NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE (NICE)

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)

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Executive summary

Alteplase is indicated for the thrombolytic treatment of acute myocardial infarction, the thrombolytic treatment of acute massive pulmonary embolism with haemodynamic instability, catheter clearance of clots and thrombolytic treatment of acute ischaemic stroke (AIS) within 0-4.5 hours of the onset of symptoms. Use in AIS within 0-3 hours of onset of symptoms was granted UK marketing approval on 30th September 2002 and Boehringer received licence approval from the MHRA to extend the time window for the use of alteplase in this indication to 4.5 hours from the onset of symptoms on 14th March 2012.

Alteplase for acute ischaemic stroke is administered in a single dose solution expressed as 0.9mg/kg. It is given as a 10% bolus followed by the remaining 90% as a 60-minute infusion. The individual maximum dose for for acute ischaemic stroke is 90 mg. The product is available in the following pack sizes, 10mg priced at £135, 20mg priced at £180 and 50mg priced at £300.

Alteplase is contraindicated in the treatment of acute ischaemic stroke where symptoms of ischemic attack beginning more than 4.5 hours prior to initiation of treatment (the licence extension has increased this to within 4.5 hours) or when time of symptom onset is unknown; 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. Alteplase is also contraindicated in 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 over 80, 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 should not be treated with alteplase. Alteplase is also not indicated for children or adolescents <18 years of age.

Clinical Evidence – 0-3 hours window of use

No new clinical data in addition to that presented in TA 122 for the use of alteplase in acute ischaemic stroke identified for its use in 0-3 hour window from the onset of symptoms for inclusion in this submission.

Thrombolysis with alteplase in acute ischaemic stroke within 0-3 hours of the onset of symptoms has been tested in patients in six randomised, placebo-controlled, phase III clinical trials.

These studies, as well as meta-analyses including a Cochrane systematic review and a pooled analysis of the alteplase RCTs, as well as a number of open-label observational cohort studies which have been formally compared with the outcomes from the RCT, provide a positive evaluation of treatment with alteplase.

The RCTs demonstrate that treatment with alteplase within 3 hours of the onset of acute ischaemic stroke is associated with significantly better 3-month outcomes in terms of neurological disability than placebo. The increased risk of early symptomatic or fatal intracranial haemorrhage associated with alteplase is offset by reduction in the proportion of patients dying or being dependent at 3 months.

The focus of analysis within this submission for patients treated within 0-3 hours of the onset of symptoms has been ECASS II and NINDS which were identified in the previous TA122 as the most relevant studies for assessment of clinical and cost effectiveness of this group of patients.

Clinical Evidence – 3-4.5 hours window of use and 0-4.5 hours window of use.

ECASS III is a randomised , double blind, placebo controlled study of patients using alteplase from 3-4.5 hours from the onset of symptoms.

ECASS III demonstrates that treatment with alteplase within 3-4.5 hours of the onset of acute ischaemic stroke is associated with significantly better 3-month outcomes in terms of neurological disability than placebo. The increased risk of early symptomatic or fatal intracranial haemorrhage associated with alteplase is offset by reduction in the proportion of patients dying or being dependent at 3 months.

ECASS III has formed the basis of assessment of the clinical and cost effectiveness of alteplase within 3-4.5 hours of the onset of symptoms and pooled with data from ECASS II and NINDs the basis of assessment of the clinical and cost effectiveness of alteplase within 0-4.5 hours of the onset of symptoms

The Economic Evaluation

The economic evaluation outlined in this section is an extension of the life-time Markov model constructed and published as part of the Health Technology Appraisal of thrombolytic therapy by Sandercock et al*.,* (2002) and used as the basis of Boehringer Ingelheim's submission to TA122. The model has been replicated using the same structure and inputs described in the text of the published appraisal. The model has been refreshed where possible with up-to-date data on costs and effects.

This evaluation robustly demonstrates the cost effectiveness of alteplase when considered in addition to standard medical and supportive management within a specialist stoke unit for its use within a 0-4.5 hour window of use, shown separately for the subgroups 0-3 hour and 3-4.5 hour window of use as outlined in the tables below:

Table 1: Base-case cost-effectiveness results (0-4.5 hour window of use)

	Alteplase	No Treatment
Technology acquisition cost	£480	£0
Other costs	£28850	£28519
Total costs	£29330	£28519
Difference in total costs	£811	
LYG	6.826	6.460
LYG difference	0.366	
QALYs	3.307	2.975
QALY difference	0.332	
ICER	£2,441	
LYG, life years gained; QALY(s), quality-adjusted life year(s); ICER, incremental cost-effectiveness ratio		

Table 2. Base-case cost-effectiveness results (0-3 hour window of use)

	Alteplase	No Treatment
Technology acquisition cost	£480	0
Other costs	£28850	£28519
Total costs	£26921	£28519
Difference in total costs	£-1598	
LYG	6.464	6.460
LYG difference	0.004	
QALYs	3.211	2.975
QALY difference	0.236	
ICER	Alteplase dominant	
LYG, life years gained; QALY(s), quality-adjusted life year(s); ICER, incremental cost-effectiveness ratio		

Table 3. Base-case cost-effectiveness results (3 – 4.5 hour window of use)

	Alteplase	No Treatment
Technology acquisition cost	480	0
Other costs	£30107	£28519
Total costs	£30587	£28519
Difference in total costs	£2068	
LYG	6.968	6.460
LYG difference	0.508	
QALYs	3.305	2.975
QALY difference	0.330	
ICER	£6272	
LYG, life years gained; QALY(s), quality-adjusted life year(s); ICER, incremental cost-effectiveness ratio		

Section A – Decision problem

1. Description of technology under assessment

1.1. Technology Name and Therapeutic Class

- Brand name: Actilyse
- Generic name: Alteplase
- Therapeutic class: Thrombolytic agents
- ATC code: B 01 A D 02

1.2. Principal mechanism of action of the technology.

Alteplase is a glycoprotein developed from recombinant technology. It is also known as recombinant tissue-plasminogen activator. It activates the conversion of plasminogen to plasmin and, by attaching to fibrin within the thrombus, initiates lysis of the clot – thrombolysis.

1.3. UK Marketing authorisation status

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.

1.4. The main issues discussed by the regulatory organisation.

In relation to the extended licence for alteplase from 0-3 hours to 0-4.5 hours the main issues discussed relate to the efficacy of the drug used from 3-4.5 hours from the onset of symptoms.

1.5. Anticipated indication in the UK

Alteplase is currently licensed and has received a UK licence for thrombolytic treatment in the following indications:

- Thrombolytic treatment in acute myocardial infarction
- Thrombolytic treatment in acute massive pulmonary embolism with haemodynamic instability
- Clearance of clots from catheters
- Fibrinolytic treatment of acute ischaemic stroke
    - 0-4.5 hours from onset of symptoms

The new regulatory submission has extended the current administration window for treatment for AIS from up to 3 hours, to up to 4.5 hours.

1.6. All completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

The Safe Implementation of Treatment in Stroke-International Stroke Thrombolysis Registry (IST-3) (Ahmed et al 2010) study will report in May 2012. The IST-3 study is not directly relevant to this appraisal since it is not a placebo controlled study, and hence does have a relevant head to head comparator, although it might provide supporting evidence. The comparator for the assessment will be no treatment and hence the relevant studies to assess clinical and cost effectiveness (at least for the reference case) are adequately provided by relevant placebo controlled randomised, controlled

studies (e.g. ECASS III for 3-4.5 hours and ECASS II for 0-3 hrs and NINDS) so that IST-3 is not needed for the assessment. IST-3 is an international, multi-centre, prospective, randomized, open, blinded endpoint trial of intravenous alteplase in acute ischaemic stroke. Suitable patients had to be assessed and able to start treatment within 6 hours of developing symptoms.

1.7. Anticipated date of licence extension

Boehringer Ingelheim received MHRA approval for a licence extension for use of alteplase up to 4.5 hours in AIS is anticipated on 14th March 2012

1.8. Regulatory approval outside the UK.

Extensive regulatory approval outside the UK exists for the 0-3 hour window of use.

1.9. Other Technology Assessments in the UK.

1.9.1. Completed technology assessments

SMC guidance issued February 2004 relating to alteplase up to 3 hours after acute ischaemic stoke (AIS) event: Alteplase (rt-PA) (Actilyse) is accepted for restricted use within NHS Scotland for the treatment of acute ischaemic stroke.

In April 2007 Alteplase received NICE a positive recommendation for thrombolytic treatment in acute ischaemic stroke within the 0-3 hour window following symptom onset.

1.9.2. Ongoing technology assessments

The SMC are currently reviewing a submission from Boehringer Ingelheim for the indicated treatment window of 3-4.5 hours; advice is expected imminently given the granting of the extended licence for the window of use of alteplase.

1.10. Unit Costs of alteplase for AIS

Table 4. Unit costs of technology being appraised

Pharmaceutical formulation	Powder in vial for intravenous infusion
Acquisition cost (excluding VAT)	10 mg, 1 pack (1x10 mg powder in vial, 1 x 10ml WFI) £120.00. 20 mg, 1 pack (1 x 20 mg powder in vial, 1 x 20ml WFI, 1 transfer device) = £180.00. 50 mg, 1 pack (1 x 50 mg powder in vial, 1 x 50ml WFI, 1 transfer device) = £300.00; 2 packs = £600.00. (MIMS September 2011).
Method of administration	Intravenous injection
Doses	0.9 mg per kg of body weight. 10% given as a bolus with the remainder given over 1 hour, maximum dose of 90mg).
Dosing frequency	Once
Average length of a course of treatment	1 hour
Average cost of a course of treatment	76kg – average weight of those receiving alteplase in the 3-4.5h cohort in the SITS-MOST observational study 0.9mg per kg. = 68.4mg £480 = 50mg (£300) + 20mg (£180)
Anticipated average interval between courses of treatments	N/A
Anticipated number of repeat courses of treatments	N/A
Dose adjustments	As per kg of body weight.

1.11. Device prices

Not applicable.

1.12. Additional tests or investigations needed

In order to confirm the absence of intracranial haemorrhage, imaging techniques are required in order to commence treatment with alteplase e.g. cranial computerised tomography (CT) or other diagnostic imaging method sensitive to the presence of haemorrhage. This is required in NHS current practice for those patients eligible for treatment with alteplase within 3 hours of the

onset of stroke symptoms as recommended by NICE. This therefore suggests that the equipment and efficient infrastructure within and between departments should already be in existence.

1.13. Need for monitoring of patients over and above usual clinical practice for this technology.

No additional monitoring is needed given the issues outlined in Section 1.12.

1.14. Other therapies likely to be administered at the same time as the intervention as part of a course of treatment.

Control of severe hypertension (blood pressure >185/110) and hyperglycaemia will also be required prior to initiation of alteplase therapy although it would be anticipated even in the absence of alteplase treatment such control would be standard clinical practice for those having had an AIS.

Context

2.1. Brief overview of the disease or condition for which the technology is being used.

Acute stroke is one of the leading factors of morbidity and mortality worldwide. It is the most substantial cause of morbidity and long-term disability in Europe, and demographic changes will result in an increase in both its incidence and prevalence (European Stroke Organisation Executive Committee, 2008). The Royal College of Physicians (2008) have stated that yearly, over 1 in 10 deaths in the UK are directly attributable to stroke with an estimated 150,000 people experiencing such an event. It is the 3rd largest cause of severe disability world wide, with 250,000 stroke survivors currently living in the UK (Royal College of Physicians, 2008).

Stroke generally is a major health concern in the UK with the 1999 figures indicating that the 11% of deaths were attributable to stroke, (NICE 2008b). These costs of stroke within England's economy amount to around £7 billion per year, with £2.8 billion of this being direct costs to the NHS, (NICE 2008b)

Approximately 80% of acute strokes are ischaemic in cause, the remainder being primarily intracranial haemorrhage (ICH). Ischaemic strokes are caused by thrombosis within the cerebral vasculature or by embolism from thrombi forming in the carotid arteries or in the heart from implanted left heart valves or thrombus forming in the left atrium usually in patients with atrial fibrillation.

During 2001-2002, respondents in a study reported by Zahran et al. (2005) with one or more chronic medical condition reported worse HRQoL than those without such conditions. For example, when patients were asked to rate their general health as excellent, very good, good, fair or poor, only 7.1% of respondents without any chronic medical condition assessed their general health as fair or poor whereas almost half of those who had experienced stroke reported fair or poor health. Only patients with congestive heart failure reported worse HRQoL than those who had experienced stroke

2.2. Number of patients assumed to be eligible.

As outlined in more detail in Section 7.1, there will be an estimated 62,033 first ever cases of acute ischaemic stroke (AIS) in England and Wales in 2012. We estimate that 12,407 based on sales 20% of these patients receiving alteplase (based on assumptions in NICE costing template). Assuming these are predominantly patients receiving the drug within a 0-3 hour window of use, and based on evidence of the time from onset that patients present at stroke units and then receive a relevant scan suggests that the number of eligible patients might increase to 21,451 as a result of the licence extension to use up to 4.5 hours from symptom onset.

2.3. Details of relevant NICE guidance or protocols for the condition for which the technology is being used.

NICE issued guidance recommending alteplase for use within 3 hours of the onset of stroke symptoms in April 2007 (Alteplase STA, 2007). There are currently no other licensed thrombolytic treatments for acute ischaemic stroke either within the 3 hour time period or the extended 4.5 hour window.

2.4. Relevant clinical pathway of care and how this is changed by the technology

Stroke patient care in the absence of specific treatment was originally generally medical and nursing care until patients could be discharged home or to long-stay care. More recently it has been recognised that specialist stroke units improve the results in terms of recovery from stroke and increasingly stroke patients are being channelled to care in such units (as echoed in NICE Stroke Guidelines 2008).

Treatment with alteplase is additive to this pathway and does not replace any current routine care. Patients suffering acute ischaemic stroke (AIS) will normally have called the emergency services so as to ensure rapid transit to hospital. In order to be eligible for treatment with alteplase, rapid examination consultation with stroke specialists and immediate CT scanning of the head

will have to occur. Treatment with alteplase must be decided upon and administration of drug commenced before 4.5 hours have elapsed from the onset of stroke symptoms. Control of severe hypertension (blood pressure >185/110) and hyperglycaemia will also be required prior to initiation of alteplase therapy although it would be anticipated even in the absence of alteplase treatment such control would be standard clinical practice for those having had an AIS. No other medications are needed at this stage.

As outlined in the NICE Stroke Pathway, immediate imaging is needed in those considered appropriate and thrombolysis with alteplase should be initiated where this is indicated.

As per the NICE clinical guideline, all patients suspected of stroke should be admitted directly to a specialist acute stroke unit following initial assessment, either from the community or from the A&E department.

Brain imaging should then be undertaken immediately should alteplase be considered. Urgent treatment has been shown to improve outcome in AIS with alteplase being recommended when used by physicians trained and experienced in the management of such a condition. This should only be undertaken in centres with facilities that enable it to be used in full accordance with its marketing authorisation.

It is assumed that the infrastructure utilised for the administration of alteplase within the 0-3 hour window will be equivalent to that of the 3-4.5 hour window. Therefore the only change to this process will be the time period in which this procedural pathway can be utilised, namely 0-4.5 hours rather than 0-3.

2.5. Current clinical practice.

Stroke physicians wishing to implement treatment with alteplase in addition to the routine management of patients with ischaemic stroke in their units will

understand the evidence that the most favourable results in treating AIS will arise in patients who can be treated as early as possible.

Early treatment in a 0-3 hour window already being undertaken has called for collaboration between the patient/family who need to be aware of what may be a stroke, the emergency services who need to understand that AIS is a medical emergency capable of being treated, accident and emergency professional staff who understand that urgent diagnosis and disposition of the patient is essential, the need for 24 hour CT scanning availability and interpretation and the stroke physician whose staff are adept at getting the shortest possible onset of stroke to treatment time (OTT), notwithstanding the contra indications, precautions and warnings and the general safety of treatment with alteplase.

This continued emphasis on, and paramount importance of, collaboration between disciplines and emergency service and health care departments would still, be required should even the time-window extension be recommended for alteplase administration – “Having more time does not mean we should be allowed to take more time,” (Hacke et al. 2008).

2.6. The main comparator for the intervention.

Since the use of alteplase in this indication is purely additive and not intended to replace any routine practice the comparator is restricted to placebo or standard medical and supportive management without thrombolysis. The rationale for such is that alteplase is currently the only licensed medical treatment in the UK for this purpose regardless of the administration time period.

As reported in Sandercock et al. (2002) those patients with AIS who do not receive thrombolytic treatment would be given aspirin immediately. Those patients for whom alteplase is administered would receive aspirin around 24hours later. It has been shown that the benefits of aspirin whether initiated 24 or 48 hours after AIS have shown to be comparable and therefore, as in

Sandercock et al. (2002), it was concluded that there was no substantial difference in outcome attributed to the delay in initiation of aspirin treatment compared to those who receive alteplase treatment initially.

2.7. Therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

The most frequent adverse event associated with alteplase is haemorrhaging resulting in a fall in haematocit and/or haemoglobin values.
If a potentially dangerous haemorrhage occurs, particularly cerebral haemorrhage, the fibrinolytic therapy must be discontinued. Generally though, it is not necessary to replace the coagulation factors due to the short half-life and the minimal effect on the systemic coagulation factors. The majority of patients who experience bleeding can be managed by interruption of thrombolytic and anticoagulant therapy, volume replacement and manual pressure applied to an incompetent vessel.
If heparin has been administered within the 4 hours prior to bleeding onset, protamine should be considered.
Should the patient be irresponsive to these measures, judicious use of transfusion products may be indicated. Antifibrinolytic agents are available as a last alternative.

2.8. The main resource use to the NHS associated with the technology being appraised.

Table 5: cost of additional staffing requirements for extended administration window

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 utilized 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)

3. Equity and equality

3.1. Identification of equity and equalities issues in existing treatment guidance / protocols

There are equity and equality issues surrounding the initial incidence of stroke, whether due to race, socioeconomic status or geographical location, and the subsequent access to health care, whether again geographical or educational. firstly the former shall be discussed.

Studies have shown the incidence of stroke in the black population is higher than in the white and is not explained by confounders such as social class, age and sex (e.g. Stewart et al, 1999).

Socioeconomic status also correlates with the incidence of stroke (Hart et al. 2000; Power et al. 2005; McFadden et al. 2009). Many studies internationally have shown that there is also a link, whether to do with the education and awareness surrounding stroke, between lower socioeconomic status and seeking medical attention.

In addition, it seems intuitive to suggest that, given the rigid time frame in which alteplase can be administered, the proximity in which a person lives to the treatment hospital should play a large role in dictating the time from symptom onset to presentation at a medical provider.

From this brief overview it can be seen that large inequalities and inequities exist within the UK between incidence of stroke and gaining access to the correct medical attention whether this be due to one or more of a few key reasons; ethnicity, socioeconomic status or location. Findings from a multitude of studies have also suggested that there is a differential in incidence and outcome of stroke based on race, gender, social class and area of the UK.

3.2. Equity or equalities issues anticipated for the appraisal of this technology.

An extended window for the use of alteplase from the onset of symptoms has the potential to provide access to treatment to patients who are presently not receiving it. Socioeconomic and geographical factors as outlined in the section above contribute to differential access levels at present.

3.3. Clinical and cost-effectiveness analysis of equity issues.

These have not been explored in the presented analyses.

4 Statement of the decision problem

Table 6: Statement of the decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
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	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	bleeding events Health-related quality of life	
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.	A life-time time horizon has been employed to capture the chronic nature of disability associated with stroke.	
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			

Section B – Clinical and cost effectiveness

Element of health technology assessment	Reference case	Section in 'Guide to the methods of technology appraisal'
Defining the decision problem	The scope developed by NICE	5.2.5 and 5.2.6
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	5.2.5 and 5.2.6
Perspective costs	NHS and PSS	5.2.7 to 5.2.10
Perspective benefits	All health effects on individuals	5.2.7 to 5.2.10
Type of economic evaluation	Cost-effectiveness analysis	5.2.11 and 5.2.12
Synthesis of evidence on outcomes	Based on a systematic review	5.3
Measure of health effects	QALYs	5.4
Source of data for measurement of HRQL	Reported directly by patients and carers	5.4
Source of preference data for valuation of changes in HRQL	Representative sample of the public	5.4
Discount rate	An annual rate of 3.5% on both costs and health effects	5.6
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	5.12
HRQL, health-related quality of life; NHS, National Health Service; PSS, Personal Social Services; QALY(s), quality-adjusted life year(s)		

5 Clinical evidence

5.1. Identification of studies

5.2.5. Strategies used to retrieve relevant clinical data,

Given the feedback from the ERG report concerned with TA122 stating that the search strategy employed in the Boehringer submission at that time was simplistic compared to that used for the Cochrane systematic review (See Wardlaw et al 2009 for most recent update of this review), it was felt necessary to take heed of this and update the approach.

The search strategy for the Cochrane review "*Thrombolysis for acute ischemic stroke (Review)"* was sensitive to all thrombolytic drugs so this was adapted to suit the needs of this search by excluding all drug terms other than those relating to alteplase. The search was limited to randomised controlled trials since this is an update of the reviews already undertaken and the results of these showed high quality randomised controlled trials for both the 0-3 hour window and 3-4.5 it was judged that data from observational studies would not be required.

Exact details of the search strategy used is provided in **section 9.2, Appendix 2.**

5.2. Study Selection

5.2.1. The study selection process.

Since the study selection process used for this submission was an update of that carried out by the Cochrane review both the inclusion and exclusion criteria for the original Cochrane study and that employed for this update are outlined below:

	Table 7. Cochrane review inclusion/exclusion criteria (All trials pre-2008) (original Cochrane review)
Inclusion criteria	*Population* All patients with definite acute ischaemic stroke (CT scan or MRI scan undertaken to exclude intracranial haemorrhage). *Interventions* • Any type of thrombolytic drug, given in any dose either through the intravenous or intra-arterial route. Exclusion of trials that were confounded by the treatment effect or where the control was receiving a non-randomised active therapy. Outcomes • The primary outcome measures were death or dependency (defined as mRS score of 3-6) and mortality by follow-up completion. All other outcomes were considered secondary. • Secondary outcomes: o Deaths from all causes within 7-10 days post-treatment. o Symptomatic intracranial haemorrhage – either symptomatic or fatal. o Fatal intracranial haemorrhage o Symptomatic infarct swelling o Deaths from all causes during the whole trial follow-up period o Poor functional outcome at the end of the follow-up, (independent, dependent, dead) Study design • Randomised controlled trial. Language restrictions • None

Exclusion criteria	Population • none Interventions • none Outcomes • None Study design • Non-RCT Language restrictions • None

Update of the Cochrane review

This original Cochrane search was updated so as to capture any other alteplase clinical trials published after the date of search in 2008.

