,148	£6,450
Annual Risk of Stroke Recurrence	0.025	0.1	£5,726	£7,280
SICH risk- Alteplase	1.15%	4.36%	£6,268	£6,279
Relative risk- Death and Death or Dependency (mRS>2) (95% CI)	Death:0.50 mRS>2: 0.72	1.33 1.04	£4,569	£3,595 (no treatment more QALYs)
Relative risk- Death and Death or Dependency (mRS >2) (+/- 1sd)	Death: 0.639 mRS>2: 0.793	1.048 0.956	£5,158	£26,490 (alteplase more QALYs)
Utility- Independent	0.69	0.79	£6,774	£5,840
Utilty- Dependent	0.29	0.47	£6,133	£6,418

The manufacturer pooled an ad hoc data set of 3-4.5 hour data from ECASS II and ATLANTIS with the ECASS III data to assess the impact of this additional data on the results. The RR for SICH in this analysis is taken from ECASS II, as this data is not available in ECASS II (3-4.5 hours) and ATLANTIS (3-4.5 hours). The manufacturer comments that this should have a minimal impact on the results as this parameter had little impact in the univariate analysis. The ERG agree with this opinion. The results of this analysis are shown in Table 43, below.

Table 43: Sensitivity analysis on the inclusion of ECASS III + ECASS II (3-4.5) + ATLANTIS (3-4.5) for the 3-4.5 hour window of use – deterministic analysis

	Independent life years (ILY)	Life years	QALYs	Cost	ICER
Standard care	2.812	6.460	2.975	£28,519	
Alteplase in addition to standard care	4.092	6.894	3.281	£30,241	£5,631

5.2.16 Model validation

The only model validation described within the MS was a comparison against other published cost-effectiveness analyses. The ERG has validated the submitted models and no major errors were identified. As described earlier, discrepancies were found in the model between the SICH rates used and those cited in the report, but these were not considered to have any significant impact on the ICER. The ERG were unable to reproduce some of the ICERS reported in the univariate sensitivity analyses, however, none of the results presented in the MS varied significantly from those obtained the ERG.

5.3 Exploratory and sensitivity analyses undertaken by the ERG

The ERG conducted a deterministic sensitivity analysis replacing the health state outcomes in the LSR study with those observed in the ECASS II study. The results are shown in Table 44, below.

Table 44: Results using ECASS III to define 6 month outcomes for standard care

	QALYs	**Cost**	**ICER**
Standard care	4.218	£31,227	£4,451
Alteplase in addition to standard care	4.375	£31,925	
Incremental	0.157	£698	

The ERG was unable to replicate the CEAC and lifetime scatter plot provided in the MS for the 0 to 4.5 hours basecase PSA analysis. The CEAC and scatter plot obtained by the ERG from the manufacturers mode are shown in figures 6 and 7 below.

Figure 6: **Cost-effectiveness acceptability curve for 0 to 4.5 hours basecase scenario obtained by the ERG**