	Table 8. Update of the Cochrane Review 2008 – Feb 14th 2012.
Inclusion criteria	*Population* Adult population aged between 18 -80 who received alteplase treatment after experiencing acute ischaemic stroke with confirmation through brain imaging (e.g.CT scan) that intracranial bleeding is not apparent. *Interventions* • 0.9mg/kg alteplase (to a max. of 90mg) with treatment administration within the 0-4.5 hour time period. 10% as initial intravenous bolus with the remaining 90% as infusion over the subsequent 60 minutes. (As per the SPC and license) vs. placebo. *Rationale for explicit search for alteplase:* • Since alteplase given intravenously is the only thrombolytic agent to have received Marketing Authorisation in GB, the inclusion of other thrombolytic agents without relevance to alteplase would have been inappropriate. Outcomes • The primary outcome measures were death or dependency (as defined by mRS score of 3-6) and mortality by follow-up completion. All other outcomes were considered secondary. Study design • Randomised controlled trials - as this was an update of the reviews already undertaken and the results of these showed high quality randomised controlled trials for both the 0-3 hour window and 3-4.5 hence data from

	observational studies would not be required. Language restrictions • Abstract published in English
Exclusion criteria	**Population** • Patients under the age of 18. • Patients over the age of 80. **Interventions** • Unlicensed dose (e.g. 0.6mg/1.1mg per kg body weight) • Unlicensed administration (e.g. intra- arterial) • Treatment administration outside the 0-4.5 hour time window. **Outcomes** • No outcomes were specified for basis of inclusion or exclusion **Study design** • Non-RCT **Language restrictions** • Non-English

The clinical trial data identified for alteplase through the original Cochrane review (Wardlaw et al. 2009) is presented in Table 9.

Table 9: Alteplase RCTs – all alteplase RCTs to 2008. Wardlaw et al. 2009

Trial	Year	Methods	Administration period	Dose
Atlantis A	2000	Double blind, randomised placebo-controlled	Within 6hours	As per SPC
Atlantis B	1999	Double blind, randomised placebo-controlled	1993-1996: 0-5 hours, 1996-end of trial: 3-5hours	As per SPC
ECASS	1995	Double blind, placebo-controlled	Within 6hours	1.1mg/kg body weight
ECASS II	1998	Double blind, randomised placebo-controlled	Within 6hours	As per SPC
ECASS III	2008	Double blind, randomised placebo-controlled	3-4 hours (first 228 patients), 3-4.5 (patient 229-821)	As per SPC
EPITHET	2008	Double blind, randomised placebo-controlled	3-6 hours	As per SPC
Haley	1993	Double blind, randomised placebo-controlled	0-1.5hours, 1.5-3 hours	0.85mg/kg body weight
NINDS	1995	Double blind, randomised placebo-controlled	0-3 hours	As per SPC
Wang	2003	3 parallel groups, 2 doses, 1 control/ chinese population	0-6 hours	Treatment group A: 0.9mg; treatment group B: 0.7mh/kg body weight; 8mg injected initially as a bolus.

5.2.1.1. Study Selection – 0 to 3 hour window of use.

As mentioned, an adapted search strategy was employed in this submission to identify any relevant additional studies (detailed in **Appendix 7**). The QUOROM flow diagram can be seen in Figure 1 which shows no new studies relevant to the 0-3 hour window of use additional to those identified previously to support TA122.

This did not reveal any other RCTs for alteplase other than those identified by the original Cochrane review.

Given that no new clinical data relating to the 0-3 hour time window was identified other than that included in the previous TA122, the previously

identified relevant studies were used as the basis of the cost effectiveness analysis for these patients in this submission (both the sub group 0-3 hours and the primary decision problem 0-4.5 hours).

The following trials were identified as relevant in TA122 to considering the clinical and cost effectiveness of the use of alteplase within a time window of 0-3 hours from the onset of symptoms:

- ATLANTIS A
- ATLANTIS B
- ECASS II
-NINDS

The Haley and ECASS I trials were thought not to be relevant to the decision problem as they utilise an unlicensed dosage regimen, Wang results were based on an unrepresentative population for the UK and the other identified studies (EPITHET and ECASS III) only included patients using alteplase in a time window of use outside of 0-3 hours. EPITHET was reported by Davies et al 2008 (n=101). EPITHET was an investigator-driven trial, supported by academic grants from the Australian National Health and Medical Research Council (NHMRC), the National Stroke Foundation, and the Heart Foundation of Australia. Boehringer Ingelheim supplied matching alteplase and placebo, but was not involved in the study design, data management, or data analysis. In addition, some questions were raised about the appropriateness of the ATLANTIS A and B since the data available for the 0-3 hour window of use involved a stratification of the data from these studies which was not pre-specified prior to randomisation.

The outline of this data is included in **Appendix 14** and Table 10 summarising these studies is included below in this section of the submission.

Table 10: Summary of studies identified as relevant to 0-3 hours window of use (identified for TA122) – outlined in detail in Appendix 14				
Trial no. (acronym)	**Intervention**	**Comparator**	**Population**	**Primary study ref.**
NINDS I – designed to assess clinical activity – focussed on changes in neurological activity within the first 24 hours post-treatment. **NINDS II** – assessing sustained clinical benefit at 3 months.	Alteplase – 0.9mg/kg body weight (max 90mg), given as 10% initial bolus with 90% administered over the following 60minutes.	Placebo	Patients experiencing ischaemic stroke with a clearly defined time of onset. A deficit measurable on the NIHSS and baseline CT scan showing an absence on intracranial haemorrhage was also required. Patients did not undergo randomisation if: • They had experienced another stroke or serious head trauma within the preceding 3 month period. • Within the previous 14 days they had undergone major surgery. • Had a history on intracranial haemorrhage • Had a systolic blood pressure above 185mm o Hg or diastolic blood pressure above 110mg Hg • Had rapidly improving or minor symptoms • Within the previous 21 days had experienced gastrointestinal haemorrhage or urinary tract haemorrhage • Had symptoms suggestive of subarachnoid haemorrhage	Marler et al. 1995
ECASS I	Alteplase – 1.1 mg/ kg body weight with an upper dose limit of 100mg per patient. 10% of the total dose was given as initial bolus over 1-2 minutes with the remaining dose administered through a 60min intravenous infusion.	Placebo	Patients aged between 18 and 80 years presenting with a stable moderate to severe hemispheric stroke syndrome (defined as moderate to high-grade hemiparesis, sensory disturbance, dysarthria or nonfluent asphasia, and occasionally hemianpia). An absence of hemorrhagic stroke should be confirmed through CT scan. Patients with the most severe hemispheric stroke syndrome presenting with hemispheric stroke syndrome presenting with hemiplegia and impairment of consciousness and/or forced head and eye deviation were excluded from the study. Patients with only mild neurological deficit defined as a Scandanavian Stroke Scale (SSS) score of greater than 50 of 58 total points, patients already improving, and patients not meeting the 6hour time window were excluded as well. Patients with pre-existing disabling neurologic disease or concomitant medical conditions, such as esophgeal varices, gastroduodenal ulcer, colitis, aortic aneurysm, and recent (within 1 -3 months) trauma, operation or punctures were also ineligible.	Hacke et al. 1995

ECASS II	Alteplase – 0.9mg/kg body weight (max 90mg), given as 10% initial bolus with 90% administered over the following 60minutes.	Placebo	Patients aged between 18 and 80 years presenting with a stable moderate to severe hemispheric stroke syndrome (defined as moderate to high-grade hemiparesis, sensory disturbance, dysarthria or nonfluent asphasia, and occasionally hemianpia). An absence of hemorrhagic stroke should be confirmed through CT scan. Patients with the most severe hemispheric stroke syndrome presenting with hemispheric stroke syndrome presenting with hemiplegia and impairment of consciousness and/or forced head and eye deviation were excluded from the study. Patients with only mild neurological deficit defined as a Scandanavian Stroke Scale (SSS) score of greater than 50 of 58 total points, patients already improving, and patients not meeting the 6hour time window were excluded as well. Patients with pre-existing disabling neurologic disease or concomitant medical conditions, such as esophgeal varices, gastroduodenal ulcer, colitis, aortic aneurysm, and recent (within 1 -3 months) trauma, operation or punctures were also ineligible.	Hacke et al. 1998
Atlantis A	Alteplase – 0.9mg/kg body weight (max 90mg), given as 10% initial bolus with 90% administered over the following 60minutes.	Placebo	Patients deemed eligible within 0-6 hours of symptom onset. Patients aged 18 through to 79 years with clinically diagnosed acute ischaemic stroke causing a measurable neurological deficit with ICH excluded through CT scan. Study drug must have been administered between 0-6 hours from symptom onset.	Clark et al. 2000
Atlantis B	Alteplase – 0.9mg/kg body weight (max 90mg), given as 10% initial bolus with 90% administered over the following 60minutes.	Placebo	Patients deemed eligible within 0-5hours of symptom onset – protocol amendment due to safety concerns between 5-6hours. This was later modified to 3-5hour post-symptom-onset administration window in light of the NINDS rt-PA publication of study results. Patients aged between 18 and 79 years of age who presented with clinically diagnosed IS causing a measurable neurologic deficit. A CT scan confirming the absence of ICH was required before randomisation was undertaken. If more than one third of the middle cerebral artery territory was seen to shown signs of cerebral ischaemia treatment was also excluded.	Clark et al. 1999

5.2.1.2. Study Selection – 3 to 4.5 window of use.

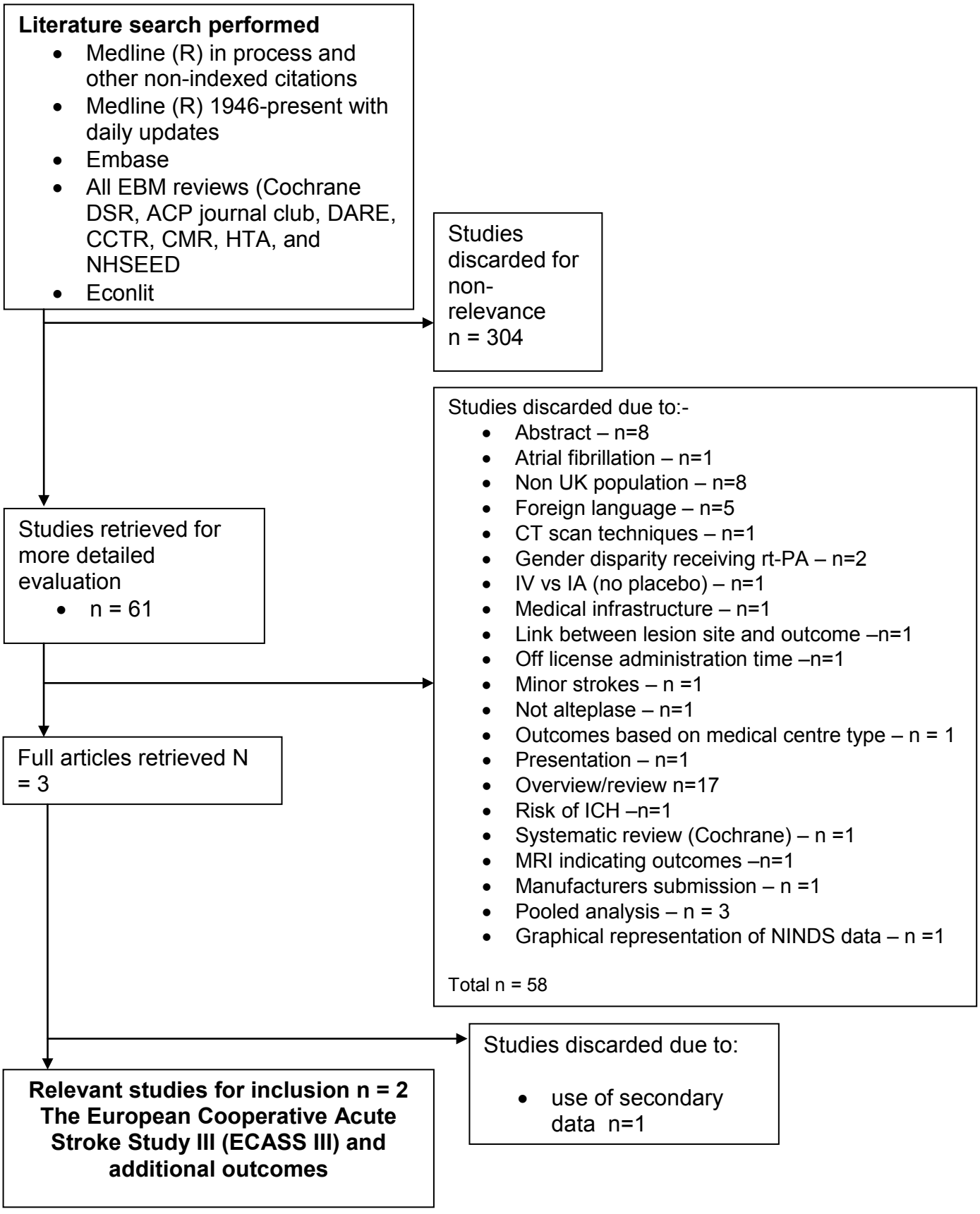
The single randomised controlled trial identified relevant to the use of alteplase in the 3-4.5 hours window of use was ECASS III. This was a head to head, RCT with placebo as comparator. As defined in the decision problem no treatment is the relevant comparator to alteplase and hence ECASS III provides a “gold standard” form of clinical data to support the analysis of clinical and cost effectiveness in this population.

It was recognised that the following studies had the potential to provide ad hoc sub group analysis data of relevance the clinical and cost effectiveness of alteplase in the 3-4.5 hour window of use:

- ATLANTIS A
- ATLANTIS B
- ECASS II
- EPITHET

Since this data is of secondary appropriateness to ECASS III in the hierarchy of evidence it has not been described in detail in Section 5. Data sets of all patients randomised for ECASS II and ATLANTIS (A & B combined) to receive placebo or alteplase within 3-4.5 hours are shown in **Appendix 15** (Sections 15.9.9. and 9.15.10.). This data was used in a pooled analysis with ECASS III as part of the sensitivity analysis for the cost effectiveness analysis of the 3-4.5 hour subgroup as outlined in Section 6.9.4.2.2. and the SA for the 0-4.5 hour window of use as outlined in Section 6.7.7. Both ECASS II and ATLANTIS were described as part of the TA 122 submission and these descriptions are included in **Appendix 14**. It was not possible to get an ad hoc sub group analysis of the EPITHET data set.

5.2.2. QUOROM statement flow diagram for ECASS III



The single new (since TA122 was issued in 2007) randomised controlled trial to be identified, with the initial report (Hacke et al. 2008) sourced by Wardlaw et al. 2009, and one additional paper (Bluhmki et al. 2009) exploring the trial sourced through the update of the review, was ECASS III. This spanned the administration window of 3-4.5 hours. Hence the evidence to support the extension of the administration time window will be the focus of the remaining sections of this submission.

5.2.3. Source of data for relevant study

Data from the ECASS III trial has been drawn from 2 sources – the core results publications was released in 2008 by Hacke et al with a further paper in 2009 presenting additional outcomes and post-hoc sub group analyses (Bluhmki et al).

5.2.4. Complete list of relevant RCTs

Table 11: List of relevant RCTs for the 3-4.5 hour window of use

Trial no. (acronym)	Intervention	Comparator	Population	Primary study ref.
ECASS III	Alteplase. Reconstituted from lyophilized powder in sterile water injection. The dose was 0.9mg/kg (to a max of 90mg) with 10% administered as an initial bolus and the remaining 90% as a continuous intravenous infusion. N.B. brain imaging undertaken prior to randomisation to confirm the absence of intracranial haemorrhage.	Placebo Reconstituted from lyophilized powder in sterile water injection with 10% administered as an initial bolus and the remaining 90% as a continuous intravenous infusion. N.B. brain imaging undertaken prior to randomisation to confirm the absence of intracranial haemorrhage	Patients were eligible for inclusion into the study if they were between 18 and 80 years of age, they had been diagnosed with acute ischemic stroke and treatment was received in the 3-4.5 hours post-symptom-onset window. Before randomisation was undertaken brain imaging (e.g. through a CT scan or MRI) was needed to confirm the absence of intracranial haemorrhage.	Hacke et al. 2008.

5.2.5. RCT which compares the intervention directly with the appropriate comparator.

ECASS III provides a head-to-head trial of the efficacy of alteplase administered in the 3-4.5 hour time window compared to placebo.

5.2.6. Excluded studies meeting search criteria

No other randomised controlled trials were identified through the systematic review.

5.2.7. Relevant non-RCTs

As discussed, a high quality RCT was identified, which provided the information required to address the decision problem and given the preference of NICE towards the “gold standard” of RCT data, it was concluded that the inclusion of observational data was unnecessary.

5.3. Summary of methodology of relevant RCTs

5.3.1. Summary of ECASS III Study

5.3.2. RCT Design of ECASS III

The third European Cooperative Acute Stroke Study (ECASS 3) [Hacke et al. 2008] was a double blind, placebo controlled, multi-centre parallel randomised control trial (RCT) of thrombolysis with alteplase 3 to 4.5 hours after AIS conducted between July 29, 2003 and November 13, 2007 at 130 sites in 19 European countries.

The rationale for the trial was to investigate the benefit/risk ratio of alteplase for acute stroke treatment in an extended time-window of 3-4.5 hours after the onset of stroke symptoms.

The trial utilised a 3 - 4 hour time-window for the first 228 patients. The acceptable OTT time-window was extended to 4.5 hours post-AIS following the report of a pooled analysis of prior trials [Hacke et al. 2004] of alteplase for AIS. 593 patients entered the trial following this protocol extension.

821 patients were enrolled (22 in the UK) and randomly assigned, in a 1:1 ratio, to either the alteplase or placebo arm. An interactive voice-randomisation system was utilised. Blocks of 4 were used to ensure a balanced distribution of group assignment at any point in the trial. The block size was withheld from the investigators. Those allocated to the alteplase trial arm received a 0.9mg dose per kilogram of body weight, administered intravenously (with an upper limit of 90mg). Injections of alteplase and the matched placebo consisted of reconstituted lyophilized powder in sterile water. An initial bolus of 10% of the total dose was given with the remaining

90% administered through continuous intravenous infusion over the following 60 minutes if there was no evidence of allergic reaction within the initial 5 minutes.

The settings used were broadly comparable to that of the UK (European centres) and alteplase was administered as per its revised extended-administration-time SPC for its licensed indication of acute ischaemic stroke treatment.

5.3.3. Eligibility Criteria in ECASS III

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 hemorrhage.
- 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.
- Patient is willing to participate voluntarily and to sign a written patient informed consent. Informed consent will be obtained from each patient or the subject's legally authorized representative or relatives, or deferred where applicable, according to the regulatory and legal requirements of the participating country.

- Patients who are unable to sign but who are able to understand the meaning of participation in the study may give an oral witnessed informed consent. These patients have to make clear undoubtfully that they are willing to participate voluntarily and must be able to understand an explanation of the contents of he information sheet.
- Willingness and ability to comply with the protocol.

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 haemorraghic 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)
- Recent (less than 10 days) traumatic external heart massage, obstetrical delivery, recent puncture of a non-compressible blood-vessel (e.g. subclavian or jugular vein puncture.
- Known bacterial endocarditis, pericarditis.
- Acute pancreatitis
- Documented ulcerative gastrointestinal disease during the last 3 months, oesophageal varices, arterial- aneurysm, arterial/venous malformation
- Neoplasm with increased bleeding risk
- Severe liver disease, including hepatic failure, cirrhosis, portal hypertension, oesaphageal varices and active hepatitis
- Major surgery or significant trauma in past 3 months
- Current or recent (within 3 months) participation in another investigational drug treatment protocol

5.3.4. Patient Characteristics at Baseline – ECASS III

Table 12: Demographic and Baseline Characteristics - ECASS III cohort			
Characteristic	**Study group**		**P Value***
	Alteplase (N=418)	Placebo (N=403)	
Age (yr)	64.9±12.2	65.6±11.0	0.36
Male sex (%)	63.2	57.3	0.1
Weight (Kg)	78.5±15	78.0±16	0.62
NIHSS Score[Δ]			0.003
Mean	10.7±5.6	11.6±5.9	
Median	9	10	
Systolic pressure (mm Hg)	152.6 ± 19.2	153.3 ± 22.1	0.63
Diastolic pressure (mm Hg)	84.4 ± 13.5	83.9 ± 13.6	0.58
Diabetes (%)	14.8	16.6	0.47
Previous use of aspiring or antiplatelet drugs (%)	31.1	32.5	0.65
Hypertension (%)	62.4	62.8	0.88
Atrial flutter or fibrillation (%)	12.7	13.6	0.67
History of stroke (%)	7.7	14.1	0.03
Smoking status (%)[¥]			0.93
Never smoked	48.6	46.2	
Ex-smoker	20.6	24.6	
Current smoker	30.6	28.8	
Time to treatment initiation			
Median	3 hr 59 min	3 hr 58 min	0.49
By 0.5 -hr period[§]			0.44
≥3.0 to ≤ 3.5 hr (%)	9.6	10.4	
>3.5 to ≤ 4.0 hr (%)	45.7	47.9	
>4.0 to ≤ 4.5 hr (%)	41.6	36.7	
Source: *Hacke et al. (2008)*			

***Any difference between groups occurred despite randomization and was therefore due to chance. Post hoc P values are merely illustrative and have not been adjusted for multiple comparisons, for which P = 0.004 would be considered to indicate statistical significance.**

[Δ] Scores on the National Institute of Health Stroke Scale (NIHSS) range from 0 to 42, with higher values reflecting more severe neurologic impairment (<5, mild impairment; ≥25, very severe impairment)

[¥] Data for smoking status were not available for one patient in the alteplase group and two patients in the placebo group.

[§] Percentages do not add up to 100 because no exact time of treatment initiation was available for 12 patients in the alteplase group and 15 patients in the placebo group; in addition, treatment was initiated after 4.5 hours in 1 patients in the alteplase group and 5 patients in the placebo group.

Table 12 presents the demographic and baseline characteristics of the ECASS III population. Patients in the cohort were broadly comparable to those likely to receive alteplase under the extended OTT in the UK. This is based upon the assumption that the population of SITS-MOST, a registry of

all licensed European use of alteplase for AIS, as a proxy for those likely to receive rt-PA in the extended time window). Mean patient age was similar (68 in SITS-MOST compared to 65.2 in ECASS III), along with similar gender balance (39.8% female in SITS-MOST compared to 39.7% in ECASS III). The likelihood of a history of stroke was slightly lower in SITS-MOST (10.1% compared to 11% in ECASS III) and baseline neurological functioning was slightly higher in SITS-MOST (mean NIHSS of 12 compared to 11.1 in ECASS III).

As can be seen (Table 12) through the examination of the p-values for the baseline characteristics, there were two, NIHSS score and history of stroke, which proved statistically significantly different between the cohorts. After the adjustment for multiple comparisons, 'history of stroke' was the single prognostic factor that differed between the treatment arms. This though, on further inspection was roughly only a 7% increase in absolute value (7.7% in the alteplase arm vs. 14.1% in the placebo arm) therefore it was felt unrealistic to suggests that this would have a significant effect on the results and was not considered damaging to the internal validity of the trial.

5.3.5. Details of outcomes measured

The primary outcome was disability at day 90 as assessed through measurement on the modified Rankin scale (mRS), a 7 point progressive functionality scale (range 0-6) where 6=dead and 0=symptom free. Outcomes were dichotomised as a favourable or unfavourable outcome as follows:

Favourable Outcome = mRS < 2
Unfavourable Outcome = mRS ≥2

The trials report provided the proportion of each model arm in each mRS group at 90±14 days (later used to calculate relative risks for the mRS determined health states in the economic evaluation).

The mRs is well-known to neurologists, acknowledged by regulatory authorities and accepted as clinically meaningful [Jones et al. 2007]. Safety

endpoints included death and symptomatic ICH (sICH). Patients were assessed by examiners who were unaware of treatment assignment. Follow-ups to prior trials [Kwiatkowski et al. 1999; Schmülling et al. 2000] suggest the effect of alteplase is complete by, and maintained beyond, 90 days; hence patient assessment took place 1, 2 and 24 hours and days 7,30 and 90

The secondary endpoints in the ECASS III trial were as follows:

- 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[1], a score of 0-1 on the NIHSS[2] and a score of 95 or higher on the Barthel Index.
- Disability status at day 90, measured by mRS 0-2 (independent outcome), and Barthel index ≥85.
- Functional status at day 30, as measured by the mRS (total score) median, the Barthel index (total score) median, NIHSS (total score) mean/median change from baseline and NIHSS (8 point improvement or 0-1).
- Functional status at day 7, measure by NIHSS (total score) as mean/median change from baseline or NIHSS score with a 4 point improvement or 0-1.
- Functional status at day 1, measured by NIHSS (total score) as measured by mean/median change from baseline.
- Functional status at day 0 (1 hour after end of treatment) as measured by mean/median change from baseline.
- Reduction in infarct volume (CT) from baseline at days 1, 7 and 30 (optional at days 7 and 30)
- Stratified endpoints of NIHSS (boundaries at 8 and 14) and mRS (0, 0-1, 0-2).
- Length of hospital stay.

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[1] The Glasgow Outcomes Scale is a 5-point scale where 1 indicated independence and 4/5 indicated severe disability or death.

[2] The National Institutes of Health and Stroke Scale (NIHSS) is a 15-item impairment scale which provides a quantitative measurement of key components of a standard neurological examination. The scale assesses level of consciousness, extraocular movements, visual fields, facial muscle function, extremity strength, sensory function, coordination (ataxia), language (aphasia), speech (dysarthria), and hemi-attention

Safety endpoints

- Overall mortality at day 90
- Stroke-related and neurological deaths
- Adverse events recording i.e. “any untoward medical occurrence in a clinical investigation patients administered a pharmaceutical product and which did not necessarily have to have a causal relationship with this treatment.”
- Symptomatic cerebral haemorrhage defined as any blood in the brain or intracranially associated with a clinical deterioration of ≥4 points of the NIHSS for which the haemorrhage has been identified as the dominating cause of the neurologic deterioration. (In addition to this per protocol definition the following alternative definitions were used to allow comparison across trials:
    - ECASS II, SITS-MOST, NINDS definition
- Cerebral herniation rate and symptomatic oedema
- Vital sign measurement

5.3.6. Primary Hypothesis of ECASS III and Statistical Analysis Approach

ECASS III was designed to test the hypothesis that the 3-4.5 hour extended administration time-window from stroke symptom onset is both effective and safe in patients who experience acute ischemic stroke.

The primary null hypothesis of interest was the degree of response with regard to the primary endpoint mRS (0-1) was inferior or not between the two treatment groups; the alternative was that alteplase was superior over placebo. The hypothesis test was undertaken as a two-sided analysis.

Based upon a pooled analysis of prior trials (Hacke et al. 2004) it was calculated that 400 patients per group were required to have 90% power to detect an odds ratio of 1.4 for the trials primary end-point. This number was exceeded in both trial arms (alteplase n=418, placebo n=403).

All efficacy end-points were calculated using intension-to-treat (ITT) analysis. For those individuals who were known to be alive but for who there was missing data, the worst-possible outcome was assigned (death). As information for baseline NIHSS score was also required, the best possible score was imputed; for all other baseline parameters, no assignment was made. In the case of missing data after baseline, missing data were imputed following the Worst and Last Observed Carried Forward (WLOCF)

5.3.7. Sub-analyses carried out

The following subgroups were predefined (Bluhmki et al. 2009):

- Time from onset of symptoms to treatment [OTT]
- Baseline NIHSS score
- Sex
- Age

Additional post-hoc analyses were undertaken due to influences from previous clinical research suggesting the efficacy of alteplase may differ in the following groups (Bluhmki et al. 2009):

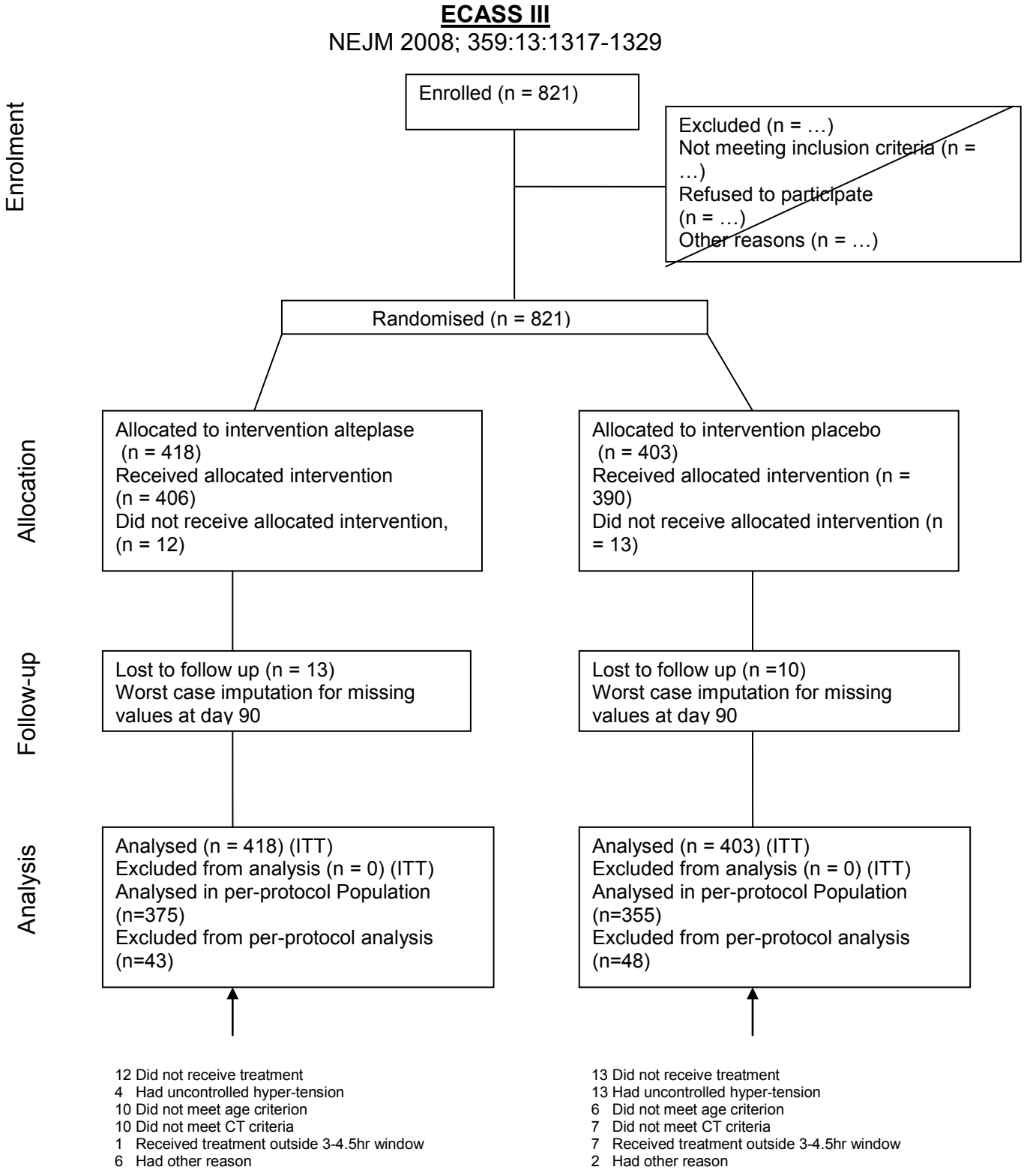
- Presence of diabetes
- Previous stroke history
- Hypertension
- Smoking status
- Previous chronic use of antiplatelet drugs
- Atrial fibrillation

The above subgroup analyses were conducted for the primary endpoint to assess efficacy and those for safety were undertaken for sICH and mortality. The statistical power of the subgroup analysis for sICH was improved by using the definition provided and used by the National Institute of Neurological Disorders and Stroke (NINDS) recombinant tissue plasminogen activator trial. It should be emphasised that all subgroup analyses were not powered to test

for significance hence the statistical relationships observed should be treated with caution.

5.3.8. CONSORT Flow Chart

Figure 2: CONSORT flow diagram – ECASS III



5.4. Critical appraisal of relevant RCTs

5.4.1. Critical Appraisal of ECASS III

Critical appraisal carried out using quality assessment check list – see Section 5.4.2.

5.4.2. Quality assessment of ECASS III

A complete quality assessment of ECASS III has been provided in the section 9.3, appendix 3.

5.4.3. Tabulated summary response to quality assessment criteria for multiple studies.

Not relevant since only one study considered relevant (ECASS III)

5.5. Results of the relevant RCTs

5.5.1. The results for all relevant outcome measures

Primary efficacy end-point

Favourable outcome - 90 days (based as outlined in Section 5.3.5. favourable outcome defined on mRS as 0-1)

52.4% (219/418) of the alteplase treatment group, compared with 45.2% (182/403) of the placebo group had a favourable outcome indicated by a score of 0 or 1 on the mRS at 90days – an absolute improvement of 7.2 percentage points (odds ratio, 1.34; 95% confidence interval [1.02,1.76]; relative risk, 1.16 [1.01, 1.34]; p=0.04).

Note as outlined in Section 6.2.3. the dichotomisation of outcomes is also done using the mRS but for reasons described in 6.2.3. the categories used are different namely:

- Independent (mRS 0-2)
- Dependent or death (mRS 3-6)

Thus, based on this definition, 33.5% (140/418) and 38.5% (155/403) of the alteplase and placebo group respectively at 90 days were dead or dependent based on an ITT analysis with a relative risk of 0.87 as shown in 6.3.1.1 table 24. Relative risks were used rather than OR based on a recommendation from the ERG during TA122 that these were more appropriate in a common condition such as stroke.

A table is provided below of patient numbers by mRS at 90 days for the placebo and alteplase arms of ECASS III to further aid clarity:

Table 13: Patient numbers by mRS for ECASS III ITT

mRS	Alteplase	Placebo
0	115	88
1	104	94
2	59	66
3	39	46
4	39	55
5	34	21
6	28	33
Total	418	403

Secondary endpoints

Global outcome measure – 90 days

The difference between alteplase and placebo corroborates with the findings from the primary outcome of the study. The global odds ratio for a favourable outcome was 1.28 (95% CI, 1.00, 1.65; p=0.0481) signifying that the odds for a favourable outcome (the ability to return to an independent lifestyle) after stroke were 28% higher with alteplase than with placebo.

The remaining “tertiary” (as referred to within the report) are now presented) outcomes are presented in Table 13.

Table 14: Odds ratios for further secondary endpoints at days 90 and 30 after treatment in the ITT and PP populations – Favourable outcome with alteplase as compared with placebo.
Source: ECASS III Trial report

Endpoint	Day 90				Day 30			
	ITT		PP		ITT		PP	
	OR (95%CI)	p[1]	OR (95%CI)	p[1]	OR (95%CI)	p[1]	OR (95%CI)	p[1]
Global outcome								
mRS 0-1	1.34 (1.02-1.76)	0.0383	1.47 (1.10-1.97)	0.0097	1.42 (1.08-1.88)	0.0132	1.46 (1.09-1.96)	0.0121
BI ≥ 95	1.23 (0.93-1.62)	0.1555	1.33 (0.99-1.80)	0.0612	1.29 (0.98-1.70)	0.0689	1.35 (1.01-1.81)	0.0446
NIHSS 0-1	1.33 (1.01-1.75)	0.0426	1.43 (1.07-1.91)	0.0165	1.52 (1.15-2.01)	0.0035	1.59 (1.18-2.13)	0.0023
GOS = 1	1.25 (0.95-1.64)	0.1118	1.32 (0.98-1.76)	0.0641	n.a.	n.a.	n.a.	n.a.
mRS 0-2	1.24 (0.93-1.65)	0.1380	1.37 (1.01-1.86)	0.0437	1.26 (0.96-1.66)	0.0967	1.32 (0.98-1.77)	0.0662
BI ≥ 85	1.15 (0.86-1.54)	0.3370	1.25 (0.91-1.71)	0.1693	1.18 (0.89-1.55)	0.2493	1.29 (0.96-1.73)	0.0955
NIHSS change ≥ 8 or =0-1	n.a.	n.a.	n.a.	n.a.	1.35 (1.03-1.78)	0.0308	1.46 (1.09-1.96)	0.0119
Stratified endpoint	1.22 (0.93-1.62)	0.1551	1.34 (1.00-1.80)	0.0524	1.23 (0.92-1.66)	0.1665	1.22 (0.89-1.66)	0.2162

Safety end-points

Table 15: adverse event overall summary in ITT population

	ITT population	
	Alteplase n (%)	Placebo n (%)
Patients randomised	418 (100.0)	403 (100.0)
Patients with any AE	327 (78.2)	319 (79.2)
Patients with investigator defined drug-related AEs	100 (23.9)	28 (6.9)
Patients with AEs leading to discontinuation of trial drug	3 (0.7)	1 (0.2)
Patients with serious AEs[1]	105 (25.1)	99 (24.6)
Fatal	32 (7.7)	34 (8.4)
Imm life threatening	21 (5.0)	21 (5.2)
Disabling	10 (2.4)	11 (2.7)
Req./Prol.hospitalisation	69 (16.5)	68 (16.9)
Other	10 (2.4)	6 (1.5)

The key safety endpoints were death and the incidence of symptomatic intracranial haemorrhage. Further safety endpoints were incidence of stroke-related and neurological deaths, incidence of cerebral herniation rate and symptomatic oedema, other adverse events and vital signs.

Adverse events were classed as drug related, through investigator opinion in 128 patients – 100 observed in the alteplase group and 28 in the placebo group.

Serious adverse were reported in 204 patients (24.8%) of whom 66 were fatal (8% overall, 7.7% in the alteplase group and 8.4% in the placebo group. As shown in Table 14, adverse events occurred at a comparable rate within the two treatment groups.

Intracranial haemorrhage (ICH) (centrally adjudicated)

ICH was centrally assessed and adjudicated for each patient by an independent adjudication committee – the Safety and Outcome Adjudication Committee (SOAC). As expected with any thrombolytic treatment, significantly more patients who had been randomised to alteplase experienced intracranial haemorrhage [(133 patients, 27.03% vs. 71 patients (17.62%) (OR 1.73; CI95%1.24,2.42; p-0.0012). The majority of these occurred within 24hours following administration of treatment. All patients (3; 0.4%) experiencing fatal intracranial haemorrhage had been randomised to alteplase.

Symptomatic intracranial haemorrhage (sICH)

sICH was recorded in 11 patients (1.34%). A significantly higher proportion of patients within the alteplase group (10 patients, 2.39%) compared with the placebo group (1 patient, 0.25%; OR 9.85; 95%CI 1.26, 77.32; p=0.008).

Confounding baseline variables

In the post hoc ITT analysis, adjusted for confounding baseline variables (logistic regression), the following were identified as significant at P<0.10.

- Baseline NIHSS score,
- Assignment of study group,
- Smoking status,

- Presence of hypertension, and
- Time between stroke onset and treatment

The adjusted analysis indicated that administration of alteplase remained significantly associated with a score of 0-1 on the mRS (favourable outcome) (odds ratio, 1.42; 95% CI [1.02-1.98] P=0.04).

ECASS 3 significantly, reliably and appropriately demonstrates the likely efficacy of alteplase in both the improvement, and extension, of life in a context relevant to this decision problem.

Pre-specified subgroup analyses

The compiled datasets for the subgroups based on favourable outcome, sICH, and mortality are shown in Figures 3-5.

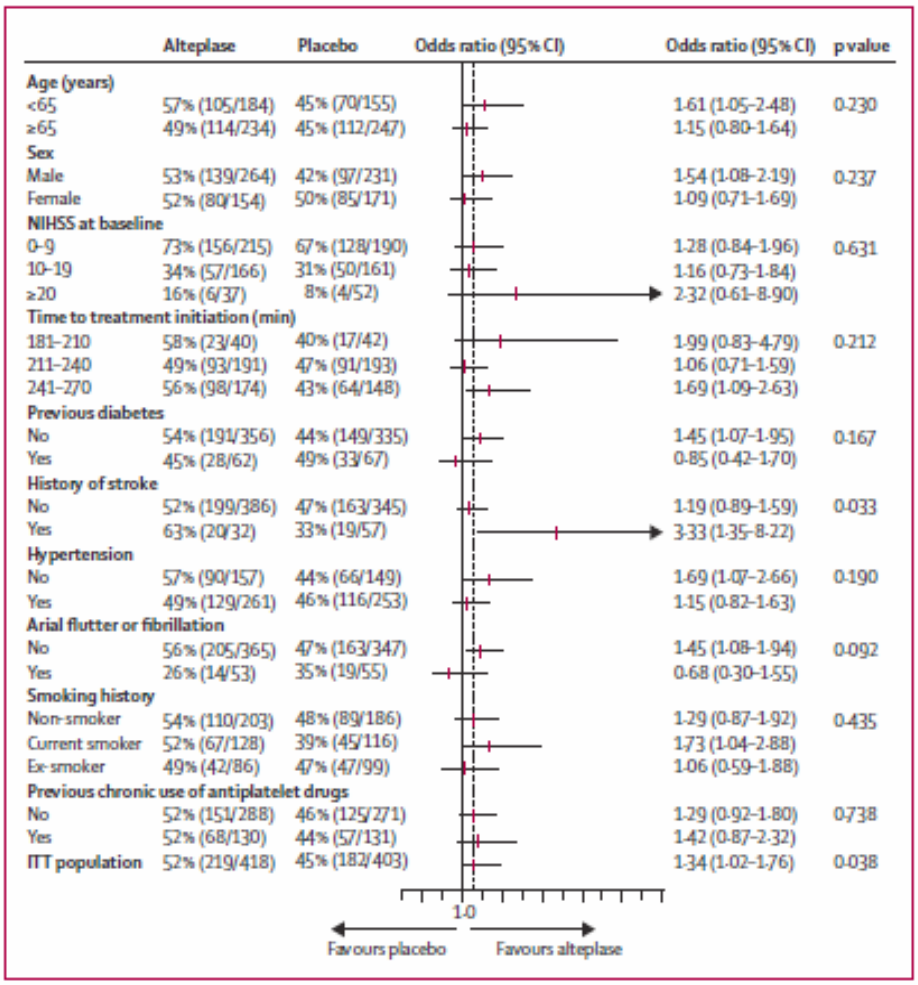


Figure 3: Subgroup analysis of favourable outcome (modified Rankin scale 0-1) at day 90 according to demographic characteristics, baseline clinical data and past medical history
Source: Bluhmki et al. 2009
Dashed vertical line represents the odds ratio for the whole Intention-to-treat (ITT) population. Data are % (n/N) unless otherwise indicated. Pvalues are for interaction based on logistic regression model with treatment, subgroup and interaction term. NIHSS = National Institutes of Health Stroke scale.