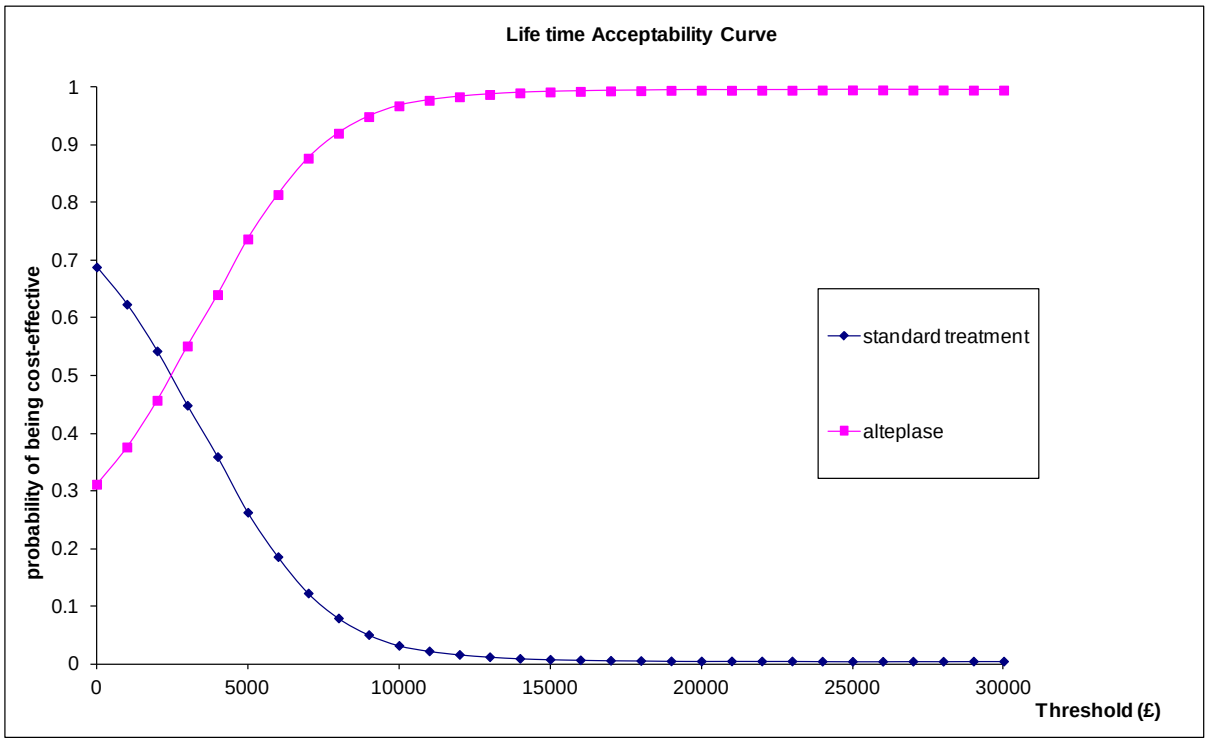
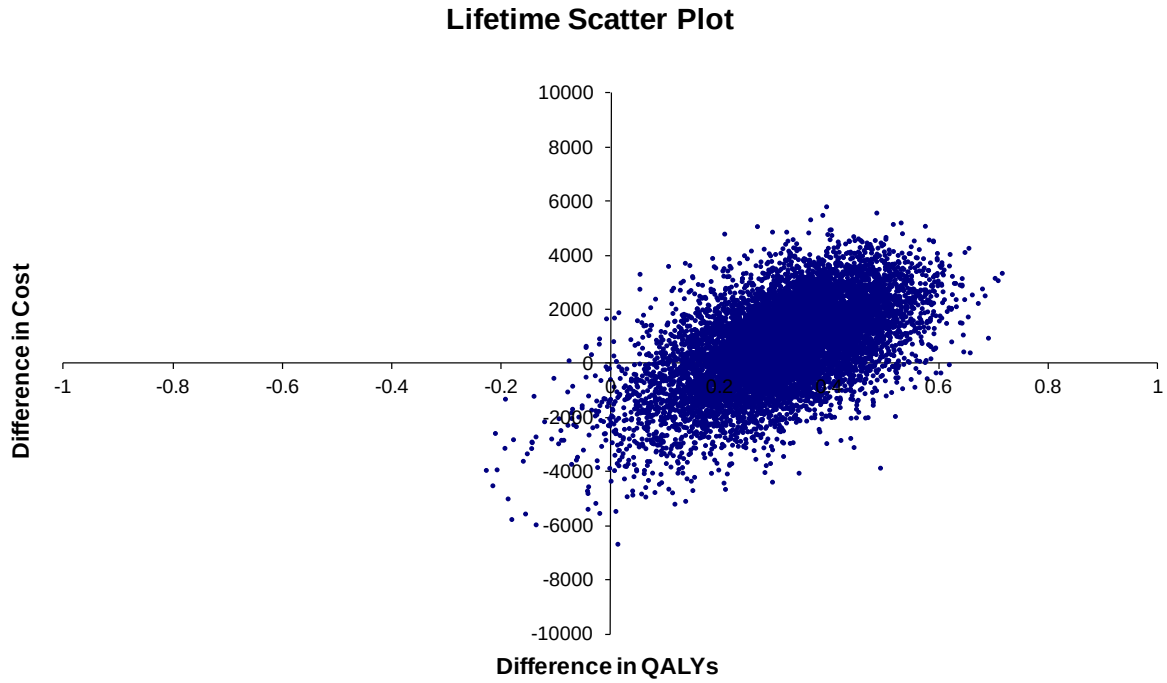


Figure 7: Cost-effectiveness plane for 0 to 4.5 hours basecase scenario obtained by the ERG



The ERG also used the submitted models to estimate the global expected value of perfect information (EVPI) for each of the three treatment time windows using a willingness to pay threshold of £20,000 per QALY. The population eligible for treatment is estimated to be 85,500, when using the figures provided in Table 52 of the MS for a 5 year period (2013 to 2018 inclusive with discounting at 3.5% per annum). This gives a population global EVPI of £324,000 for all patients who are able to receive treatment within 4.5 hours. However, the global EVPI is much higher when considering the 0 to 3 hour and 3 to 4.5 hour time windows separately as there is greater uncertainty in the RRs for death and death or dependency when considering just those studies which are applicable to each separate sub-population.. The global population EVPI is £6,593,000 for treatment within 0 to 3 hours across a population of 65,400 over 5 years, and £5,119,000 for treatment within 3 to 4.5 hours, across a population of 20,100 over 5 years. However, as discussed in section 2, the rate of treatment with alteplase may be nearer 8% than the 20% assumed in Table 52 of the MS, so the population EVPI could be as low as 40% of the values given here.