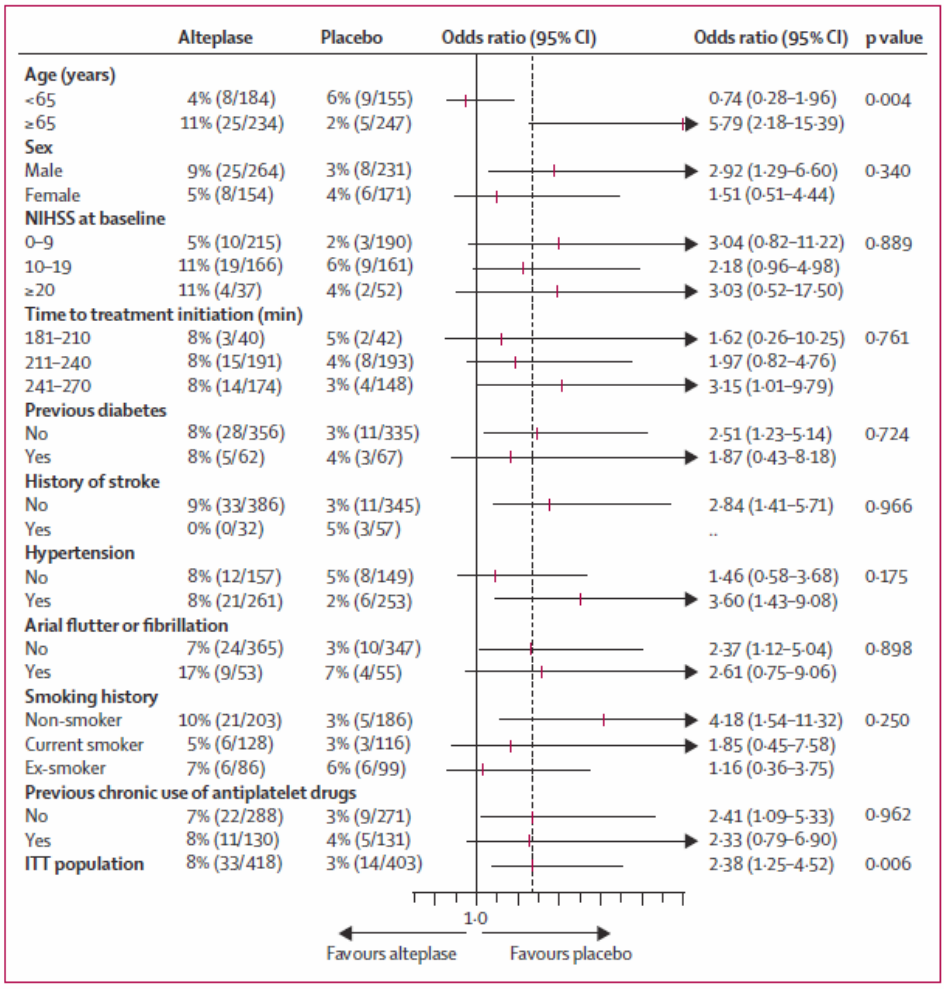


Figure 4: Subgroup analysis of Symptomatic Intracranial haemorrhage according to demographic characteristics, baseline clinical data and past medical history.
Source: Bluhmki et al. 2009
Dashed vertical line represents the odds ratio for the whole Intention-to-treat (ITT) population. Data are % (n/N) unless otherwise indicated. Pvalues are for interaction

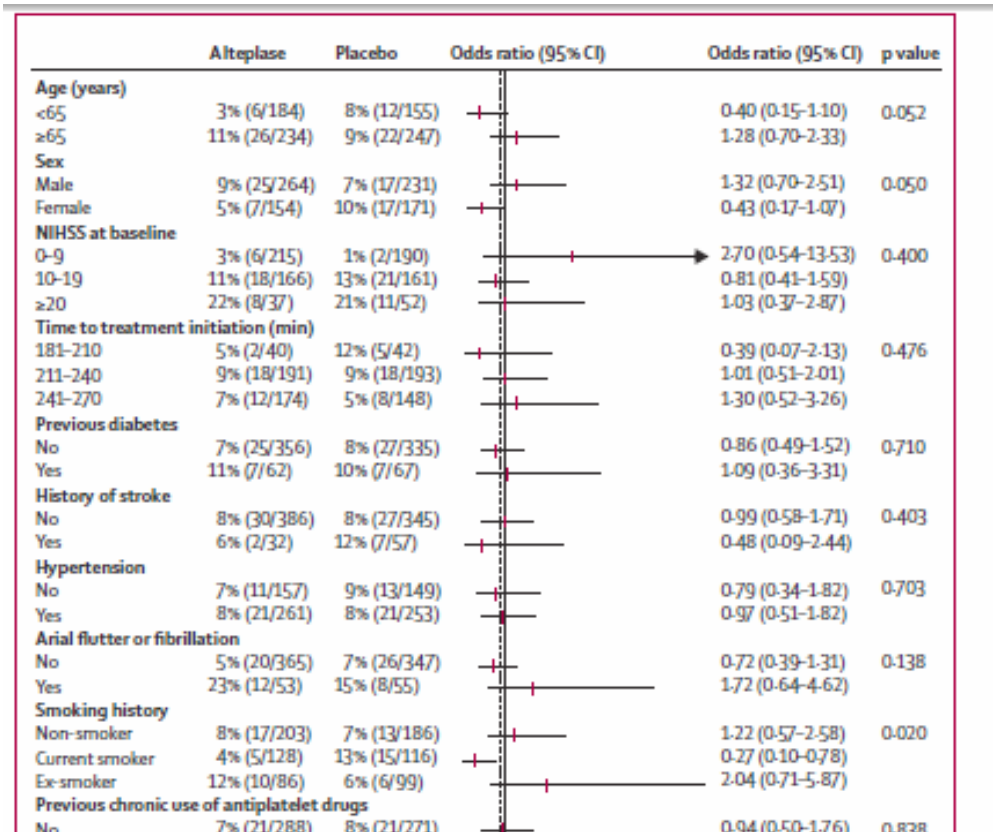


Figure 5: Subgroup analysis of mortality according to demographic characteristics, baseline clinical data and past medical history.
Source: Bluhmki et al. 2009
Dashed vertical line represents the odds ratio for the whole Intention-to-treat (ITT) population. Data are % (n/N) unless otherwise indicated. Pvalues are for interaction based on logistic regression model with treatment, subgroup and interaction term.

It should be emphasised that, for any of the above subgroup analyses, the results should be treated with caution. As the study was not powered to detect significance between such groups, the study will not provide confident results and could be "regarded as mainly hypothesis generating" (Bluhmki et al. 2009).

5.5.2. Graphical representation of results

Not considered appropriate

5.6. Meta-analysis

Meta-analyses carried out relevant to this appraisal were as follows to support the base case assessment of clinical and cost effectiveness:

- ECASS II (0-3 hrs) and NINDs – 0 to 3 hour window – repeat of that carried out for TA122 – shown in Appendix 15
- ECASS III, ECASS II (0-3 hrs) and NINDs – 0 to 4.5 hour window of use – shown in Appendix 15

Meta-analyses carried out relevant to this appraisal were as follows to support the sensitivity analyses to support the assessment of clinical and cost effectiveness:

- ECASS II (0-3 hrs) and NINDs and ATLANTIS A and B (0-3hrs) – 0 to 3 hour window – repeat of that carried out for TA122 – shown in Appendix 15
- ECASS III, ECASS II (3-4.5 hr), ATLANTIS A and B (3-4.5hrs) – 3 to 4.5 hour window of use – shown in Appendix 15
- ECASS III, ECASS II (3-4.5 hrs) and NINDs and ATLANTIS A and B (3-4.5 hrs) – 0 to 4.5 hour window of use – shown in Appendix 15
- ECASS III, ECASS II (0-3 hr), ECASS II (3-4.5 hr) and NINDs and ATLANTIS A and B (0-3 hr), ATLANTIS A and B (3-4.5hrs) – 0 to 4.5 hour window of use – shown in Appendix 15

These meta-analyses were carried out primarily to support the cost effectiveness analysis and the rationale for the outcomes analysed is outlined in the cost effectiveness section 6.3.1.1. These outcomes were:

- Relative risk of dependency or death
- Relative risk of death
- Rate of symptomatic intracranial haemorrhage.

Metaanalysis was carried using both a fixed and random effects model

5.7. Indirect and mixed treatment comparisons

No indirect and mixed treatment comparisons were carried out since none relevant to this appraisal

5.8. Non-RCT evidence

Although, no non-RCT evidence is considered directly relevant to this submission, for reasons outlined in Section 5.2.1. to provide some context to the results it is noted that the Safe Implementation of Treatment in Stroke-International Stroke Thrombolysis Registry (SITS-ISTR) observational study has reported the efficacy and safety of the extension of the time window for intravenous alteplase treatment from within 3 h to within 4·5 h after stroke onset (Ahmed et al 2010).

- This study had no placebo or “no treatment” arm and so contained no comparison of direct relevance to the decision problem.

The study aimed to assess the implementation of the wider time window, its effect on the admission-to-treatment time, and safety and functional outcome in patients recorded in SITS-ISTR. Patients treated according to the criteria of the European Summary of Product Characteristics, except for the time window, were included. Patients were grouped according to whether they were registered into SITS-ISTR before or after October, 2008.

The study measured admission-to-treatment time and rates of symptomatic intracerebral haemorrhage, mortality, and functional independence at 3 months.

23 942 patients were included in SITS-ISTR between December, 2002, and February, 2010, of whom 2376 were treated 3–4·5 h after symptom onset.

The proportion of patients treated within 3–4·5 h by the end of 2009 was three

times higher than in the first three quarters of 2008 (282 of 1293 [22%] *vs* 67 of 1023 [7%]). The median admission-to treatment time was 65 min both for patients registered before and after October, 2008 (p=0·94).

The key results of this study were:

- 10 531 (57%) of 18 317 patients treated within 3 h of stroke and 1075 (60%) of 1784 who were treated within 3–4·5 h were functionally independent at 3 months (adjusted OR 0·84,95% CI 0·75–0·95; p=0·005).

- 2287 (12%) of 18 583 patients who were treated within 3 h and 218 (12%) of 1817 who were treated within 3–4·5 h had died by the 3-month followup (adjusted OR 1·26, 95% CI 1·07–1·49; p=0·005)

- 352 (2%) of 21 204 patients treated within 3 h and 52 (2%) of 2317 treated within 3–4·5 h of stroke had symptomatic intracerebral haemorrhage at 3 months (adjusted odds ratio [OR] 1·44, 95% CI 1·05–1·97; p=0·02).

The conclusion of the authors (Ahmed et al 2010) were as follows:

- Since October, 2008, thrombolysis within 3–4·5 h after stroke has been implemented rapidly, with a simultaneous increase in the number of patients treated within 3 h; admission-to-treatment time has not increased.

- Safety and functional outcomes are less favourable after 3 h, but the wider time window now offers an opportunity for treatment of those patients who cannot be treated earlier. Thrombolysis should be initiated within 4·5 h after onset of ischaemic stroke, although every effort should be made to treat patients as early as possible after symptom onset.

5.9. Adverse events

5.9.1. Relevant trials to assess safety outcomes

ECASS III was designed to assess both the efficacy and safety of alteplase. Safety was assessed through the incidence of mortality and symptomatic intracranial haemorrhage. Please refer to section 5.1 to 5.5 for details of the trial.

5.9.2. Adverse Event Results

Table 16: Prespecified safety End Points and Other Serious Adverse Events

Adverse Events	Alteplase Group		Placebo Group		Odds ratio (95% CI)			Risk Difference
	N= 418		N= 403					
	#	%	#	%	OR	LB CI	UB CI	
Prespecified safety end points								
Any ICH	113.0	27.0	71.0	17.6	1.73	1.24	2.42	0.0942
Symptomatic ICH								
According to ECASS III definition	10.0	2.4	1.0	0.2	9.85	1.26	77.32	0.0214
According to ECASS II definition	22.0	5.3	9.0	2.2	2.43	1.11	5.35	0.0303
Accordinding to SITS-MOST definition	8.0	1.9	1.0	0.2	7.84	0.98	63.00	0.0167
According to NINDS definition	33.0	7.9	14.0	3.5	2.38	1.25	4.52	0.0442
Fatal ICH	3.0	0.7	0.0	0.0	X	x	x	0.0072
Symptomatic edema	29.0	6.9	29.0	7.2	0.96	0.56	1.64	-0.0026
Death	32.0	7.7	34.0	8.4	0.90	0.54	1.49	-0.0078
Other serious adverse events								
Total	105.0	25.1	99.0	24.6	1.030109	0.7505	1.4139	0.0055
Infectious	16.0	3.8	23.0	5.7	0.657582	0.3422	1.2638	-0.0188
Neoplastic	4.0	1.0	3.0	0.7	1.288245	0.2865	5.7922	0.0021
Blood and lymphatic	0.0	0.0	2.0	0.5	x	x	x	-0.0050
Endocrine	0.0	0.0	1.0	0.2	x	x	x	-0.0025
Metabolic and nutritional	2.0	0.5	0.0	0.0	x	x	x	0.0048
Psychiatric	3.0	0.7	4.0	1.0	0.721084	0.1604	3.2423	-0.0027
Neurological	60.0	14.4	48.0	11.9	1.239525	0.8251	1.862	0.0244
Eye	1.0	0.2	0.0	0.0	x	x	x	0.0024
Cardiac	22.0	5.3	16.0	4.0	1.34375	0.6952	2.5975	0.0129
Vascular	10.0	2.4	10.0	2.5	0.963235	0.3966	2.3395	-0.0009
Respiratory	14.0	3.3	24.0	6.0	0.547236	0.2789	1.0735	-0.0261
Gastrointestinal	5.0	1.2	8.0	2.0	0.59776	0.1939	1.8429	-0.0079
Hepatobiliary	3.0	0.7	3.0	0.7	0.963855	1.934	4.804	-0.0003
Skin	1.0	0.2	0.0	0.0	x	x	x	0.0024
Musculoskeletal	1.0	0.2	3.0	0.7	0.319744	0.0331	3.0864	-0.0051
Renal	4.0	1.0	2.0	0.5	1.937198	0.3528	10.6355	0.0046
Reproductive system	1.0	0.2	0.0	0.0	x	x	x	0.0024
Congenital	0.0	0.0	1.0	0.2	x	x	x	-0.0025
General	1.0	0.2	3.0	0.7	0.319744	0.0331	3.0864	-0.0051
Associated with injury	4.0	1.2	5.0	1.2	0.769082	0.205	2.8848	-0.0028
Surgical	1.0	0.2	0.0	0.0	x	X	x	0.0024

N.B. “x” indicates the inability to perform the required calculation due to either the numerator or denominator within the calculation taking the value of zero.

5.9.3. Overview of safety in relation to decision problem

ECASS III provides data to assess the safety of the administration of alteplase in the 3-4.5 hour window of use. The only significant difference in adverse events between the two treatment groups was the higher occurrence of intracranial haemorrhage recorded in the alteplase arm. This is a known event associated with any thrombolytic treatment with the benefit-risk ratio being carefully weighed.

The model accounts for this adverse event implicitly with the cost of the additional CT scan to confirm diagnosis included and the utility effects and costs impact of such an event factored into the values for the independent and dependent health state valuations.

5.10. Interpretation of clinical evidence

5.10.1. Principal findings from ECASS III highlighting the clinical benefit and harms

ECASS III shows that alteplase used within 3-4.5 hours after acute ischaemic stroke significantly reduces, compared to placebo, unfavourable outcomes for stroke as defined by the modified Rankin scale. An unfavourable outcome is defined as slight disability or worse (mRS>1), or death (mRS=6).

- Alteplase demonstrated efficacy in improving favourable outcomes at 90 days with relative risk of 1.16 (95% CI [1.01 to 1.34]; P=0.04) and odds ratio of 1.34 (95% CI 10.2 to 1.76). 52.4% (n=219) experienced a favourable outcome 90 days after AIS compared to 45.2 %(182 of 403) in the placebo group.

- In comparison, the results for favourable outcomes, using the same criteria as ECASS III, from the two studies identified by the ERG in TA122 as being most appropriate to assess efficacy in the 0-3 hour window of use group showed the following results:

    - NINDS (n=624) Adjusted OR (95% CI) for a favourable 3-month outcome associate with alteplase was 2.11 (1.33, 3.35) in the 0-90 minute stratum and 1.69 (1.09, 2.62) in the 91-180 minute stratum.

- ECASS II (n=158). In the stratified analysis of the primary and secondary end-points (0-3 and 3-6 hours OTT) there were no significant differences between alteplase and placebo. However, the numbers of patients treated within 3 hours were small, alteplase 81 and placebo 77.

- The pooled analysis presented in the cost effectiveness Section 6.3.1.1. (Table 24) using a different dichotomisation based on mRS. This was one deemed most appropriate to populate values in the HE (see Section 6.2.3. for rationale). It shows a RR of death or dependency (defined as mRS scores of 3-6) for ECASS II and NINDS pooled of 0.81 (CI: 0.72-0.92) compared to one for ECASS III of 0.87 (CI: 0.72-1.04)

- The authors of the report of the observational study, SITS-ISTR, as outlined in Section 5.9 noted that safety and functional outcomes are less favourable after 3 h, but the wider time window to 4.5 hours offers an opportunity for treatment of those patients who cannot be treated earlier.

- In ECASS III, mortality between treatment groups was not statistically significant. 66 patients died 32 of which were in the alteplase group (7.7% of the 418 participants) and 34 of the 403 in the placebo group (8.4%).

- As expected with any thrombolytic drug, there was a greater incidence of symptomatic intracranial haemorrhage in the alteplase group with 10 of the 418 patients (2.4%) experiencing such an event. This was significantly higher than the incidence of sICH in the placebo group (1 of the 403 patients [0.3%]). It was seen that the incidence of intracranial haemorrhage was no higher when administering alteplase in the extended window, when comparing the more restricted administration time frame, already being used and recommended by NICE within the NHS, of 0-3 hours (Bluhmki et al 2009).

- The incidence of all other adverse events between the placebo and alteplase treatment arms were not statistically significantly different (Hacke et al. 2008).

5.10.2. Summary of the strengths and limitations of the clinical-evidence base of the intervention.

ECASS III was an internally and externally valid RCT showing the efficacy of alteplase in improving the 90-day outcome of stroke patients. The patient cohort has similar patient baseline characteristics to the UK demographic.

Though the trial is generally robust there are a few areas of weakness. As detailed in **Appendix 2 Section 9.2.6**., the double-blinding aspect of a clinical trial for a drug such as alteplase is particularly challenging for the following two reasons:

1. The biological which alteplase (or any thrombolytic therapy) has may be apparent.

2. When shaken with a saline solution or water, alteplase will froth. The placebo solution did not produce this reaction.

The trial was also multinational and therefore, although as just mentioned, the baseline characteristics of the cohort were similar to that of the UK demographic, the majority, with only 22 being recruited from the UK, were foreign.

There is also the issue that the trial ran for 90 days, the point at which the final patient data was recorded. The relative risks between treatment with alteplase and that of no treatment has therefore been applied at a constant rate until 12 months after treatment administration.

5.10.3. Brief statement of the relevance of the evidence base to the decision problem.

ECASS III provides information on the ratio of favourable or unfavourable outcomes (a composite of disablement and death) between the different treatments, alteplase and placebo. This is, in essence, what the decision problem captures and hence the trial allows the examination of pertinent data.

5.10.4. Factors that may influence the external validity of ECASS III to patients in routine clinical practice;

The administration of alteplase in the ECASS III trial was undertaken as per the licensing and the SPC. See section 5.3.3. for further detail. This would therefore reflect it's proposed use in UK clinical practice.

6. Cost effectiveness

6.1. Published cost-effectiveness evaluations

6.1.1. Identification of relevant previous health economic studies

A systematic literature review was carried out to identify relevant previous studies. This is outlined in **Appendix 10** which includes the QUORUM flow chart of the search carried out and the process used for the identification of studies (9.10.7.) which identified no relevant previous economic studies of relevance to this submission.

No evidence was identified to suggest any refinement of or improvements on the HE model previous used in the submission by Boehringer Ingelheim for TA122 which was based upon work by Sandercock et al 2002.

The following points are noted as a summary of the other main studies looked at::

- Following FDA approval of alteplase for the treatment of acute ischemic stroke, the study of Fagan et al (Fagan et al 1998) was the first sourced economic evaluation. The model principles outlined in that study were referenced to some extent in all subsequent studies. Several studies were local adaptations of the Fagan et al study as outlined in **Appendix 10.**

- Those studies that adopted a differing approach, (to some extent), simplified the outcome health states to independent, dependent and dead, rather than the 6 states defined by the modified Rankin Score disability grading. The main studies of note that used this approach (Sandercock et al 2002 and Chambers et al 2002) were of greater relevance as they were from a UK perspective.

- In TA122 (alteplase for acute stroke), the study of Sandercock et al better reflected the decision problem and therefore could be adapted for the purposes of this appraisal, as evidenced by TA122.

- One further point of significance is that the majority of studies found that a thrombolytic strategy using alteplase dominated the standard care comparator.

In addition, the literature search identified the published documents from the NICE appraisal, TA122- Alteplase for the Treatment of Acute Ischemic Stroke. The following points of note from the health economic approaches taken to support that assessment are as follows:

- Alteplase previously underwent appraisal by NICE for the treatment of acute ischemic stroke in the 0-3 hour window.

- The cost-effectiveness model developed for this model was adapted for Sandercock et al 2002.

- Data from the Lothian Stroke Register was used to determine the outcomes for patients on standard care and efficacy data from a meta-analysis was used to adjust the outcome distribution using odds ratios for patients eligible for alteplase treatment.

- The model considered outcomes at 6 and 12 months after the index stroke followed by a lifetime Markov model.

- Post-stroke health states in the model followed those assigned by Sandercock et al 2002.

- The model was deemed generally appropriate by the appraisal committee and the evidence review group and it was concluded in the base-case analysis that alteplase dominated standard care over the life time horizon.

6.1.2. Brief Overview of previous relevant HE studies

No relevant studies were identified although those of potential relevance which were rejected are outlined in Section 9 together with a brief commentary on each of the short listed HE studies from the literature search.

6.1.3. Quality assessment for each cost-effectiveness study identified.

Complete quality assessments of the shortlisted studies using the Drummond and Jefferson checklist are available in **Appendix 9**

6.2. De Novo Analysis

6.2.1. Patient groups included in the health economic analysis.

The model has the potential to reflect the use of alteplase across it's full licence. The model has been used to estimate ICERs for 0-4.5 hour window of use for alteplase and the subgroups 0-3 hrs and 3-4.5 hr 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 model was populated with patients likely to receive alteplase for AIS (based on SITS-MOST [Wahlgren et.al. 2007], 39.8% female, aged 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 clinical practice.

In addition, the proportion of independent and dependent post-stroke health states and death at 6 months amongst this patient group, in the absence of alteplase treatment, was populated in the model with data representative of the population of England and Wales, as were transition probabilities between health states from 6 to 12 months (Wardlaw et al. 1998).

6.2.2. Diagrammatical representation of the health economic model

A Markov Model (schematic shown in Figure 4) was constructed to perform the economic evaluation. The analytic technique used was a cost utility analysis using probabilistic sensitivity analysis.

The economic model is an extension of the economic model constructed and published as part of the Health Technology Appraisal (HTA) of thombolytic

therapy by Sandercock et al., (2002). The model has been replicated using the same structure and inputs described in the text of the published appraisal, with parameters updated with up-to-date data on costs and effects where possible. In particular the economic evaluation extends the Sandercock (2002) analysis further by:

- Incorporating the relative risk for the 3-4.5 hour treatment window sub-group as reported in ECASS III. Use of the relative risk for this treatment window enables the effectiveness estimate to reflect the anticipated extended product licence.

The model is split into 3 stages:

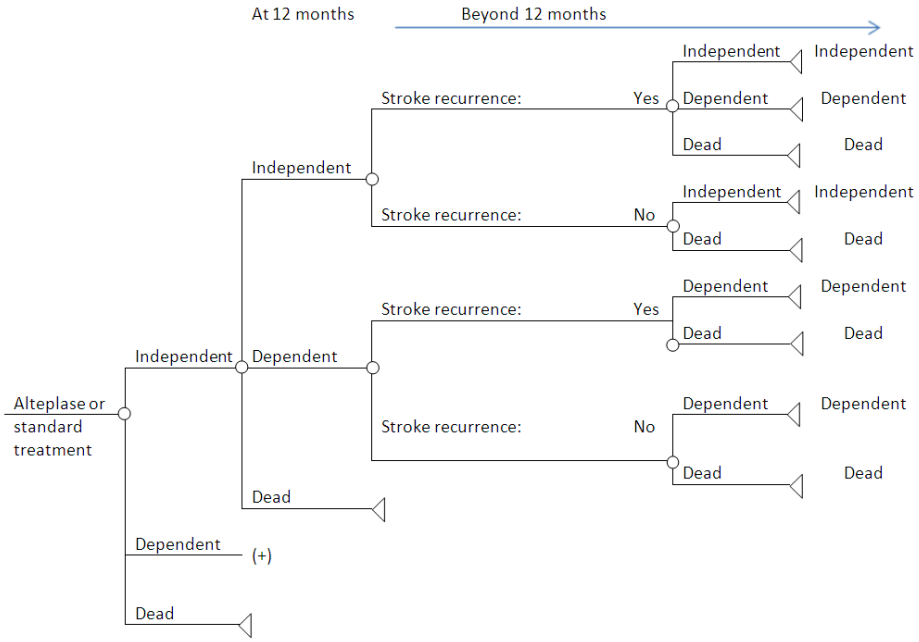
- Patients enter phase one with AIS with confirmed eligibility for alteplase treatment.
- They leave after 6 months and continue to phase 2 which spans the 6-12 month period.
- The third phase continues for all further 12 month cycles.

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 was 6 and 12 months after a stroke. This data provided information on the proportion of independent and dependent post-stroke health states and death at 6 months, in the absence of alteplase treatment, and transition probabilities between health states from 6 to 12 months (Wardlaw et al. 1998).

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 live patients who did not experience a recurrent stroke either stayed in the same health state or died.

Figure 6: Model schematic



6.2.3 Justification of model structure in terms of clinical pathway

The model illustrates the treatment pathways which patients can take. Patients enter the model at the point of treatment where they either receive alteplase or standard care. Depending on the outcome of treatment at 6months, patients experience one of three outcomes:

- Independent (mRS<3)
- Dependent (mRS>2)
- Dead

The definition of health states used is the same as that used by Sandercock et al (2002) and formed the basis of the HE model submitted as part of TA122 and for which reliable utility and resource use estimations exist. As the primary endpoint of surviving ECASS 3 patients was a dichotomised mRS based upon a 'favourable' (mRS<2) or 'unfavourable' (mRS>1) outcome (which included death), rather than the 'independent' (mRS<3) and

'dependent or dead' (mRS>2) dichotomisation of previous economic evaluations relative risks were recalculated based on the preferred dichotomisation of previous evaluations All analysis was intention to treat in nature.

A systematic review as detailed in section 6.1 (and **Appendix 10**), revealed the model published by Sandercock et al. (2002) to be the most robust. It was concluded that is was the most thorough examination of this decision problem within the UK setting. Therefore this structure has been used over and above the others within published literature. The NICE TA122 (alteplase administered between 0-3 hours of symptom onset) also used this model, for which, within the FAD it states: "*The Committee discussed the manufacturer's economic model. It considered the model structure and the lifetime timeframe to be appropriate".*

Chambers et al. (2002), Sinclair et al. (2001), and Fagan et al. (1998), disaggregated deaths associated with symptomatic intracranial haemorrhage (sICH). The main adverse event associated with alteplase over placebo is SICH. The cost and utility associated with SICH and further vascular events are captured in the Sandercock et al. (2002) study by the proportion of patients who enter the dead, dependent and independent health states. The rate of sICH is, in addition, a separate parameter in the model to assign additional resource use to this event (an additional CT scan).

6.2.4. Definition of what is captured by model health states

The three health states capture the costs and utilities associated with living with stroke independently or dependently or being dead. They were defined based upon the modified Rankin Scale (mRS). Surviving mRS scored of <3 was classified as 'Independent' and a mRS score of 3-5 was classified as 'Dependent'. Those who did not survive were absorbed into the 'Dead' state.

6.2.5. Main aspects of the condition captured by the model

The model structure reflects the population, intervention and comparators outlined in the decision problem. The structure captures the following outcomes outlined in the decision problem and the final scope:

- Disability and neurological deficit (defined as independent life years gained)
- Proportion of patients making good functional (defined as independent life years gained) recovery 6 months after treatment
- Survival

The model reflects the stability of disablement in the beyond 12 months timeframe allows for the possibility of stroke recurrence and accounts for the increase in mortality rates for those who experience a recurrent stroke.

The model captures the resource use and costs associated with these differing health states.

6.2.6. Additional Key Features of the Model

Table 17 Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	Full life time of the model (until each patient was in the 'dead' state).	As per the NICE reference case – the appropriate time horizon for the comparison of treatments should be adequate to cover the period of time in which costs or effects from the treatment will differ. For a treatment affecting the chronic disability associated with stroke a life-time time horizon is appropriate.	NICE, Updated guide to the methods of technology appraisal (2008)
Cycle length	6 months for year 1. Yearly for the subsequent years continuing until entire cohort has entered the 'dead' state.	The initial cycle length of 6 months was chosen to utilise the data from the LSR which was recorded at 6months and 12 months for the cohort.	Wardlaw et al. (1998)
Half-cycle correction	Yes	As per the NICE reference case.	NICE, Updated guide to the methods of technology appraisal (2008)
Were health effects measured in QALYs; if not, what was used?	QALYs were used to measure health effects.	As per the NICE reference case.	NICE, Updated guide to the methods of technology appraisal (2008)
Discount of 3.5% for utilities and costs	3.5% common discounting	As per the NICE reference case.	NICE, Updated guide to the methods of technology appraisal (2008)
Perspective (NHS/PSS)	NHS and PSS. Includes all direct costs to the above parties.	As per the NICE reference case.	NICE, Updated guide to the methods of technology appraisal (2008)
NHS, National Health Service; PSS, Personal Social Services; QALYs, quality-adjusted life years			

6.2.7. Analysis in relation to market authorisation.

The economic evaluation assumes that alteplase is used inline with its extended licensed indication. See draft SPC (**Appendix 1**)

6.2.8. Model in relation to clinical continuation rule.

Not applicable – alteplase is administered over a short period (1 hour) which gives no opportunity or advantage in applying clinical continuation rules.

6.3. Clinical Parameters and Values

6.3.1. Implementation of clinical data in model

The implementation of clinical data within the model was done differently for the three phases of the model as described in Section 6.2.2. The approach used is described separately for each phase.

6.3.1.1. Implementation of clinical data in Phase I (0-6 months)

As outlined in Section 5.2.1., the following studies were identified as 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 hour window of use.

The above studies were used to generate efficacy parameter values for inclusion in the baseline cost effectiveness analyses.

In addition, the inclusion of 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. Both these studies, 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 hr window of use data set from ECASS II (n=265) which was included in the sensitivity analysis.

51% 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 7.1. 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 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) 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 score of 3-5 and this definition was used as the basis of the relative risk calculations. The data used to generate these estimates is included in **Appendix 15** which includes unpublished data from ECASS III and data included in the Cochrane review by Wardlaw et al (2006) (for ECASS II (0-3 hours), ATLANTIS A and B (0-3 hours) NINDs) and

unpublished ad hoc subgroup analysis ECASS II (3-4.5 hours) and ATLANTIS (3-4.5 hours). The relevant pooled analyses as outlined earlier in this section used to generate these relative risk parameters are also included in **Appendix 15**. In all pooled analyses, a random effects model assumption is used for these parameters in the submission cost effectiveness analyses.

The relative risks used in the base case model are outlined in Tables 18 and 19 below.

Table 18: Relative risks of death used in cost effectiveness analyses (metaanalysis uses random effects model)

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	Metaanalysis	ECASS II (0-3) + NINDs	1.05	0.55	2.03
0-3 hours	sensitivity analysis	Metaanalysis	ECASS II (0-3) + NINDs + ATLANTIS A & B (0-3)	1.15	0.62	2.16
3-4.5 hours	base case	Single study data analysis	ECASS III	0.82	0.5	1.33
3-4.5 hours	sensitivity analysis	Metaanalysis	ECASS III + ECASS II (3-4.5) + ATLANTIS (3-4.5)	0.85	0.43	1.67
0-4.5 hours	base case	Metaanalysis	ECASS II (0-3) + NINDs + ECASS III	0.89	0.67	1.18
0-4.5 hours	sensitivity analysis	Metaanalysis	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		
0-4.5 hours	sensitivity analysis	Metaanalysis	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 19: Relative risks of death or dependency used in cost effectiveness analyses (metaanalysis uses random effects model)

Relevant Time Window	Analysis used in	Method to generate parameter value	Studies used	Mean estimate	Lower CI	Upper CI
0-3 hours	base case	Metaanalysis	ECASS II (0-3) + NINDs	0.81	0.72	0.92
0-3 hours	sensitivity analysis	Metaanalysis	ECASS II (0-3) + NINDs + ATLANTIS A & B (0-3)	0.82	0.72	0.93
3-4.5 hours	base case	Single study data analysis	ECASS III	0.87	0.72	1.04
3-4.5 hours	sensitivity analysis	Metaanalysis	ECASS III + ECASS II (3-4.5) + ATLANTIS (3-4.5)	0.87	0.74	1.04
0-4.5 hours	base case	Metaanalysis	ECASS II (0-3) + NINDs + ECASS III	0.83	0.75	0.92
0-4.5 hours	sensitivity analysis	Metaanalysis	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		
0-4.5 hours	sensitivity analysis	Metaanalysis	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

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 (see **Appendix 16** for the details of this literature review). The study used to populate this parameter value was the Lothian Stroke Register (LSR) (Wardlaw et al. 1998) – 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. Parameter values used in the model are shown in the Table 20 below:

Table 20: 6 month health state distributions for no treatment arm

	Independent	Dependent	Dead
No Treatment	0.3953	0.3256	0.2791

The RRs of death and of dependency from ECASS III were used to modify the 6 month baseline distribution for those receiving alteplase, rather than the odds ratio (OR) as featured in Sandercock et al. 2002. This decision was made on the basis of comments from the ERG in NICE TA122 [Jones et al. 2007], which noted that the use of ORs in such a context is inappropriate since the events are insufficiently rare to justify the substitution of ORs for RRs.

Outcomes of those experiencing disability or death due to symptomatic intracranial haemorrhage (sICH) or AIS are conflated in the model as in the studies used to estimate death and dependency relative risks i.e. captured in the overall distribution of patients between the states independent, dependent, and dead, which in turn captures relevant utility valuations. Should a sICH occur an additional CT scan was attributed to the treatment process and hence the extra cost was included. 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 [Hacke et al. 2008] and was 0.25%. This study was

used to source this data because alternative sources for this parameter included in this submission(as shown in Table 21) were pooled analyses of studies from which the extraction of such a parameter value were more problematic. 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 21 (actual values used shown in **Appendix 15**).

Table 21: Relative Risk of symptomatic ICH

Relevant Time Window	Analysis used in	Method to generate parameter value	Studies used	Mean estimate	Lower CI	Upper CI
0-3 hours	base case	Metaanalysis	ECASS II + NINDs	3.94	0.61	25.47
0-3 hours	sensitivity analysis	Metaanalysis	ECASS II + NINDs + ATLANTIS A & B	4.24	1.52	11.83
3-4.5 hours	base case	Single study data analysis	ECASS III	12.0		
0-4.5 hours	base case	Metaanalysis	ECASS II + NINDs + ECASS III	4.18	1.39	12.63
0-4.5 hours	sensitivity analysis	Metaanalysis	ECASS II + NINDs + ATLANTIS A & B + ECASS III	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		

6.3.1.2. 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 Lothian Stroke Registry [Wardlaw et al. 1998] [Sandercock et al. 2002] (as

identified as most appropriate on systematic literature review – See **Appendix 16**). The parameter values used in the model are shown below in Table 22:

Table 22: Phase 2 (6 to 12 month) transition probabilities (extracted from LSR (Wardlaw et al. 1998) [Sandercock et al. 2002])			
	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

6.3.1.3. 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 patients could suffer a recurrent stroke or otherwise (likelihood taken from Sandercock et al. 2002 based upon LSR (Wardlaw et al. 1998) – identified on systematic literature review as the most appropriate source for this data – see **Appendix 16)**). The rate was assumed the same for both patients who had been treated with alteplase and those who had not which is supported by the following quote; “thrombolytic therapy does not seem to influence the risk of spontaneous stroke recurrence...” (Schmülling et al. 2000) after their study revealed similar stroke recurrence in these patient cohorts. The likelihood of a fatal event given a recurrent stroke was taken from the LSR (Wardlaw et al. 1998).The parameter values used in the model to estimate the annual transition probability of experiencing a recurrent stroke and having done so of dieing are shown in the Table 23 below:

Table 23: Annual risk of stroke recurrence and the associated risk of mortality		
Annual risk of stroke recurrence at 1 year	0.05	Wardlaw et al. (1998)
Annual stroke mortality among patients with recurrent stroke	0.25	Wardlaw et al. (1998)

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 were in a dependent state at 12 months and beyond were assumed to be unable to move to an independent state. Those who were in an independent state at 12 months and beyond were unable to move to a dependent state unless they survived a recurrent stroke in which case they had an equal likelihood of entering each of the living health states (ie. A 50:50 split of these patients to independent and dependent health states). The systematic literature review outlined in **Appendix 16** identified no source data for these parameter values. These assumptions were also made in the NICE STA for alteplase (0-3hours), Sandercock et al (2002) and Fagan et al. 1998).

Patients in Phase III in addition who did not transition into the recurrent stroke state had a transition probability of moving into the death state. This transition probability was based upon an age and history of stroke adjusted mortality rate (constructed using 2007-2009 ONS life tables [ONS 2009] for England and Wales) gender weighted according to the population of the SITS-MOST study [Wahlgren et al. 2007] and 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 [Hardie et al. 2003] (for details of relevant literature review see Appendix 16). Alternatively they could remain in the same health state.

6.3.2 Calculation of transition probabilities

The relative risks of death and of death dependency from ECASS 3 were used to modify the 6 month baseline distribution of those not receiving thrombolytic treatment to reflect the treatment effect of alteplase.

% Dead at 6 months given Alteplase = % Dead at 6 months given ST * RR_{DEATH}

% Dependent at 6 months given Alteplase = (% Dependent or Dead at 6 months given ST *$RR_{DEPENDENT\ OR\ DEAD}$) - % Dead at 6 months given Alteplase

% Independent at 6 months given Alteplase = 1 – (% Dead or Dependent at 6 months given Alteplase)

Relative Risks (RR), rather than the Odds Ratios (OR) featured in Sandercock et al.,were used. This modification was made on the basis of comments made by the ERG in NICE TA122 [Jones et al. 2007] (the initial alteplase AIS appraisal) in which it was noted that the use of ORs in an appraisal such as this was inappropriate (as the events concerned in this circumstance are not sufficiently rare to justify the substitution of ORs for RRs). Relative risk of death or dependency was used in this submission to allow more direct comparison to TA122 which were in the re-analysis of the data for model requested by the ERG to provide valuation for this parameter (together with RR_{DEAD}).

6.3.3. Variation of Transition Probabilities with Time

The assumptions about the transition probabilities varying with time in the model are outlined in Section 6.3.1. Additional evidence to support the assumptions about transition probabilities over time are outlined below:

- It was assumed that the alteplase treatment effect was complete at 90 days and maintained at 6 months (rendering all transition probabilities post phase 1 equal in both the alteplase and standard treatment arms). This assumption is based upon follow-ups to the NINDS [Kwaitkowski et al. 1999] and Cologne trials [Schmülling et al. 2000] (studies of alteplase with a 0-3 OTT window). The 12 month results and the comparisons which the author made for the NINDS study are detailed below.

Table 24: Outcomes six months and one year after the onset of stroke
Source: Kwaitkowski (1999)

Time Point and Assessment Instrument	Percentage of Patients with Favorable Outcomes*		Odds Ratio (95% CI)†	Relative Risk (95% CI)†	P Value
	t-PA (N=312)	Placebo (N=312)			
6 Months after stroke					
Global test‡	—	—	1.7 (1.3–2.3)	—	<0.001
Barthel index	50	37	1.7 (1.2–2.4)	1.4 (1.1–1.6)	0.001
Modified Rankin scale	41	29	1.8 (1.3–2.5)	1.4 (1.2–1.8)	0.001
Glasgow Outcome Scale	43	31	1.6 (1.2–2.3)	1.4 (1.1–1.7)	0.004
12 Months after stroke					
Global test‡	—	—	1.7 (1.2–2.3)	—	0.001
Barthel index	50	38	1.6 (1.1–2.1)	1.3 (1.1–1.5)	0.005
Modified Rankin scale	41	28	1.8 (1.3–2.5)	1.5 (1.2–1.8)	0.001
Glasgow Outcome Scale	43	32	1.6 (1.1–2.2)	1.3 (1.1–1.6)	0.006

*Scores of 95 or 100 on the Barthel index, 0 or 1 on the modified Rankin scale, and 1 on the Glasgow Outcome Scale were considered to indicate a favorable outcome.

†The Mantel–Haenszel test was used for univariate analyses, with groups stratified according to clinical center and the time to treatment (0 to 90 minutes and 91 to 180 minutes). For the global tests (which used logit-link function), the same stratifying variables were included as covariates. CI denotes confidence interval.

‡There is no published method by which to compute relative risk.

The data in Table 24 shows 6 and 12 month outcomes. 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 Barthel Index, suggesting fair stability within outcomes over a 12 month period. 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. As already discussed in Section 6.3.1, complete stability is reached with disability status at the 12month post-stroke point, where patients cannot change in non-morbidity disability status (independent and dependent) unless a subsequent stroke is experienced.

6.3.4 Linkage of intermediate outcomes to final outcomes

As described in Sections 6.3.1-6.3.3 outcomes at 6 months were linked through assumptions about movement between health states and

parameter values for transition probabilities to life time outcomes.

6.3.5 Clinical Assessment of parameter values

This not considered a necessary part of the model development

6.3.6. All variables included in the cost-effectiveness analysis,

Table 25 Summary of variables applied in the economic model

Variable	Value	CI (distribution)	Reference to section in submission
Patient Starting Age	68 Years	59 to 75 (normal)	6.2.1.
Proportion of female patients	39.8%	Fixed value	6.2.1.
Efficacy of Alteplase			
Relative Risk- Death	0.818	0.504 – 1.328 (lognormal)	6.3.1.1.
Relative Risk- Dependency ar dependency	0.87	0.72-1.04 (lognormal)	6.3.1.1.
Risk of sICH			
Alteplase	2.39%	1.15%-4.36% (beta)	6.3.1.1.
Standard Treatment	0.25%	0.01-1.37% (beta)	6.3.1.1.
Survival Post Year 1			
Mortality multiplier for stroke patients	2.5	Point estimate only	6.3.1.3
Annual stroke risk post Year 1	0.05	Point estimate only	6.3.1.3.
Mortality risk following recurrent stroke	0.25	Point estimate only	6.3.1.3.
CI, confidence interval			

6.3.7. Extrapolation of costs and outcomes in the model

No extrapolation approaches have been employed.

6.3.8. List of all assumptions in the de novo economic model.

All assumptions in the model together with relevant justifications are outlined in Section 6.3.1.

6.4. Measurement and valuation of health effects

6.4.1. Aspects of the condition that most affect patients' quality of life.

Patients who experience stroke are subject to a greater fall in their quality of life the more disablement they incur as a consequent. Hence, those who are dependent post-stroke have a lower HRQoL than those who are independent (inherently linked to the mRS score).

6.4.2. Change in patient's HRQL over the course of the condition.

See section 6.3.3.

6.4.3. HRQL data collected in the clinical trials

Not applicable.

6.4.4. Mapping to generate HRQL data

Not applicable.

6.4.5. Systematic search of HRQL data

The systematic literature search identified no new data to populate the HE model utility values for dependent and independent stroke health states other than previously used in the model submitted as part of TA 122. These were from Dorman et al (2000) as outlined below. The search strategy including QUORUM flow chart is outlined in **Appendix 12** together with a description of

the studies scrutinised and considered not relevant. No other studies were found which provided utility valuations separately for independent and dependent stroke states.

6.4.5.1. Dorman et al. (2000)

The Dorman et al study was based in Scotland and reports values collected using the EQ-5D from a subsample (n=147) of the 1,131 patients included in the International Stroke Trial (IST) for three levels of stroke dependency (recovered, independent, and dependent). The preferences of the UK general public were used to convert these EQ-5D scores into QALY values. These utility values have also been used in NICE TA122, TA90 and Sandercock et al. 2002.

The paper aimed to establish whether the Lindley et al. (1994) modified questions, assessing disability and outcome after stroke for use in large scale trials, are accurate. The author aimed to examine the validity of these in the current IST. The modified dependency question was scrutinised to assess whether it was a valid method of measuring dependency and whether the combined use of the two questions is a valid technique to assess and categorise patients into one of the three outcome groups (dependent, independent with problems and recovered (independent without persisting problems) and whether these can be used to assess a the overall QoL.