The manufacturer's model assumes that the distribution of patients entering the independent and dependent states following a recurrent stroke is equal. The ERG tested this assumption by setting the proportion of patients entering the independent and dependent states to 40% and 60% and alternately to 60% and 40% for the independent and dependent states, respectively. Increasing the numbers of

patients that are dependent after a recurrent stroke increased the base-case ICER by approximately £100 per QALY and decreasing the numbers of patients that are dependent lowered the base-case ICER by approximately £100 per QALY.

5.4 Conclusions of the cost-effectiveness section

The economic model described in the MS is considered by the ERG to meet the NICE reference case[8] and is in-line with the decision problem specified in the scope. The ERG considers that it was appropriate to conduct separate analyses for the sub-population of patients who are eligible for treatment within 0 to 3 hours and for the sub-population who are eligible for treatment within 3 to 4.5 hours. As discussed in section 4.2.6, there is some evidence to suggest an interaction between treatment effect and time from symptom onset to treatment. The efficacy estimates for these two sub-populations suggest that the balance of risks and benefits may be slightly different and these differences translate into differing cost-effectiveness estimates, even though the confidence intervals for the efficacy estimates are overlapping and there is no significant heterogeneity between the two treatment windows.

The cost-effectiveness results showed that alteplase either dominated standard care or had a central ICER well below £20,000 per QALY depending on the onset to treatment window considered. The results were generally robust under the sensitivity analyses conducted. The only factor having a significant impact was the lack of precision around the efficacy estimates. Applying the upper and lower 95% confidence intervals for both death and death or dependency as point estimates within the model resulted in a large variation in the ICER for both the 3 to 4.5 hour treatment window and the 0 to 4.5 hour treatment window. The fact that the PSA samples independently from the relative risks of death and death or dependency without taking into account the correlation between these two variables, may mean that it doesn't provide an accurate description of the uncertainty around the mean costs and QALYs. The ERG considers it unlikely that this would have a significant impact on the central ICER.

6. IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

None of the additional clinical and economic analysis undertaken by the ERG resulted in central ICERs that varied from the manufacturers results in any meaningful way.

7. END OF LIFE

End of life considerations were not considered by the ERG to be relevant to this appraisal as the median survival following first ever AIS is between four and five years[45].

8. OVERALL CONCLUSIONS

The ERG had no major concerns regarding the completeness of the submission or the robustness of the evidence presented. The evidence presented in the MS reflects the decision problem identified in the scope. The analyses presented were restricted to participants for whom alteplase was administered within 4.5 hours of symptom onset, and so this accurately reflected the NICE scope.

The RCTs included were generally of good quality with regard to randomisation and having blinded outcome assessors. Trial data from ad-hoc subgroup analyses which do not represent a true randomised comparison were excluded from the main results and only considered in sensitivity analyses. The main area of uncertainty with regard to clinical effectiveness relates to differences in stroke severity at baseline, which potentially favour alteplase, in two of the three key trials.

The economic model described in the MS is considered by the ERG to meet the NICE reference case. The model structure was considered to be appropriate and the ERG has no major concerns regarding the selection of data used within the model. In the cost-effectiveness analysis the main driver of decision uncertainty is the lack of precision around the efficacy estimates.

8.1 Implications for research

There is a lack of long-term data (beyond 1 year) on the impact of alteplase on dependence free survival which is an important driver of both costs and HRQoL. Longer-term follow-up is expected from the IST-3 trial which planned to measure survival, dependency and HRQoL using the EQ-5D at 18 months in a sub-set of patients[29]. As suggested by Wardlaw *et al.*, further meta-analysis of patient level data from the existing trials to explore baseline factors which might modify the effect of treatment, may be useful in providing guidance on targeting alteplase treatment to those patients who can benefit the most.[50]

9. REFERENCES

1. Khaja, A.M., Grotta, J.C. Established treatments for acute ischaemic stroke. *The Lancet* 2007; 369(9558):319-330.

2. Wardlaw, J.M., Zoppo, G., Yamaguchi, T., Berge, E. Thrombolysis for acute ischaemic stroke.[update of Cochrane Database Syst Rev. 2000;(2):CD000213; PMID: 10796329]. *Cochrane Database of Systematic Reviews* 2003;(3):CD000213.