The modified simple questions were assessed using 152 sequential patients from the Lothian Stroke Register. This was undertaken prospectively from the registry of inpatients and outpatients using those experiencing first and secondary stokes.

The utilities generated from the patients' categorical responses to the EQ-5D were converted using the preferences from the UK general public. These gave the following results:

Table 26: Health state utilities

	Mean score on EQ-5D for groups defined by their responses to modified simple questions (95% CI of the mean)		
LSR series (n=147)	**Dependent**	**Independent**	**Recovered**
EQ-5D utility	0.38 (0.29-0.47)	0.74 (0.69 -0.79)	0.88 (0.80-0.96)

Source: **Dorman et al. 2000**

The utility values associated with the health states as outlined above are not fitted perfectly to the model as they disaggregate the results for independent and recovered. Within the model, as the 'independent state' is a mRS score of <2 this would include the recovered and independent score. To ensure fairness and take a conservative view on the utilities it was decided to use the independent utility score rather than aggregating the recovered and independent scores.

It should be noted here that the Dorman et al (2000) study used the Barthel Index to classify disablement associated with stroke whereas the model assumes the use of mRS. It has been assumed that these would classify independent, dependent and recovered in an equivalent manner.

6.4.7. Key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

Not applicable.

6.4.8 Impact of adverse events upon HRQL

The conclusions drawn from the ECASS III trial data was that there were no significant difference in any other adverse events between treatment groups.

6.4.9. HRQL data used in the cost effectiveness model

Table 27: Summary of quality-of-life values for cost-effectiveness analysis

Health State	Utility value	Plausible range		Reference in submission	Justification
		Low	High		
Independent	0.74	0.69	0.79	Dorman et al 2000.	The single study which met the criteria of the literature search.
Dependent	0.38	0.29	0.47	Dorman et al 2000.	The single study which met the criteria of the literature search.
Dead	0	N/A	N/A	Assumption in EQ-5D valuation	The single study which met the criteria of the literature search.

6.4.10 Clinical Expert assessment of HRQL data

Not applicable.

6.4.11. Patient experience in the health states in terms of HRQL

Please see section 6.3.3.

6.4.12. Identified health effects excluded from the analysis

It is assumed that the estimation of HRQL in dependent and independent stroke patients resulting from the responses to the EQ-5D questionnaire amongst patients with stroke from the Dorman et al study (See Section 6.4.6. for fuller description) and which was used to estimate parameter values in the

model adequately captured all relevant health effects associated with these health states.

6.4.13. Baseline quality of life relative to health states

Not relevant to this model where HRQL was specified only for the three health states of dependent, independent and death

6.4.14. HRQL over time

In the model HRQL associated with the three health states was assumed to remain constant

6.4.15. Amendment of values in sections 6.4.3 to 6.4.8

Not applicable.

6.5. Resource identification, measurement and valuation

6.5.1. Reference costs and the payment by results (PbR) tariff associated with acute ischaemic stroke.

"The use of the drug alteplase for stroke (coding rules dictate that there will only be one reported use in a spell) will continue to receive a targeted adjustment when HRG AA22Z (non-transient stroke or cerebovascular accident, nervous systems infection or encephalopathy) is coded with unbundled HRGXD07Z (fibrinolytic drugs band 1) XD07Z is an unbundled HRG that contains OPCS-4 code X83.3 (fibronolytic drugs)", (DoH, 2011)

"Where patients are thrombolysed using alteplase in accordance with the NICE technology appraisal guidance (NICE TA122, 2007), they will continue to receive the targeted adjustment of £828 in addition to best practice payments. This adjustment covers the drugs themselves, and the additional cost of nurse input and the follow-on brain scan", (DoH, 2011).

Events included in the economic evaluation with PbR codes are:

- Ischaemic stroke (by mRs 0-2, 3-4, 5, 6)
    - AA04Z Intracranial Procedures Except Trauma with Non-Transient Stroke or Cerebrovascular Accident, Nervous system infections or Encephalopathy Category 4
    - AA10Z Intracranial Procedures Except Trauma with Non-Transient Stroke or Cerebrovascular Accident, Nervous system infections or Encephalopathy Category 3
    - AA16Z Intracranial Procedures Except Trauma with Non-Transient Stroke or Cerebrovascular Accident, Nervous system infections or Encephalopathy Category 1 or 2
    - AA22Z Non-Transient Stroke or Cerebrovascular Accident, Nervous system infections or Encephalopathy

Cost of post-event disability for IS/HS/ICH

The acute phase of rehabilitation is included under AA22Z (Non-Transient Stroke or Cerebrovascular Accident, Nervous system infections or

Encephalopathy). However, long-term stroke rehabilitation costs are not rebundled and no tariffs published. The PbR states that these are to be negotiated locally (code VC04Z)

6.5.2. Relevance of NHS reference costs or PbR tariffs to this appraisal

The NHS reference costs and PbR are not sufficient for the appraisal of alteplase as they do not provide a disaggregated differential cost for a dependent or independent outcome which is required for the analysis.

6.5.3. Systematic search of relevant resource data

Based on the clinical data and the structure of the model, costings for three health states were required – independent, dependent and dead, based on the stratified mRS scores. Should the patient experience sICH, the cost of an additional CT scan is required due to the need to confirm diagnosis.

The search strategy used to identify relevant resource data is outlined in **Appendix 13** which includes a description of the studies for which publications were scrutinised to determine relevance. The consequence of this search was to confirm that the most relevant source of data to cost the model health states is the same as used previously in the model submitted as part of TA122. This is the a study by Youman et al (2003).

The objective of Youman et al. (2003) was to assess the impact of stroke on the health care system in the UK. Stroke cost was stratified using the Barthel index. The study calculated the costs using 434 patients with a mean age of 76 and data from 2001/02. A clinical trial undertaken at a suburban acute care facility in the UK provided the per patient level data for the following:

- Demographic and risk factors for stroke on admission
- Total resource use for stroke over 1 year (divided into hospital and other health services, social services and information care resources)

- Setting to which the patient was discharged (home or an institution, or dead)
- Setting of the patient after 1 year of the stroke
- Stroke subtype and disability (Barthel Index),

Patients were recruited from a population based stroke register and enrolled on presentation which was no later than 72 hours after stroke-onset.

The costs were disaggregated into the following stroke severities: mild, moderate, severe and fatal stroke. The cost of stroke is recorded for a year with acute costs being included for the initial 3 months. A Markov model was then created and utilised to produce costs for a 5 year period following the initial event in 3 month cycles.

The search therefore excluded all of the publications, except one paper, Youman et al. (2003) from which to collect suitable cost data.

All direct costs to the NHS and PSS were considered.

Administration Costs

The administration costs incurred though the use of alteplase were based upon the resource use figures detailed by Sandercock et al. (2002)

Table 28: Additional staffing requirements for the alteplase in the extended administration window

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 utilized 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)

The total incremental staffing cost was therefore £1,316.29.

Procurement costs

Following the earlier assumption that patients in SITS-MOST were representative of those patients who would receive alteplase in UK clinical

practice (See section 5.3.5), the mean body-weight of subjects in the 3-4.5h cohort from the SITS-MOST [Wahlgren et al. 2008] trial (76kg) was used to calculate the cost of rt-PA itself for a typical eligible patient.

Average dose received per patient = 76kg * 0.9mg/kg = 68.4mg[3]

Cost of 68.4mg alteplase = 50mg pack + 20mg pack = £300 + £180 = £**480**

The total initial cost of alteplase treatment is therefore estimated to be £1316.29 + £480 = £1796.29.

To allow prognosis confirmation, the RCP (ISWP, 2008) currently recommend the undertaking of medical imaging irrespective of the intention to use thrombolytic. Therefore, no additional CT scan was attributed to the alteplase model arm due to the requirement of ICH exclusion before the administration of ICH exclusion before rt-PA administration

For patients experiencing a symptomatic intracranial haemorrhage a CT scan would be undertaken. The cost of this is £100 (covering one area) was attributed to the cost stream of those experiencing a sICH (in line with best clinical practice [ISWP 2008]. It is assumed that all other costs are captured in the 6 month health states for patients.

The standard treatment pathway required an extra dose of aspirin to be administered within the first 24 hours of treatment (due to the delay in administration required following thrombolysis) was deemed negligible (with 32 300mg tablets costing 31p [MIMS, December 2011).

Beyond the initial 24 hour period, apart from the costs of sICH mentioned above, the cost associated with each model arm is solely attributable to health states of those in the model arm rather than the treatment allocation.

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[3] Consistent with mean alteplase dose of 68mg as reported in the SITS-MOST trial (Wahlgren, 2008)

6.5.4 Clinical Experts input into resource use assumptions

No clinical experts were approached to assess the applicability of the values.

6.5.5 Health State Costs

A study by Youman et al. 2003 formed the basis for acute and post-acute care costing as reflected in the costs associated with the health states (dependent, independent and death). As shown in Table 30 differing costs were applied in the first two cycles (0-6 months and 6-12 months) than in post year one cycles for the dependent and independent health states.

As detailed in Section 6.5.3. Youman et al. 2003 analysed resource use data from a large, randomised, prospective study of alternative strategies of stroke care in the UK [Kalra et al. 2000]. The study included resource use in primary care, hospital and utilisation of social services over the 12 months following stroke. The authors of this costing study applied 2001/2002 PSSRU costs to these resource use figures and calculated the cost of 3 months of stroke care (both hospitalised, institutionalised and in the home) according to stroke severity (defined by the Barthel Index).

For the purposes of this study it was 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. 2003. The annual cost of care (for the first and subsequent years) was calculated for each model health state. In the first year of care it was assumed that patients were hospitalised for the initial 3 months irrespective of health state.

The cost of a fatal stroke event was taken from Youman et al. 2003.

This same methodology and source of costing was used by the NICE technology assessment report group in TA90 (clopidogrel and dipyridamole)

[Jones et al. 2003] and in TA122. For the purpose of this appraisal the costs reported by Youman were updated to 2012/13 prices via the PSSRU HCHS inflation index [PSSRU 2010].

Table 29 : Data used to calculate the annual cost of stroke care as reported in Youman et al. 2003 converted to 2012/13 prices with the PSSRU HCHS inflation index.

Parameter	Value	CI		Probabilistic Values (Beta-Pert Distribution)
3-month cost of ongoing care at home (including accommodation)	£445	£266	£623	£516
3-month cost of ongoing care in an institution (including accommodation)	£5,280	£5,003	£6,634	£5,252
Mild Stroke				
3-month cost of acute event	£6,953	£6,216	£7,686	£7,271
Proportion discharged home	100			
Proportion discharged to an institution	0			
Proportion dead	0			
Moderate Stroke				
3-month cost of acute event	£6,567	£6,008	£7,125	£6,371
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	£15,140
Proportion discharged home	0.732			
Proportion discharged to an institution	0.172			
Proportion dead	0.096			
Proportion of mild strokes amongst independent stroke patients	0.413			
Proportion of moderate strokes amongst independent stroke patients	0.587			
Cost of independent stroke year 1	£8,131	£6,961	£9,314	£8,359
Cost of independent stroke post-year 1	£1,872	£1,156	£2,610	£2,243
Cost of dependent stroke year 1	£18,487	£16,559	£21,031	£19,955
Cost of dependent stroke post-year 1	£5,458	£4,669	£7,068	£6,068
Cost of acute event fatal stroke	£9,247	£7,424	£13,461	£9,990
CT Scan	£110	£55	£220	£108
Calculated cost of independent stroke year 1	0.413*(£6953 +3*£445)+0.587*(£6567+3*(0.959/(1-0.033)*£445+0.0081/(1-0.033)*£5280))=**£8131**			
Calculated cost of independent stroke post year 1	0.413*4*£445+0.587*4*(0.959/(1-0.033)*£445+0.008/(0-0.033)*£5280)=**£1872**			
Calculated cost of dependent stroke year 1	£14394+3*(0.732/(1-0.096)*£445+0.172/(1-0.096)*£5280)=**£18487**			
Calculated cost of dependent stroke post year 1	4*(0.732/(1-0.096)*£445+0.172/(1-0.096)*£5280)=**£5458**			

Costs associated with adverse events

The single increase in cost associated with an adverse event is the additional cost relating to the CT scan needed when a sICH is experienced.

Additional Costs

No additional costs were identified.

6.6. Sensitivity analysis

6.6.1. Exploration of uncertainty around structural assumptions been investigated.

As discussed in section 6.2.2. the model structure chosen depicts three post-stroke phases- acute treatment, recovery after survival in year 1 and then long-term outcomes beyond the first year of survival. The structure assumes that patients present for treatment within the licensed time window and in effect models the dichotomous alternatives between thrombolytic treatment and no thrombolytic treatment.

Others aspects of the model which may be deemed to introduce structural uncertainty include the choice to assume patients cannot transition from dependency to independent health states beyond 12 months of the model time horizon.

The assumption that patients face the same transition probabilities in months 6-12 regardless of whether thrombolytic treatment was given or not is again reasonable in that there is no evidence that alteplase has an effect beyond the acute phase of treatment. This assumption may also be considered to be conservative, in that it does not confer any additional advantage to alteplase treatment. Lastly, the structural assumption in the definition of post-stroke health states could be further explored- as noted in section 6.1; other cost-effectiveness studies have considered each mRS score as a separate health state. However, for the purposes of this analysis, the approach of Sandercock et al as adapted in TA122 appears to be appropriate and exploration of further health states is unlikely to be informative, if the definitions of ‘independent’ and ‘dependent’ are accepted as valid and reasonable.

6.6.2. Deterministic sensitivity analysis

Table 30: Values used in deterministic sensitivity analysis (0-4.5 hour window of use – baseline model)

Variable	Deterministic Value	Range		Source / Rationale
		Low	High	
Patient Characteristics				
Starting Age	68	59	75	SIT-MOST 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 (reported range)
Cost of dependent stroke (Year 1)	£18,487	£16,559	£21,031	Youman et al (reported range)
Cost of independent stroke (post Year 1)	£1,872	£1,156	£2,610	Youman et al (reported range)
Cost of dependent stroke (post Year 1)	£5,458	£4,669	£7,068	Youman et al (reported range)
Cost of acute event- fatal stroke	£9,247	£7,424	£13,461	Youman et al (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
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
Utilty- Dependent	0.38	0.29	0.47	Dorman et al

6.6.3. Probabalistic Sensitivity Analysis.

Probabilistic sensitivity analysis (PSA) was undertaken. Table 31 summarises the variables included in the PSA along with the distributions assigned to each variable. The choice of distribution was informed with reference to 'Decision Modelling for Health Economic Evaluation' (Briggs, 2006).

Table 31: Assumptions for 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
Relative risk- Death	0.818	0.504	1.32	Lognormal distribution, derived from Hacke et al

Relative risk- Dependency	0.885	0.776	1.198	Lognormal distribution, derived from Hacke et al
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

6.7. Results

6.7.1 Comparing model outcomes to trial outcomes

Given that ECASS III is the only trial, as opposed to a pooled analysis, used to generate outcome CE results presented in this submission the baseline distribution between health states was reset to reflect the distribution in the placebo arm of ECASS III (a change from the base case which sources a UK based study for this parameter – the Lothian Stroke Registry – see Section 6.3.1.1. for rationale) as shown in the table below (based on patient numbers shown in **Appendix 15**)

Table 32: Health State Distribution at 3 months (ECASS III)

	Alteplase	**Placebo**
Independent	0.66507177	0.61538462
Dependent	0.267942584	0.30272953
Dead	0.066985646	0.08188586

As would be anticipated the health states of the alteplase arm in the model in this circumstance reflect those from the trial. This is shown in the table below:

Table 33: Health states at 6 months (model assumes health states at 6 months equate to those at 3 months found in clinical trials

	Independent	Dependent	Dead
No treatment	0.6154	0.3027	0.0819
Alteplase	0.6651	0.2679	0.067

6.7.2. Markov Trace

Shown in Table 34 Below:

	Standard Treatment			Table 34: Markov Trace			alteplase					
Year	Independent	Dependent	Dead	Recurrent stroke			Independent	Dependent	Dead	Recurrent stroke		
0	1.0000			Independent	Dependent	Dead	1.0000			Independent	Dependent	Dead
0.5	0.3953	0.3256	0.2791				0.4981	0.2535	0.2484			
1	0.3821	0.2783	0.3397				0.4640	0.2345	0.3015			
2	0.3485	0.2538	0.3647	0.0072	0.0176	0.0083	0.4232	0.2139	0.3280	0.0087	0.0175	0.0087
3	0.3168	0.2307	0.3894	0.0119	0.0292	0.0220	0.3847	0.1944	0.3541	0.0145	0.0291	0.0232
4	0.2866	0.2087	0.4142	0.0149	0.0365	0.0391	0.3481	0.1759	0.3803	0.0181	0.0363	0.0414
5	0.2579	0.1878	0.4390	0.0165	0.0406	0.0581	0.3132	0.1583	0.4066	0.0201	0.0404	0.0615
6	0.2305	0.1679	0.4640	0.0172	0.0423	0.0780	0.2800	0.1415	0.4330	0.0209	0.0421	0.0825
7	0.2048	0.1491	0.4886	0.0172	0.0424	0.0979	0.2487	0.1257	0.4590	0.0209	0.0421	0.1035
8	0.1804	0.1314	0.5130	0.0168	0.0412	0.1172	0.2191	0.1107	0.4848	0.0204	0.0410	0.1240
9	0.1574	0.1146	0.5372	0.0160	0.0392	0.1356	0.1912	0.0966	0.5104	0.0194	0.0390	0.1434
10	0.1360	0.0991	0.5605	0.0149	0.0367	0.1528	0.1652	0.0835	0.5351	0.0181	0.0364	0.1616
11	0.1163	0.0847	0.5829	0.0137	0.0338	0.1686	0.1412	0.0714	0.5588	0.0167	0.0336	0.1784
12	0.0979	0.0713	0.6046	0.0125	0.0307	0.1830	0.1189	0.0601	0.5817	0.0152	0.0305	0.1936
13	0.0812	0.0591	0.6251	0.0112	0.0275	0.1959	0.0986	0.0498	0.6034	0.0136	0.0274	0.2072
14	0.0662	0.0482	0.6440	0.0099	0.0244	0.2073	0.0804	0.0406	0.6234	0.0121	0.0242	0.2193
15	0.0530	0.0386	0.6611	0.0087	0.0213	0.2174	0.0643	0.0325	0.6415	0.0105	0.0212	0.2299
16	0.0415	0.0302	0.6764	0.0075	0.0184	0.2260	0.0504	0.0255	0.6577	0.0091	0.0183	0.2391
17	0.0316	0.0230	0.6898	0.0064	0.0157	0.2334	0.0384	0.0194	0.6719	0.0078	0.0156	0.2469
18	0.0235	0.0171	0.7011	0.0054	0.0133	0.2396	0.0285	0.0144	0.6838	0.0066	0.0132	0.2535
19	0.0169	0.0123	0.7104	0.0045	0.0110	0.2448	0.0206	0.0104	0.6937	0.0055	0.0110	0.2589
20	0.0118	0.0086	0.7178	0.0037	0.0091	0.2490	0.0144	0.0073	0.7015	0.0045	0.0090	0.2634
21	0.0081	0.0059	0.7233	0.0030	0.0073	0.2525	0.0098	0.0050	0.7073	0.0036	0.0073	0.2671
22	0.0053	0.0039	0.7274	0.0024	0.0059	0.2552	0.0064	0.0033	0.7116	0.0029	0.0058	0.2700
23	0.0034	0.0024	0.7303	0.0019	0.0046	0.2574	0.0041	0.0021	0.7147	0.0023	0.0046	0.2723
24	0.0020	0.0014	0.7324	0.0015	0.0036	0.2591	0.0024	0.0012	0.7169	0.0018	0.0036	0.2741
25	0.0011	0.0008	0.7338	0.0011	0.0028	0.2604	0.0013	0.0007	0.7184	0.0014	0.0028	0.2755
26	0.0005	0.0004	0.7346	0.0009	0.0022	0.2614	0.0007	0.0003	0.7192	0.0011	0.0022	0.2766

Table 34:
Markov Trace

	Standard Treatment						alteplase					
Year	Independent	Dependent	Dead	Recurrent stroke			Independent	Dependent	Dead	Recurrent stroke		
				Independent	Dependent	Dead				Independent	Dependent	Dead
27	0.0003	0.0002	0.7350	0.0007	0.0016	0.2622	0.0003	0.0002	0.7197	0.0008	0.0016	0.2774
28	0.0001	0.0001	0.7353	0.0005	0.0012	0.2628	0.0001	0.0001	0.7200	0.0006	0.0012	0.2780
29	0.0000	0.0000	0.7354	0.0004	0.0009	0.2632	0.0000	0.0000	0.7201	0.0005	0.0009	0.2785
30	0.0000	0.0000	0.7354	0.0003	0.0007	0.2636	0.0000	0.0000	0.7201	0.0003	0.0007	0.2788
31	0.0000	0.0000	0.7354	0.0002	0.0005	0.2638	0.0000	0.0000	0.7201	0.0003	0.0005	0.2791
32	0.0000	0.0000	0.7354	0.0002	0.0004	0.2640	0.0000	0.0000	0.7201	0.0002	0.0004	0.2793
33	0.0000	0.0000	0.7354	0.0001	0.0003	0.2641	0.0000	0.0000	0.7201	0.0001	0.0003	0.2794
34	0.0000	0.0000	0.7354	0.0001	0.0002	0.2643	0.0000	0.0000	0.7201	0.0001	0.0002	0.2795
35	0.0000	0.0000	0.7354	0.0001	0.0002	0.2643	0.0000	0.0000	0.7201	0.0001	0.0002	0.2796
36	0.0000	0.0000	0.7354	0.0001	0.0001	0.2644	0.0000	0.0000	0.7201	0.0001	0.0001	0.2797
37	0.0000	0.0000	0.7354	0.0000	0.0001	0.2644	0.0000	0.0000	0.7201	0.0000	0.0001	0.2797
38	0.0000	0.0000	0.7354	0.0000	0.0001	0.2645	0.0000	0.0000	0.7201	0.0000	0.0001	0.2798
39	0.0000	0.0000	0.7354	0.0000	0.0001	0.2645	0.0000	0.0000	0.7201	0.0000	0.0001	0.2798
40	0.0000	0.0000	0.7354	0.0000	0.0000	0.2645	0.0000	0.0000	0.7201	0.0000	0.0000	0.2798

6.7.3. Details of how the model assumes QALYs accrued over time.

QALYs are simply accrued by adjusting the utility weight for the 'independent' and 'dependent' health states by the proportion of patients expected to be in those states in each annual cycle over the time horizon of the model. The initial 6 month cycles were accounted for, and a 3.5% discount rate applied in the base case analysis. QALYs were then summed over all cycles for the alteplase arm and the standard treatment arm of the model to give the total expected QALYs over the lifetime horizon. A half-cycle correction was applied.