3. Dorman, P.J., Waddell, F., Slattery, J., Dennis, M., Sandercock, P. Is the EuroQol a valid measure of health-related quality of life after stroke? *Stroke* 1997; 28(10):1876-1882.

4. Youman, P., Wilson, K., Harraf, F., Kalra, L. The economic burden of stroke in the United Kingdom. *Pharmacoeconomics* 2003; 21(Suppl 1):43-50.

5. Jones, M.L., Holmes, M. Alteplase for the treatment of acute ischaemic stroke: A Single Technology Appraisal. *Health Technol Assess* 2009; 13:15-21.

6. National Institute for Health and Technology Appraisal (NICE). NICE technology appraisal guidance 122. Alteplase for the treatment of acute ischaemic stroke. 2007. London.

7. Lees, K.R., Bluhmki, E., von, K.R., Brott, T.G., Toni, D., Grotta, J.C. et al. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. *Lancet* 2010; 375(9727):1695-1703.

8. National Institute for Health and Technology Appraisal (NICE). Guide to the methods of technology appraisal. 2008. London.

9. Rothwell, P.M., Coull, A.J., Silver, L.E., Fairhead, J.F., Giles, M.F., Lovelock, C.E. et al. Population-based study of event-rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories (oxford vascular study). *The Lancet* 2005; 366(9499):1773-1783.

10. Kavanagh S, Campbell J, Hoffman A, Roughton M, Rudd A, Could G et al. Stroke Improvement National Audit Programme (SINAP), Comprehensive Report, Patient admissions between April 2010 and September 2011 . 2012. London, Royal College of Physicians.

11. Rudd, A.G., Hoffman, A., Grant, R., Campbell, J.T., Lowe, D. Stroke thrombolysis in England, Wales and Northern Ireland: how much do we do and how much do we need? *Journal of Neurology, Neurosurgery & Psychiatry* 2011; 82(1):14-19.

12. Committee for proprietory medicinal products. Summary information on a referral opinion following arbritration. Pursuant to article 29 of directive 2001/83/EC for Actilyse. 2002. European Agency for the Evaluation Medicinal Products (EMEA).

13. Boehringer Ingelheim Ltd. Submission by Boehringer Ingelheim to support the Single Technology Appraisal by NICE of alteplase for the treatment of acute ischaemic stroke (review of technology appraisal 122) . 2012.

14. Van Swieten, J.C., Koudstaal, P.J., Visser, M.C., Schouten, H.J., Van Gijn, J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1988; 19(5):604-607.

15. Wardlaw, J.M., Murray, V., Berge, E., Del Zoppo, G.J. Thrombolysis for acute ischaemic stroke. *Cochrane Database Syst Rev* 2009; 4.

16. Del Zoppo, G.J., Saver, J.L., Jauch, E.C., Adams, H.P. Expansion of the time window for treatment of acute ischemic stroke with intravenous tissue plasminogen activator: A science advisory from the American heart association/american stroke association. *Stroke* 2009; 40(8):August.

17. National Institute for Health and Technology Appraisal (NICE). Alteplase for the treatment of acute ischaemic stroke (review of technology appraisal 122): Final Scope. 2012. National Institute for Health and Clinical Excellence.

18. The Joint Formulary Committee. British National Formulary. 2012. BMJ Group and Pharmaceutical Press. 2012.

19. Clark, W.M., Albers, G.W., Madden, K.P., Hamilton, S. The rtPA (alteplase) 0- to 6-hour acute stroke trial, part A (A0276g): results of a double-blind, placebo-controlled, multicenter study. Thrombolytic therapy in acute ischemic stroke study investigators. *Stroke* 2000; 31(4):811-816.

20. Clark, W.M., Wissman, S., Albers, G.W., Jhamandas, J.H., Madden, K.P., Hamilton, S. Recombinant tissue-type plasminogen activator (Alteplase) for ischemic stroke 3 to 5 hours after symptom onset. *JAMA: the Journal of the American Medical Association* 1999; 282(21):2019-2026.

21. Hacke, W., Kaste, M., Fieschi, C., von, K.R., Davalos, A., Meier, D. et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators. *Lancet* 1998; 352(9136):1245-1251.

22. Davis, S.M., Donnan, G.A., Parsons, M.W., Levi, C., Butcher, K.S., Peeters, A. et al. Effects of alteplase beyond 3 h after stroke in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET): a placebo-controlled randomised trial. *Lancet Neurology* 2008; 7(4):299-309.

23. Wang, S.Y., Wang, X.L., Zeng, H., Zuo, Y., Hu, N., Li, X.Y. et al. [Early intravenous thrombolysis with recombinant tissue plasminogen activator for acute cerebral infarction]. [Chinese]. *Zhongguo Wei Zhong Bing Ji Jiu Yi Xue/Chinese Critical Care Medicine/Zhongguo Weizhongbing Jijiuyixue* 2003; 15(9):542-545.

24. Hacke, W., Kaste, M., Fieschi, C., Toni, D., Lesaffre, E., von, K.R. et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). *JAMA* 1995; 274(13):1017-1025.

25. Hacke, W., Kaste, M., Bluhmki, E., Brozman, M., Davalos, A., Guidetti, D. et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *New England Journal of Medicine* 2008; 359(13):1317-1329.

26. Haley, E.C., Jr., Brott, T.G., Sheppard, G.L., Barsan, W., Broderick, J., Marler, J.R. et al. Pilot randomized trial of tissue plasminogen activator in acute ischemic stroke. The TPA Bridging Study Group. *Stroke* 1993; 24(7):1000-1004.

27. Sandercock, P., Lindley, R., Wardlaw, J., Dennis, M., Innes, K., Cohen, G. et al. Update on the third international stroke trial (IST-3) of thrombolysis for acute ischaemic stroke and baseline features of the 3035 patients recruited. *Trials* 2011; 12(1):252.

28. Marler JR and The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. The National Institute

of Neurological Disorders and Stroke rt-PA Stroke Study Group. *New England Journal of Medicine* 1995; 333(24):1581-1587.

29. Sandercock, P., Lindley, R., Wardlaw, J., Dennis, M., Lewis, S., Venables, G. et al. Third international stroke trial (IST-3) of thrombolysis for acute ischaemic stroke. *Trials [Electronic Resource]* 2008; 9:37.

30. Ahmed, N., Wahlgren, N., Grond, M., Hennerici, M., Lees, K.R., Mikulik, R. et al. Implementation and outcome of thrombolysis with alteplase 3-4.5 h after an acute stroke: an updated analysis from SITS-ISTR. *Lancet Neurology* 2010; 9(9):866-874.

31. Bluhmki, E., Chamorro, A., Davalos, A., Machnig, T., Sauce, C., Wahlgren, N. et al. Stroke treatment with alteplase given 3.0-4.5 h after onset of acute ischaemic stroke (ECASS III): additional outcomes and subgroup analysis of a randomised controlled trial. *Lancet Neurology* 2009; 8(12):1095-1102.

32. The IST-3 collaborative group. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial. *The Lancet* 2012.

33. Kwiatkowski, T.G., Libman, R.B., Frankel, M., Tilley, B.C., Morgenstern, L.B., Lu, M. et al. Effects of tissue plasminogen activator for acute ischemic stroke at one year. National Institute of Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator Stroke Study Group. *New England Journal of Medicine* 1999; 340(23):1781-1787.

34. Boehringer Ingelheim Ltd. Submission by Boehringer Ingelheim to support the Single Technology Appraisal by NICE of alteplase for the treatment of acute ischaemic stroke (review of technology appraisal 122): Response to request from NICE for clarification. 2012.

35. Systematic Reviews: Centre for Reviews and Dissemination's guidance for undertaking reviews in health care. 2009;

36. Food and Drug Administration. Clinical review for PLA 96-0350. 1996. 2006.

37. Sandercock, P., Berge, E., Dennis, M., Forbes, J., Hand, P., Kwan, J. et al. A systematic review of the effectiveness, cost-effectiveness and barriers to implementation of thrombolytic and neuroprotective therapy for acute ischaemic stroke in the NHS. *Health Technology Assessment (Winchester, England)* 2002; 6[26], i-102.

38. Kwiatkowski, T., Libman, R., Tilley, B.C., Lewandowski, C., Grotta, J.C., Lyden, P. et al. The impact of imbalances in baseline stroke severity on outcome in the National Institute of Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator Stroke Study.[see comment]. *Annals of Emergency Medicine* 2005; 45(4):377-384.

39. Higgins, J.P.T., Green, S., Collaboration, C. Cochrane handbook for systematic reviews of interventions. 5 ed. Wiley Online Library, 2008.

40. Chambers, M.G., Koch, P., Hutton, J., Chambers, M.G., Koch, P., Hutton, J. Development of a decision-analytic model of stroke care in the United States and Europe. *Value in Health* 2002; 5(2):82-97.