6.7.4. Life years and QALYs accrued for each clinical outcome

Table 35 Model outputs by clinical outcomes (0-4.5 hours window of use)

Outcome	LY	QALY	Cost (£)
Alteplase			
Independent	4.255	2.5369	11267
Dependent	2.571	0.7708	18063
Total	6.826	3.3077	29330
Standard Treatment			
Independent	2.812	2.0807	8537
Dependent	3.648	0.8946	19982
Total	6.460	2.9753	28519
LY, life years; QALY, quality-adjusted life year *Notes: Cost of Alteplase administration is split equally between independent and dependent states* *Costs of fatal stroke etc. included in dependent state costs*			

6.7.5. Details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost.

Table 36: Summary of QALY gain by health state (0-4.5 hour window of use – baseline model)

Health state	QALY Alteplase	QALY Standard Treatment	Increment	Absolute increment	% absolute increment
Independent	2.5369	2.0807	0.3616	0.4562	
Dependent	0.7708	0.8946	-0.1238	0.1238	
Total	3.3077	2.9753	0.3324	0.3324	100%
QALY, quality-adjusted life year Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee					

Table 37 Summary of costs by health state (0-4.5 hour window of use – baseline model)

Health state	Cost Alteplase	Cost Standard Treatment	Increment	Absolute increment	% absolute increment
Independent	11267	8537	2730	2730	
Dependent	18063	19982	-1919	1919	
Total	29330	28519	811	811	100%
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee					

Table 38: Summary of predicted resource use by category of cost

Item	Cost Alteplase	Cost Standard Treatment	Increment	Absolute increment	% absolute increment
Mean total treatment cost	480	0	480	480	26.7%
Administration cost	1316	0	1316	1316	73.3%
Total	1796	0	1796	1796	100%
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee					

6.7.6. Base Case Incremental Cost Effectiveness Ratios

Table 39: Base-case results (0-4.5 hour window of use) – deterministic model

	Independent life years (ILY)	life years	QALYs	Cost	ICER (QALY)
No treatment	2.812	6.460	2.975	£28,519	£2,441
with alteplase	4.255	6.826	3.308	£29,330	

6.7.7. Results of deterministic sensitivity analysis.

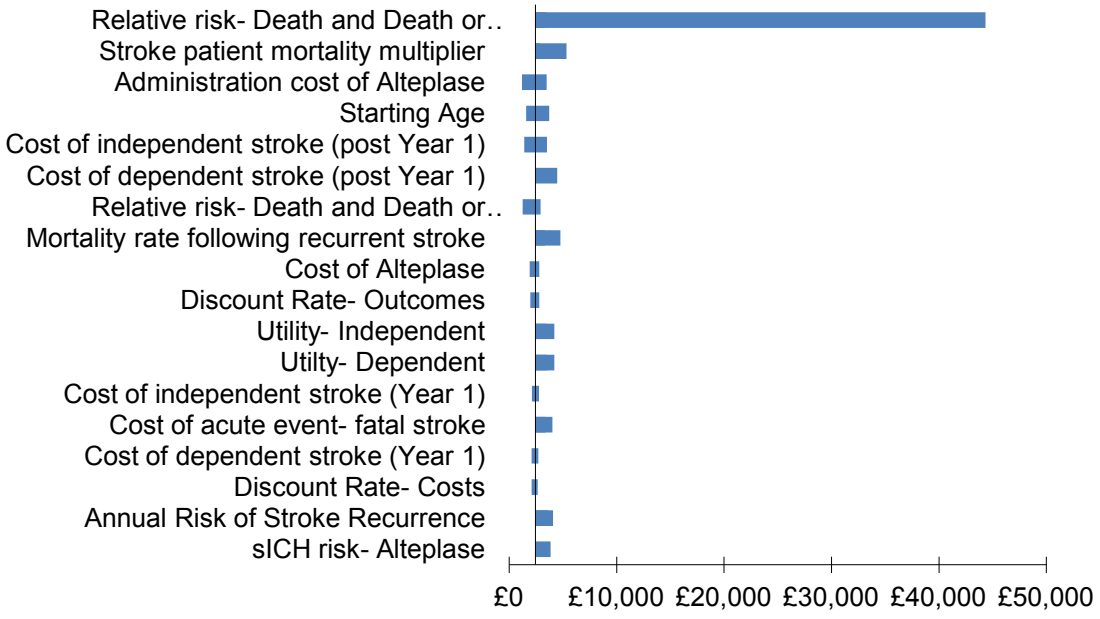
Table 39 displays the results of the one-way sensitivity analysis conducted with the upper and lower parameter values from section 6.6.2.

Table 40: One way sensitivity analysis (0-4.5 hour window of use)

Variable	Lifetime	
	Low	High
Starting Age	£1,581	£3,715
Discount Rate- Costs	£2,074	£2,638
Discount Rate- Outcomes	£1,962	£2,797
Cost of Alteplase	£1,899	£2,802
Administration cost of Alteplase	£1,178	£3,491
Cost of independent stroke (Year 1)	£2,118	£2,767
Cost of dependent stroke (Year 1)	£2,698	£2,101
Cost of independent stroke (post Year 1)	£1,404	£3,507
Cost of dependent stroke (post Year 1)	£4,471	£2,508
Cost of acute event- fatal stroke	£4,018	£3,379
Stroke patient mortality multiplier	£2,902	£5,339
Mortality rate following recurrent stroke	£3,331	£4,765
Annual Risk of Stroke Recurrence	£3,621	£4,092
sICH risk- Alteplase	£3,823	£3,832
Relative risk- Death and Death or Dependency (95% CI)	£3,462	£44,342 (no treatment, more QALYs)
Relative risk- Death and Death or Dependency (+/- 1sd)	£2,933	£1,261 (alteplase more QALYs)
Utility- Independent	£4,216	£3,500
Utilty- Dependent	£3,515	£4,195

The sensitivity analysis data was used to generate tornado diagrams:

Figure 7: Tornado Diagram:Alteplase vs. No Treatment (0-4.5 hr window of use)



Three additional deterministic sensitivity analyses were carried out. Firstly, given the exclusion of ATLANTIS A and B (0-3 hrs) from the pooled analysis to generate parameter values for the model as outlined in Section 6.3.1.1. and 5.2.1. it was explored what impact their inclusion would have on ICERs as shown in the table below:

Table 41: SA results (0-4.5 hour window of use) (pooled analysis of ECASS II (0-3), NINDS, ATLANTIS A and B (0-3), ECASS III) – deterministic analysis

	Independent life years (ILY)	life years	QALYs	Cost	ICER (QALY)
No treatment	2.812	6.460	2.975	£28,519	£1,788
with alteplase	4.201	6.726	3.262	£29,031	

Secondly, as outlined in Section 6.3.1.1. the pooled analysis is weighted more towards use at 3-4.5 hours than in clinical practice. Reweighting the results to

reflect clinical practice (as outlined in Section 6.3.1.1.) provides ICERs as shown in the table below:

Table 42: SA results (0-4.5 hour window of use) (reweighting pooled analysis of ECASS II (0-3), NINDS, ECASS III to reflect clinical practice) – deterministic analysis

	Independent life years (ILY)	life years	QALYs	Cost	ICER (QALY)
No treatment	2.812	6.460	2.975	£28,519	alteplase dominant
with alteplase	4.272	6.598	3.244	£28,155	

Thirdly, as outlined in Section 5.2.2. and 6.3.1.1. an ad hoc data set of 3-4.5 hour data from ECASS II and ATLANTIS was obtained. This was included in a pooled analysis of ECASS III, ECASS II (0-3), NINDS, ATLANTIS A & B (0-3 hrs) to identify the impact that its inclusion had upon ICERs. This is shown in Table 43 . (RR for sICH based on a pooled analysis of ECASS III, ECASS II (0-3), NINDS, ATLANTIS A & B (0-3 hrs) were used in the model since they were not sourced for ECASS II (3-4.5 hrs) and ATLANTIS (3-4.5 hrs); since the model as shown in the one way SA is not sensitive to values associated with this parameter this should have minimal impact on the results):

Table 43: SA results (0-4.5 hour window of use) (pooled analysis of ECASS II (0-3), NINDS, ATLANTIS A and B (0-3), ECASS III + ECASS II (3-4.5) + ATLANTIS (3-4.5)) – deterministic analysis

	Independent life years (ILY)	life years	QALYs	Cost	ICER (QALY)
No treatment	2.812	6.460	2.975	£28,519	
with alteplase	4.150	6.649	3.224	£28,837	£1,283

6.7.8. Results of the Probabalistic Sensitivity Analysis

Table 44 give the results of the probabilistic sensitivity analysis. The analysis was derived from the results of 10,000 Monte Carlo simulations using the distributions assigned to parameters as detailed in section 6.6.3

Table 44: Base-case results (0-4.5 hour window of use) – probabalistic model

	No treatment			with alteplase			
	Average	lower 95%CI	Upper 95% CI	Average	lower 95%CI	Upper 95% CI	ICER
QALYS	2.910	2.685	3.206	3.255	2.939	3.607	£2,194
Costs	£28,179	£25,693	£30,829	£28,935	£25,525	£31,990	
ILY	2.757	2.749	2.764	4.195	3.842	4.438	
Life years	6.312	6.291	6.329	6.679	6.119	7.120	

Similarly, a cost-effectiveness acceptability curve was generated. This is presented with the associated scatter plot of the iterations used to produce the cost-effectiveness acceptability curve.

Figure 8: Scatter Plot (0-4.5 hour window of use)

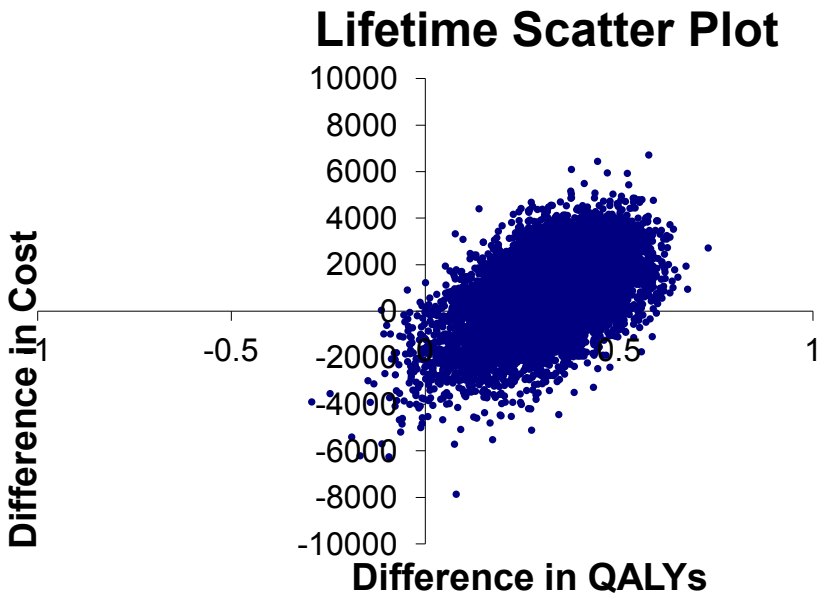
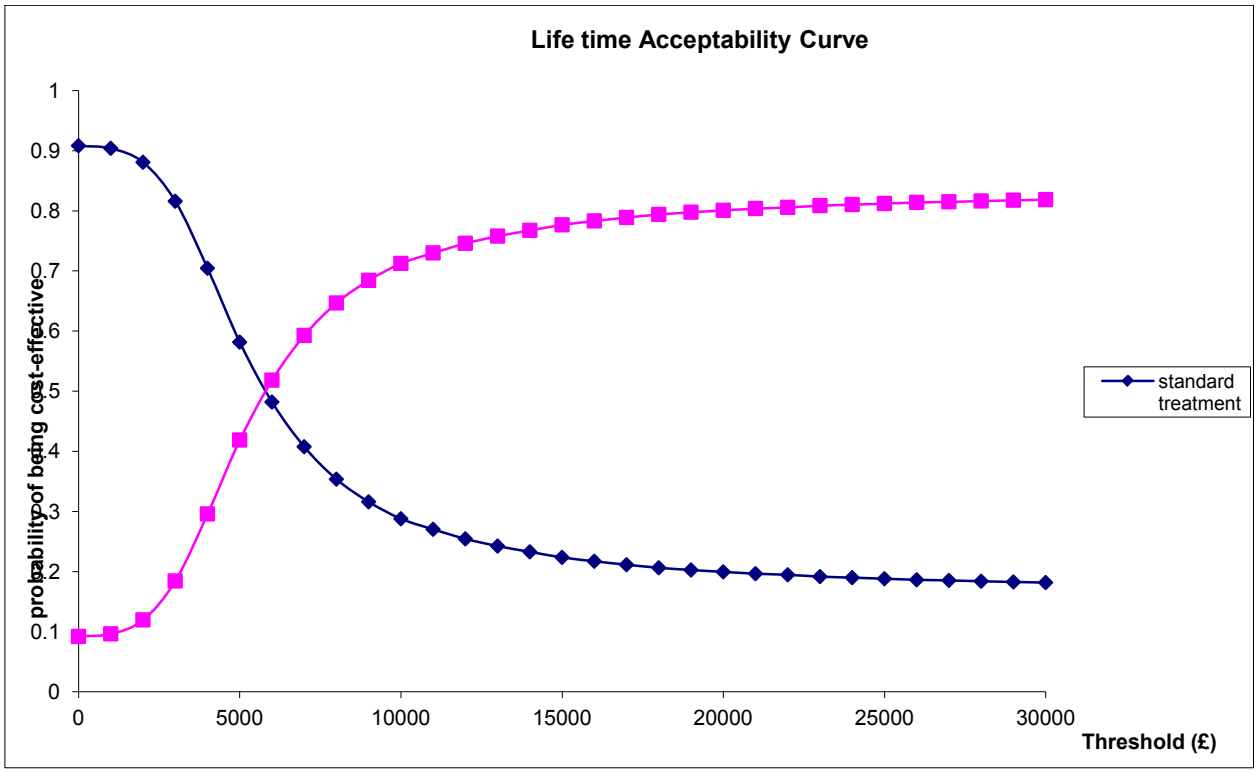


Figure 9: Cost acceptability curve (0-4.5 hour window of use)



6.7.9. Results of scenario analysis.

No scenario analysis was considered appropriate for this analysis.

6.7.10. Main findings of each of the sensitivity analyses.

The deterministic one way sensitivity analysis in Section 6.7.7 identifies that results are potentially sensitive to the values assigned to RR of death and RR of dependency. Since these are interlinked they have been varied together in the sensitivity analysis and it is note worthy that at less favourable valuations for alteplase, no treatment does not become a cost effective option. Namely:

- At the upper 95% CI valuation of RR for death and RR for death or dependency, no treatment provides more QALYs at more cost at an unfavourable ICER of £44,342

- At the 66% CI valuation of RR for death and RR for death or dependency, alteplase provides more QALYs at more cost at an ICER of £1,261 which does not provide a clear indication that no treatment of the cost effectiveness of no treatment.

  The probabilistic sensitivity analysis which takes into account uncertainty around all relevant parameters suggests a high degree of probability that alteplase is a cost effective option compared to no treatment with a probability that it is a cost effective option at a £20,000 per QALY threshold of about 80%.

6.7.11. The key drivers of the cost-effectiveness results.

As identified in Section 6.7.10 the key drivers of the CE results are assumptions around RR of death and death or dependency**.**

6.8. Validation

6.8.1. Methods used to validate and quality assure the model.

The results of the analysis were compared with the cost-effectiveness studies identified in section 6.1. With the significant difference being that this analysis considered the 3-4.5 hour treatment window, the results are similar- with a

low ICER (or in many cases a dominant result). Therefore it would appear that the existing body of literature supports the results of this current analysis.

6.9. Subgroup analysis

6.9.1. Rationale for Subgroup Analysis

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 (Extension to existing licence being sought by Boehringer)

6.9.2. Characteristics of patients in subgroup

See Section 6.9.1.

6.9.3. Statistical Analysis undertaken

As outlined in Section 6.3.1.1. the base case analysis in this submission is based on pooled analysis of studies which individually were limited to alteplase use either in the 0-3 hour or 3-4.5 hour window of use after the onset of symptoms. Subgroup analysis was therefore based upon clinical parameters value estimates generated from the relevant studies, namely:

- Pooled analysis of NINDs and ECASS II – 0-3 hour use
- ECASS III – 3-4.5 hour use

6.9.4. Results of Sub group Analysis

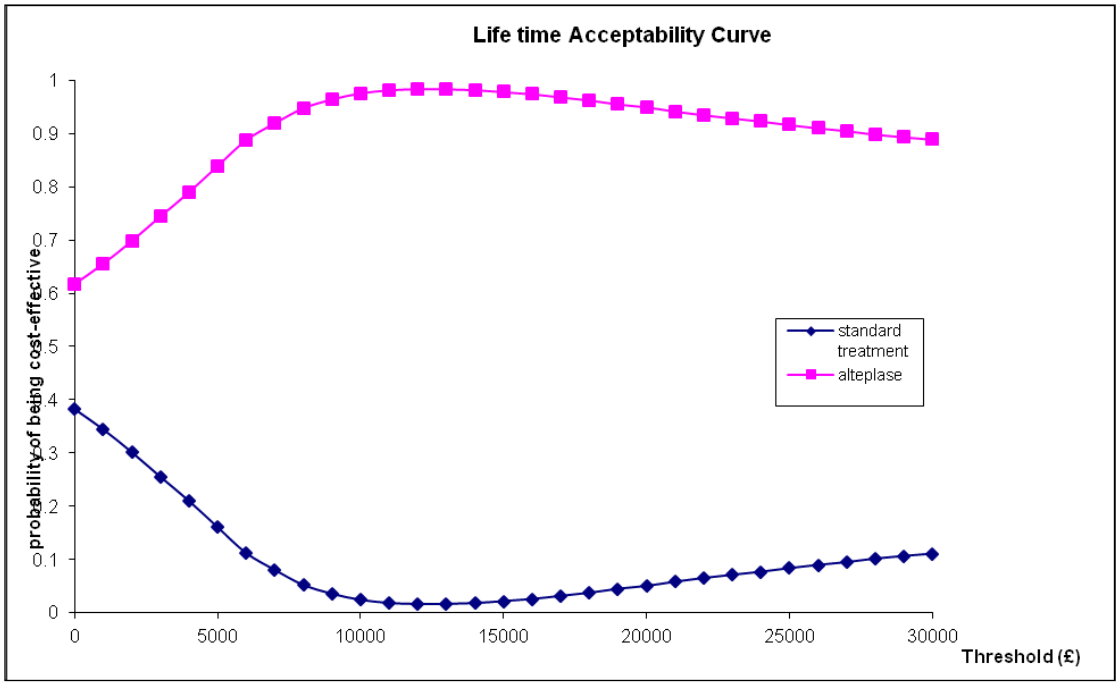
6.9.4.1 Subgroup Analysis: 0-3 hours of use

As outlined in Section 5.2.1. no new studies were identified relating to the use of alteplase in the 0-3 hour therapeutic window that were not considered as part of TA122. Given this a limited analysis of the cost effectiveness of this subgroup is presented below.

Table 45: Base-case results (0-3 hour window of use) – deterministic model

	Independent life years (ILY)	life years	QALYs	Cost	ICER (QALY)
No treatment	2.812	6.460	2.975	£28,519	alteplase dominant
with alteplase	4.299	6.464	3.211	£27,401	

Figure 10: Cost acceptability curve (0-3 hour window of use)



As outlined in Section 5.2.1. in the comments from the ERG, as part of TA122, there was a certain degree of consideration given to the applicability of including studies ATLANTIS A and B (0-3 hr data) in the pooled analysis to estimate clinical efficacy of alteplase in 0-3 hour window of use even though concern was expressed that this involved data from a subgroup analysis not pre-specified prior to randomisation. Results based on the inclusion of ATLANTIS A and B are given below:

Table 46: Sensitivity analysis results (0-3 hour window of use) – deterministic model (inclusion of ATLANTIS A & B in pooled analysis)

	Independent life years (ILY)	life years	QALYs	Cost	ICER (QALY)
No treatment	2.812	6.460	2.975	£28,519	alteplase dominant
with alteplase	4.230	6.224	3.118	£26,470	

6.9.4.1.4. Main findings of the sensitivity analysis (0-3 hour window of use).

The PSA indicates a 90% probability that alteplase use at 0-3 hours after the onset of symptoms is a cost effective option.

Both for baseline assumptions and the inclusion of ATLANTIS A and B in the pooled analysis to generate clinical efficacy parameters, alteplase remains dominant to no treatment.

6.9.4.2. Subgroup Analysis: 3-4.5 hour 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 are presented below.

6.9.4.2.1. Base Case Incremental Cost Effectiveness Ratios (Subgroup analysis: 3-4.5 hour use)

Table 47: Base-case results (3-4.5 hour window of use) – deterministic model

	Independent life years (ILY)	life years	QALYs	Cost	ICER (QALY)
No treatment	2.812	6.460	2.975	£28,519	£6,272
with alteplase	4.097	6.968	3.305	£30,587	

6.9.4.2.2. Deterministic Sensitivity Analysis (Subgroup Analysis: 3-4.5 hour window of use)

Table 48 displays the results of the one-way sensitivity analysis conducted with the upper and lower parameter values from section 6.6.2.