41. Wardlaw, J.M., Lewis, S.C., Dennis, M.S., Counsell, C., McDowall, M. Is visible infarction on computed tomography associated with an adverse prognosis in acute ischemic stroke? *Stroke* 1998; 29(7):1315-1319.

42. Wahlgren, N., Ahmed, N., D+ívalos, A., Ford, G.A., Grond, M., Hacke, W. et al. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. *The Lancet* 2007; 369(9558):275-282.

43. Fagan, S.C., Morgenstern, L.B., Petitta, A., Ward, R.E., Tilley, B.C., Marler, J.R. et al. Cost-effectiveness of tissue plasminogen activator for acute ischemic stroke. NINDS rt-PA Stroke Study Group.[see comment]. *Neurology* 1998; 50(4):883-890.

44. Office for National Statistics. National Population Projections, 2010-based projections. 2011; available from http://www.ons.gov.uk/ons/publications/re-reference-tables.html?edition=tcm%3A77-229866 (accessed Dec. 2011).

45. Hardie, K., Hankey, G.J., Jamrozik, K., Broadhurst, R.J., Anderson, C. Ten-year survival after first-ever stroke in the Perth Community Stroke Study. *Stroke* 2003; 34(8):1842-1846.

46. Schmulling, S., Grond, M., Rudolf, J., Heiss, W.D. One-year follow-up in acute stroke patients treated with rtPA in clinical routine. *Stroke* 2000; 31(7):1552-1554.

47. Jones, L., Griffin, S., Palmer, S., Main, C., Orton, V., Sculpher, M. et al. Clinical effectiveness and cost-effectiveness of clopidogrel and modified-release dipyridamole in the secondary prevention of occlusive vascular events: a systematic review and economic evaluation. *Health Technology Assessment (Winchester, England)* 2004; 8(38):iii.

48. McKevitt, C., Dundas, R., Wolfe, C. Two simple questions to assess outcome after stroke. *Stroke* 2001; 32, 681-686.

49. Kalra, L., Evans, A., Perez, I., Knapp, M., Donaldson, N., Swift, C. Alternative strategies for stroke care: a prospective randomised controlled trial. *Lancet* 2000; 356[9233], 894-899.

50. Wardlaw, J.M., Murray, V., Berge, E., del Zoppo, G., Sandercock, P., Lindley, R.L. et al. Recombinant tissue plasminogen activator for acute ischaemic stroke: an updated systematic review and meta-analysis. *The Lancet* 2012.

51. Review Manager 5.1 2011.

APPENDIX 1

Brief summary of studies falling outside of NICE scope (treatment within 0 to 6 hours instead of 0-4.5 hours)

The EPITHET[22] and IST-3[32]trials both administered alteplase at the licensed dose 0.9mg/kg (max 90mg). However, they did not administer alteplase solely within 4.5 hours of symptom onset, and so some participants fall outside of the UK marketing authorisation. Trial results from EPITHET (3-6 hours) and IST-3 (0-6 hours) are included in the tables below. For comparison, data are also presented from other trials (ATLANTIS A & B[19,20] and ECASS II[21]) which provide comparisons of alteplase with placebo which fall outside of the NICE scope because they do not conform with the treatment timeframe specified in the marketing authorisation. It is accepted that this includes data from some patients treated after 4.5 hours and therefore falls outside the licensed indication and NICE scope. Risk Ratios were calculated using RevMan 5.[51]

The IST-3 trial was a multicentre, open-label RCT comparing alteplase plus standard treatment with standard treatment (although the pilot phase had been double-blinded and placebo-controlled).[29,32] There were 156 sites in 12 countries (Europe, including the UK, Australasia, Canada, Mexico). The number of patients enrolled was 3035 with 1515 patients randomised to alteplase and 1520 to the control group. Fifty three percent of patients were older than 80 years of age, and so were outside of the UK marketing authorisation. Treatment was administered within 0-6 hours from symptom onset (mean time 4.2 hours in the alteplase group). Thirty three percent were treated more than 4.5 hours after treatment onset.

The primary outcome of IST-3 was alive and independent at 6 months follow-up as measured by an Oxford Handicap Score (OHS) of 0 to 2. This made comparison with included trials difficult, as other trials used the modified Rankin Scale (mRS) and reported at 3 months follow-up, although a recent systematic review of alteplase[50] considered OHS and mRS equivalent. At 6 months, 554 (37%) patients in the alteplase group versus 534 (35%) in the control group had an OHS of 0 to 2. This did not reach statistical significance, adjusted (by age, stroke severity, time, and presence or absence of visible acute ischaemic change) odds ratio 1·13 (95% CI 0·95–1·35) p=0·181. Sub-group data were available, for the primary outcome, for those aged 80 or under (not restricted to 0-4.5 hours), and for 0-3 and 3-4.5 hours from symptom onset (although this was not restricted to patients meeting licence criteria). The trial had used a minimisation algorithm for randomisation which included age and delay in randomisation.[27] The table below shows death and dependency (OHS 3-6), which may be seen as equivalent to mRS 3-6 as reported by other trials.

When a favourable outcome was assessed, that is an OHS 0 to 1, this significantly (p=0·018) favoured alteplase (24%) over control (21%), adjusted OR 1·26 (95%CI 1·04 to 1·53). Within 7 days of treatment, IST-3 reported a significantly (p=0.001) higher death rate in the alteplase group (11%) than in the control group (7%) adjusted OR 1·60 (95% CI 1·22–2·08). However, by 6 months the mortality rate was 27% for both groups. Symptomatic intracranial haemorrhage (SICH) was defined as significant neurological deterioration accompanied by clear evidence of significant intracranial haemorrhage on the post-randomisation scan (or autopsy if not re-scanned and death occurred after 7 days). Within 7 days, there was a significantly (p<0.0001) higher rate of SICH in the alteplase group (7%) than in the control group (1%) OR 6.94 (4.07-11.8).

EPITHET was a phase II RCT with a small sample size (n=52 for alteplase and n=40 for placebo).[22] The analysis presented was per protocol, unlike the trials included in the MS which reported intention to treat analyses. The trial concentrated on mismatch patients, that is patients who have a mismatch in perfusion-weighted MRI and diffusion weighted MRI. However, as this was not tested for until after randomisation, some other stroke patients were included. There was no upper age limit for trial inclusion (there were 25 patients aged over 80[50]). Mean time to treatment was 293 minutes for the alteplase group and 291 minutes for the placebo group. Median NIHSS at baseline was 14 for the alteplase group and 10 for the placebo group (if restricted to patients with mismatch, medians were 14 and 11 respectively). The primary outcome was infarct growth attenuation in mismatch patients. It also included the outcome of "good functional outcome" defined as a mRS of 0 to 2 at 90 days follow-up. At 3 months follow-up, for mismatch patients, 19/37 (45%) alteplase, and 17/43 (40%) of the placebo group had mRS of 0 to 2, which did not differ significantly between groups (p=0.663). It is likely that the study was underpowered to address this outcome. When restricted to a mRS of 0 to 1, the comparison was also non-significant (p=0.153), alteplase 36%, placebo 21%.

Table 45 All-cause mortality: trial comparisons falling outside of the marketing authorisation (treatment within 6 hours from symptom onset)

Study	Time from symptom onset to treatment (hours)	Mortality Outcomes	Alteplase group	Placebo group	Risk Ratio (95% CI)	Absolute risk difference (alteplase vs. placebo group)
ATLANTIS A [15,19]	0-6	All-cause mortality at 3 months	16/71 (22.5%)	5/71 (7.0%)	3.20 (1.24-8.26)	+15.5%
ATLANTIS A [19]	5-6	All-cause mortality at 3 months	8/22 (36.4%)	1/24 (4.2%)	8.73 (1.18-64.28)	+32.2%
ATLANTIS B [15]	0-5	All-cause mortality at 3 months	33/307 (10.7%)	21/306 (6.9%)	1.57 (0.93-2.64)	+3.8%
ATLANTIS B [20]	3-5	All-cause mortality at 3 months	30/272 (11.0%)	19/275 (6.9%)	1.60 (0.92-2.77)	+4.1%
ECASS II [15]	0-6	All-cause mortality at 3 months	43/409 (10.5%)	42/391 (10.7%)	0.98 (0.65-1.64)	-0.2%
EPITHET [15,22]	3-6	All cause mortality at 3 months	13/52 (25.0%)	7/49 (14.3%)	1.75 (0.76-4.02)	+10.7%
IST-3 [32]	0-6	All cause mortality at 7 days	163/1515 (11%)	107/1520 (7%)	1.53 (1.21-1.93)	+4%
IST-3 [32]	0-6	All cause mortality at 6 months	408/1515 (27%)	407/1520 (27%)	1.01 (0.89-1.13)	0%

Table 46 Death or dependency: trial comparisons falling outside of the marketing authorisation (treatment within 6 hours from symptom onset)

Study	Time from symptom onset to treatment (hours)	Death or dependency Outcomes	Alteplase group	Placebo group	Risk Ratio (95% CI)	Absolute risk difference (alteplase vs. placebo group)
ATLANTIS A[15]	0-6	Death or dependency at 3 months mRS 3-6	64/71 (90.1%)	56/71 (78.9%)	1.14 (0.99-1.32)	+11.2%
ATLANTIS B[15]	0-5	Death or dependency at 3 months mRS 3-6	141/307 (45.9%)	135/306 (44.1%)	1.04 (0.87-1.24)	+1.8%
ECASS II[15,21]	0-6	Death or dependency at 3 months mRS 3-6	187/409 (45.7%)	211/391 (54.0%)	0.85 (0.74-0.97)	-8.3%
EPITHET[15]	3-6	Death or dependency at 3 months mRS 3-6	28/52 (53.8%)	29/49 (59.2%)	0.91 (0.65-1.28)	-5.4%
EPITHET[22]	3-6	Death or dependency at 3 months mRS 3-6	29/51 (56.9%)	29/49 (59.2%)	0.96 (1.06-1.34)	-2.3%
EPITHET[22]	3-6 subgroup of mismatch patients	Death or dependency at 3 months mRS 3-6	23/42 (55%)	26/43 (60%)	0.91 (0.63-1.31)	-5%
IST-3[32]	0-6	Death or dependency **OHS 3-6 at 6 months**	961/1515 (63%)	986/1520 (65%)	0.98 (0.93-1.03)	-2%
IST-3[32]	0-6	Death or dependency **OHS 3-6 at 6 months** **Sub-group age 80 or younger**	367/698 (52.6%)	373/719 (51.9%)	1.01 (0.92-1.12)	+0.7%
IST-3[32]	0-6	Death or dependency **OHS 3-6 at 6 months** **Sub-group age over 80**	594/817 (72.7%)	611/799 (76.5%)	0.95 (0.90-1.01)	-3.8%

Study	Time from symptom onset to treatment (hours)	Death or dependency Outcomes	Alteplase group	Placebo group	Risk Ratio (95% CI)	Absolute risk difference (alteplase vs. placebo group)
IST-3[32]	0-3 subgroup†	Death or dependency **OHS 3-6 at 6 months**	299/431 (69.4%)	323/418 (77.3%)	0.90 (0.83-0.97)	-7.9%
IST-3[32]	3-4.5 subgroup†	Death or dependency **OHS 3-6 at 6 months**	395/577 (68.5%)	374/600 (62.3%)	1.10 (1.01-1.19)	+6.1%
IST-3[32]	4.5-6 subgroup	Death or dependency **OHS 3-6 at 6 months**	267/507 (52.7%)	287/500 (57.4%)	0.92 (0.82-1.03)	-4.7%

† Within timeframe for treatment specified in marketing authorisation (0 to 4.5 hours), but included patients aged over 80

Table 47 SICH: trial comparisons falling outside of the marketing authorisation (treatment within 6 hours from symptom onset)

Study	Time from symptom onset to treatment (hours)	SICH Outcomes	Alteplase group	Placebo group	Risk Ratio (95% CI)	Absolute risk difference (alteplase vs. placebo group)
ATLANTIS A[15]	3-6	SICH within 10 days	6/61 (9.8%)	0/58 (0%)	12.37 (0.71-214.78)	+9.8%
ATLANTIS A[19]	0-6	SICH within 10 days	8/71 (11.3%)	0/71 (0%)	17.00 (1.00-289.05)	+11.3%
ATLANTIS A[19]	5-6	SICH within 10 days	4/22 (18.2%)	0/24 (0%)	9.78 (0.56-171.91)	+18.2%
ATLANTIS B[15]	3-5	SICH within 10 days	18/284 (6.3%)	4/256 (1.6%)	4.06 (1.39-11.83)	+4.7%
ATLANTIS B[15,20]	0-5	SICH within 10 days	21/307 (6.8%)	4/306 (1.3%)	5.23 (1.82-15.07)	+5.5%
ATLANTIS B[20]	3-5	SICH within 10 days	19/272 (7.0%)	3/275 (1.1%)	6.40 (1.92-21.39)	+5.9%
ECASS II[21]	0-6	SICH within 10 days	36/409 (8.8%)	13/391 (3.4%)	2.65 (1.43-4.92)	+5.4%
EPITHET[15,22]	3-6	SICH within 10 days	4/52 (7.7%)	0/49 (0%)	8.49 (0.47-153.70)	+7.7%
IST-3[32]	0-6	SICH within 10 days	104/1515 (7%)	16/1520 (1%)	6.52 (3.87-10.99)	+6%