Table 48: Values in One way sensitivity analysis (3-4.5 hour window of use)

Variable	Deterministic Value	Range		Source / Rationale
		Low	High	
Patient Characteristics				
Starting Age	68	59	75	SIT-MOST reported range (2007)
Resource Use and Discounts				
Discount Rate- Costs	3.50%	0%	6%	
Discount Rate- Outcomes	3.50%	0%	6%	
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	£6,931	£9,314	Youman et al (reported range)
Cost of dependent stroke (Year 1)	£18,487	£16,559	£21,031	Youman et al (reported range)
Cost of independent stroke (post Year 1)	£1,872	£1,156	£2,610	Youman et al (reported range)
Cost of dependent stroke (post Year 1)	£5,458	£4,669	£7,068	Youman et al (reported range)
Cost of acute event-fatal stroke	£9,247	£7,424	£13,461	Youman et al (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				

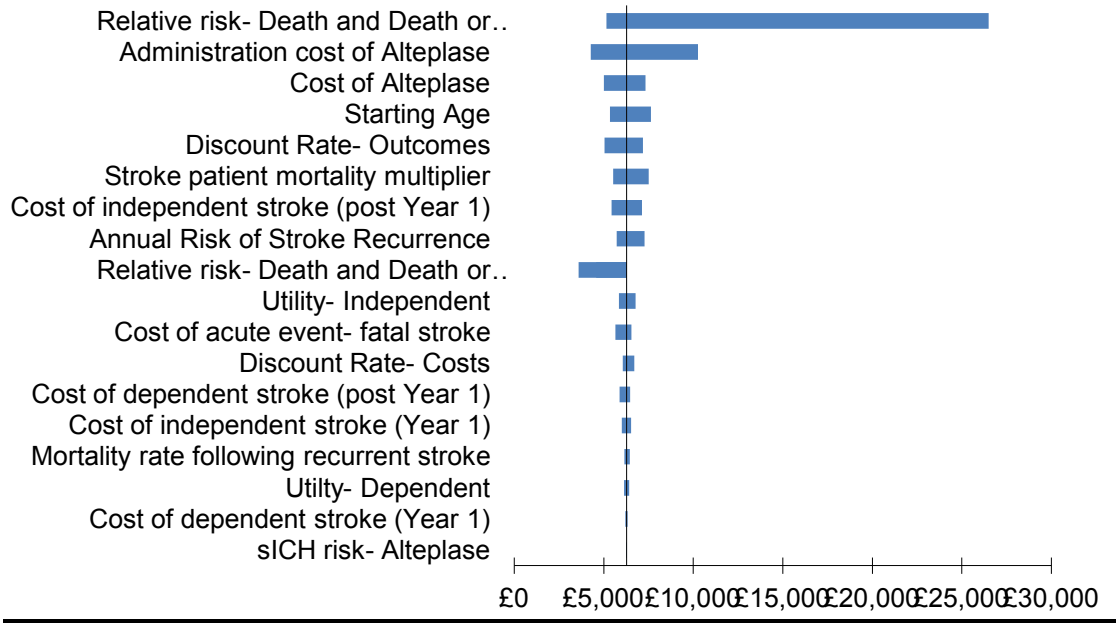
sICH risk- Alteplase	2.39%	1.15%	4.36%	Hacke et al
Relative risk- Death or Dependency	0.871	0.725	1.046	Derived from Hacke et al (95% CI)
Relative risk- Death	0.818	0.504	1.328	Derived from Hacke et al (95% CI)
Relative risk- Death or Dependency	0.871	0.793	0.956	Derived from Hacke et al (+/- 1 sd)
Relative risk- Death	0.818	0.639	1.048	Derived from Hacke et al (+/- 1 sd)
Utility Values				
Utility- Independent	0.74	0.69	0.79	Dorman et al
Utilty- Dependent	0.38	0.29	0.47	Dorman et al

Table 49: One way sensitivity analysis (3-4.5 hour window of use)

Variable	Lifetime	
	Low	High
Starting Age	£5,354	£7,634
Discount Rate- Costs	£6,701	£6,053
Discount Rate- Outcomes	£5,037	£7,193
Cost of Alteplase	£5,000	£7,330
Administration cost of Alteplase	£4,277	£10,263
Cost of independent stroke (Year 1)	£6,013	£6,534
Cost of dependent stroke (Year 1)	£6,320	£6,208
Cost of independent stroke (post Year 1)	£5,440	£7,129
Cost of dependent stroke (post Year 1)	£6,466	£5,877
Cost of acute event- fatal stroke	£6,539	£5,655
Stroke patient mortality multiplier	£5,523	£7,502
Mortality rate following recurrent stroke	£6,148	£6,450
Annual Risk of Stroke Recurrence	£5,726	£7,280
sICH risk- Alteplase	£6,268	£6,279
Relative risk- Death and Death or Dependency (95% CI)	£4,569	£3,595 (no treatment more QALYs)
Relative risk- Death and Death or Dependency (+/- 1sd)	£5,158	£26,490 (alteplase more QALYs)
Utility- Independent	£6,774	£5,840
Utilty- Dependent	£6,133	£6,418

The sensitivity analysis data was used to generate tornado diagrams:

Figure 11: Tornado Diagram:Alteplase vs. No Treatment (3-4.5 hr window of use)



As outlined in Section 5.2.2. and 6.3.1.1. an ad hoc data set of 3-4.5 hour data from ECASS II and ATLANTIS was obtained. This was included in a pooled analysis with ECASS III to identify the impact that its inclusion had upon base case ICERs. This is shown in Table 49 (RR for sICH based on ECASS II were used in the model since they were not sourced for ECASS II (3-4.5 hrs) and ATLANTIS (3-4.5 hrs); since the model as shown in the one way SA is not sensitive to the values associated with this parameter should have minimal impact on the results):

Table 50: SA results (3-4.5 hour window of use) (pooled analysis of ECASS III + ECASS II (3-4.5) + ATLANTIS (3-4.5)) – deterministic analysis

	Independent life years (ILY)	life years	QALYs	Cost	ICER (QALY)
No treatment	2.812	6.460	2.975	£28,519	£5,631
with alteplase	4.092	6.894	3.281	£30,241	

6.9.4.2.3. Results of the Probabalistic Sensitivity Analysis (3-4.5 hour window of use)

Table 51 give the results of the probabilistic sensitivity analysis. The analysis was derived from the results of 10,000 Monte Carlo simulations using the distributions assigned to parameters as detailed in section 6.6.3

Table 51: Base-case results (3-4.5 hour window of use) – probabalistic model

	No treatment			with alteplase			
	Average	lower 95%CI	upper 95% CI	Average	lower 95%CI	Upper 95% CI	ICER
QALYS	2.929	2.654	3.223	3.185	2.791	3.667	£5,504
Costs	£28,238	£25,448	£32,323	£29,649	£25,652	£34,841	
ILY	2.760	2.748	2.768	3.939	3.254	4.701	
Life years	6.319	6.288	6.343	6.641	6.005	7.242	

Figure 12: Scatter Plot (3-4.5 hour window of use)

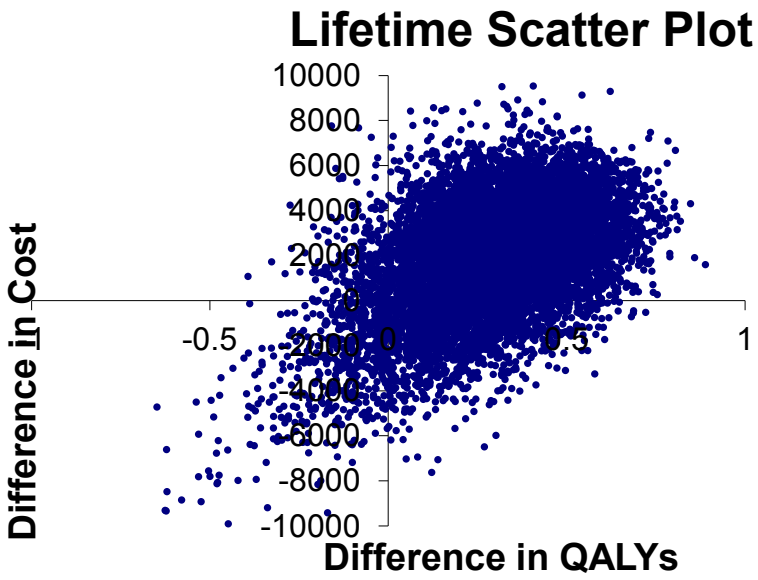
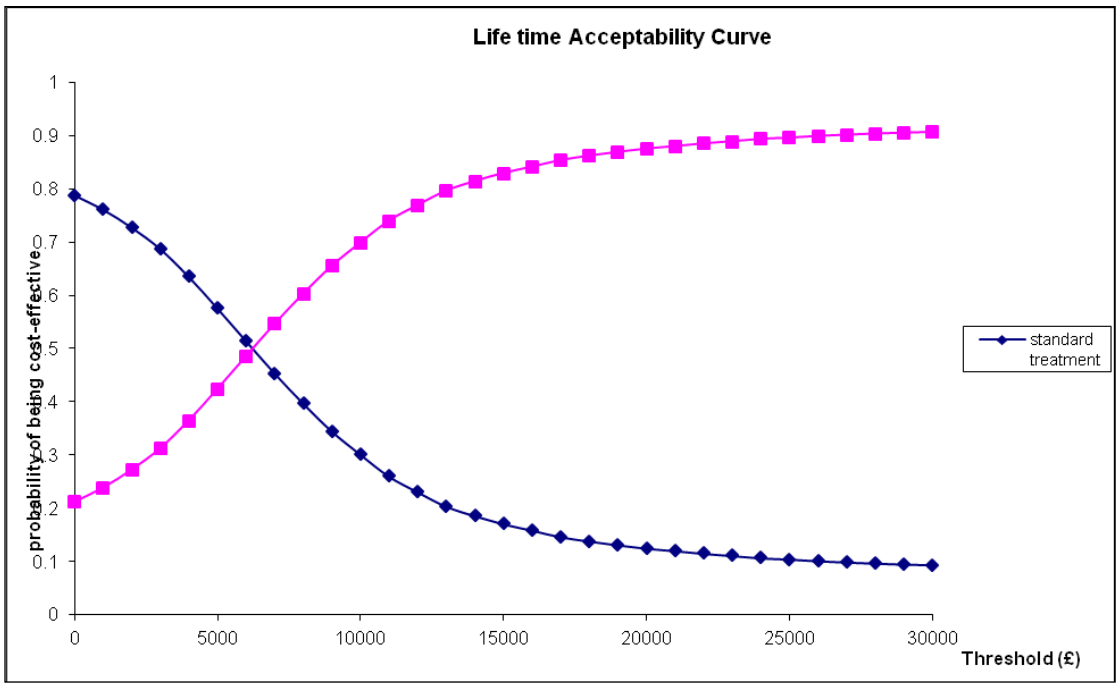


Figure 13: Cost acceptability curve (3-4.5 hour window of use)



6.9.4.2.4. Main findings of the sensitivity analysis (3-4.5 hour window of use).

The deterministic one way sensitivity analysis in Section 6.9.4.2.2. identifies that results are potentially sensitive to the values assigned to RR of death and RR of dependency or death. Since these are interlinked they have been varied together in the sensitivity analysis. At less favourable valuations for alteplase, no treatment becomes a cost effective option. Namely:

- At the upper 95% CI valuation of RR for death and RR for death or dependency, no treatment provides more QALYs at a favourable cost per QALY of £3,595

This evidence needs to be considered in relation to the following:

- At the upper 66% CI valuation of RR for death and RR for death or dependency, alteplase provides more QALYs at an ICER of £26,490

In determining the relevance of the sensitivity of ICERs to these variables, it needs to be decided as to whether the level of certainty provided by a 95% CI is too rigorous for decision making about the probability that a product is cost effective and whether a 66% CI may be more appropriate.

The probabilistic sensitivity analysis which takes into account uncertainty around all relevant parameters suggests a high degree of probability that alteplase is a cost effective option compared to no treatment with a probability that it is a cost effective option at a £20,000 per QALY threshold of about 90%.

6.9.5. Relevant subgroups not considered

Relevant subgroups considered

6.10. Interpretation of economic evidence

6.10.1. Consistency of economic evaluation results with the published economic literature

The results of this analysis appear to be consistent with identified cost-effectiveness studies. Several previous studies, e.g. Fagan et al found alteplase treatment to be the dominant strategy over the lifetime time horizon. Several factors may have influence on this slight difference between study results- such as the time window being considered, the setting of the study and what clinical evidence was used to inform the model (some studies, such as Fagan et al were based on single trials such as the NINDS-rtPA trial).

Therefore, these differences between the present analysis and previous studies could be construed as minor as the magnitudes of the differences are relatively small. In addition this analysis is based on the work of Sandercock et al, which was identified to be the cost-effectiveness study with the greatest relevance to this analysis and which also formed the basis of the model submitted as part of the (positively accepted) TA122. Furthermore, the methodological issues discussed in the critical appraisal of the studies indentified in section 6.1 indicate that the approach of TA122 and this analysis may be more robust than the contrasting studies.

6.10.2. Economic evaluation relevance to all groups of patients who could potentially use the technology

The analysis is relevant to all groups who may potentially benefit from the technology

6.10.3. Strengths and weaknesses of the evaluation.

Identified strengths:

- The model was based on an existing and recognised structure, allowing comparision and validation with existing cost-effectiveness studies, and TA122.

- Costs were taken from a comprehensive UK burden of disease study which have been used in other technology appraisals (e.g. TA122, TA236 Ticagrelor)
- ICER estimates were similar to those produced in the identified body of cost-effectiveness literature.
- Utility weights were taken from published data and based on UK population weights.
- Sensitivity analysis supported the conclusions of base case analysis

Weaknesses:

- The analysis assumes that the outcomes from the Lothian Stroke Registry (patients registered between 1990-2000) are representative of current practice without thrombolytic treatment.
- It is assumed that patients in the long-term (post 12months) portion of the model face the same mortality risk regardless of functional status. The analysis of Slot et al (2008) suggests that patients in a severely disabled state following a stroke event may have a significantly lower life expectancy.
- Risk of recurrent stroke is likely to be affected by preventative treatments, which is not taken into account in the model

The identified weakness regarding higher mortality with poor functional status after stroke is likely to lead to an underestimation of the cost-effectiveness of alteplase treatment, as one outcome of thrombolytic therapy is a greater proportion of patients in an 'independent' health state.

Consideration of preventative strategies could be considered beyond the requirements of this analysis, which in essence considers acute treatment. Therefore whilst the risk of stroke recurrence may differ in practice, assuming

the same risk between treatment arms allows comparison of long-term outcomes following the acute treatment phase.

By considering the 3-4.5 hour time window in isolation, it is possible to inform both the clinical and cost-effectiveness decision-making process. It is apparent that use of thrombolytic treatment is more successful in the 0-3 hour window, therefore if the clinician has a good estimate of the time elapsed from the onset of the stroke, a more informed judgement of the risk-benefit of alteplase treatment can be made.

6.10.4. Further analyses that could be undertaken to enhance the robustness/completeness of the results.

No additional analyses considered relevant

Section C. Implementation

7. Assessment of factors relevant to the NHS and other parties

7.1. Patients eligible for treatment in England and Wales

The estimated annual numbers of patients eligible for alteplase treatment in England and Wales under the old 0-3 hour time-window, as well as the new 0-4.5 hour window are presented in Table 52 below. The details on how these estimates were derived are outlined in the following paragraphs.

Table 52: Number of patients eligible for alteplase treatment

	2012	2013	2014	2015	2016	2017
Total number of patients with first ever acute ischaemic stroke (AIS)	62,033	63,317	64,456	65,521	66,359	67,213
Estimated number of patients receiving alteplase treatment under the existing OTT time window of 0-3 hours *(assuming that 20% of all AIS patients receive alteplase treatment)*	12,407	12,663	12,891	13,104	13,272	13,443
Number of patients considered eligible for alteplase under the extended OTT time window licence of 0-4.5 hours *(assuming a 30.8% increase over the existing alteplase patient population)*	16,228	16,564	16,862	17,140	17,360	17,583
Additional patients on alteplase as a result of licence extension	**3,821**	**3,900**	**3,970**	**4,036**	**4,088**	**4,140**

It should be noted that the figures in Table 52 are based upon first ever stroke events. This may be a conservative assumption given that although alteplase is contraindicated in those with a prior stroke and concomitant diabetes and those who have had a stroke in the last 3 months, some patients with a prior AIS will receive the drug. It is noted that the NICE costing template for alteplase (0-3hrs) assumes a 33% uplift to the eligibility figures based on first ever stroke use to take into account recurrent strokes.

First, the total numbers of acute ischaemic stroke (AIS) patients in England and Wales were derived using population projections published by the Office of National Statistics (2011), along with age and gender-specific incidence rates of first-ever ischaemic stroke from the OXVASC study by Rothwell et al.

(2005). It was assumed that the incidence of ischaemic stroke remained constant over time. These estimations are presented in Table 53 for the years 2012 through 2017.

Table 53: Estimated numbers of first ever AIS patients in England and Wales

Parameter	2012	2013	2014	2015	2016	2017
18-34 years old						
Males[a]	6,591,645	6,683,677	6,751,558	6,801,725	6,830,936	6,857,529
Incidence of first-ever AIS[b,c]	-	-	-	-	-	-
Number of AIS patients[d]	-	-	-	-	-	-
Females	6,287,754	6,357,853	6,408,891	6,442,551	6,462,307	6,479,405
Incidence of first-ever AIS	-	-	-	-	-	-
Number of AIS patients	-	-	-	-	-	-
35-44 years old						
Males	3,749,513	3,682,145	3,637,962	3,623,127	3,614,273	3,609,909
Incidence of first-ever AIS	0.00035	0.00035	0.00035	0.00035	0.00035	0.00035
Number of AIS patients	1,312	1,289	1,273	1,268	1,265	1,263
Females	3,780,266	3,707,358	3,650,690	3,623,566	3,595,185	3,570,269
Incidence of first-ever AIS	0.00021	0.00021	0.00021	0.00021	0.00021	0.00021
Number of AIS patients	794	779	767	761	755	750
45-54 years old						
Males	3,878,146	3,926,004	3,965,399	3,987,832	3,997,384	3,988,492
Incidence of first-ever AIS	0.00055	0.00055	0.00055	0.00055	0.00055	0.00055
Number of AIS patients	2,133	2,159	2,181	2,193	2,199	2,194
Females	3,967,977	4,018,900	4,064,838	4,091,182	4,106,978	4,102,548
Incidence of first-ever AIS	0.00024	0.00024	0.00024	0.00024	0.00024	0.00024
Number of AIS patients	952	965	976	982	986	985
55-64 years old						
Males	3,142,347	3,123,964	3,135,205	3,164,816	3,220,783	3,287,787
Incidence of first-ever AIS	0.00187	0.00187	0.00187	0.00187	0.00187	0.00187
Number of AIS patients	5,876	5,842	5,863	5,918	6,023	6,148
Females	3,270,163	3,251,959	3,265,992	3,298,305	3,356,701	3,428,352
Incidence of first-ever AIS	0.00119	0.00119	0.00119	0.00119	0.00119	0.00119
Number of AIS patients	3,891	3,870	3,887	3,925	3,994	4,080
65-74 years old						
Males	2,454,165	2,548,504	2,615,273	2,671,034	2,723,819	2,761,298
Incidence of first-ever AIS	0.00649	0.00649	0.00649	0.00649	0.00649	0.00649
Number of AIS patients	15,928	16,540	16,973	17,335	17,678	17,921
Females	2,671,381	2,767,211	2,834,494	2,892,634	2,949,921	2,991,377
Incidence of first-ever AIS	0.00407	0.00407	0.00407	0.00407	0.00407	0.00407
Number of AIS patients	10,873	11,263	11,536	11,773	12,006	12,175
75-80 years old						
Males	963,524	984,627	1,007,205	1,027,485	1,033,169	1,046,723
Incidence of first-ever AIS[e]	0.00913	0.00913	0.00913	0.00913	0.00913	0.00913
Number of AIS patients	8,797	8,990	9,196	9,381	9,433	9,557

Females	1,168,711	1,183,511	1,202,098	1,220,400	1,224,101	1,236,370
Incidence of first-ever AIS	0.00982	0.00982	0.00982	0.00982	0.00982	0.00982
Number of AIS patients	11,477	11,622	11,805	11,984	12,021	12,141
Total number of first ever AIS patients	**62,033**	**63,317**	**64,456**	**65,521**	**66,359**	**67,213**

Notes:

a. All population estimates were obtained from the Office of National Statistics.

b. Age and sex-specific incidence of first-ever stroke as reported in the OXVASC Study (2005).

c. The OXVASC Study reported incidence for the <35 years age group. This incidence rate was applied to the population in the range of 18-34 years in line with the licensed indication.

d. The number of AIS is calculated by multiplying the population of the demographic by the annual incidence rate of first-ever ischaemic stroke for each respective age group.

e. The OXVASC Study reported incidence for the 75-84 years age group. This incidence rate was applied to the population in the range of 75-80 years in line with the licensed indication.

Key: AIS – Acute Ischaemic Stroke

The costing template accompanying NICE guidance TA 122 estimates that 20% of eligible patients will receive alteplase under the old licensed time window of 0-3 hours. The validity of this estimate was checked using the recent sales figures for Actilyse (alteplase) before it was applied to the total AIS patient population to approximate the number of AIS patients receiving alteplase treatment under the current licensed 0-3 hour time window.

The total sales for Actilyse (alteplase) in the UK in 2011 was £7,618,140. While Actilyse is also indicated for thrombolytic treatment in acute myocardial infarction as well as in acute massive pulmonary embolism with haemodynamic instability, it is assumed that the vast majority of Actilyse sales would be for its indication for treatment of AIS. Hence by assuming that all of the 2011 UK sales of Actilyse was for its AIS indication, the sales of Actilyse for AIS in England and Wales was calculated by multiplying the total UK sales figure by the proportion of the UK population that is from England or Wales (i.e. 88.7%; Office of National Statistics, 2011). Using an average drug acquisition cost of £480 per patient, it was calculated that 14,081 or 23.2% of all AIS patients in England and Wales (estimated at 60,711) had received alteplase treatment in 2011. Given that the preceding calculations had assumed that all of the Actilyse sales were for AIS, it can be seen that the estimate of 20% as provided by the costing template is relatively consistent with the sales results.

In order to estimate the number of alteplase recipients in the subsequent years, it was further assumed that the percentage of all AIS patients receiving alteplase treatment (i.e. 20%) would remain constant.

It should be pointed out that this figure of 20% is significantly higher than the 7% eligibility rate that was reported by two earlier studies from North America (Barber et al., 2001; Kleindorfer et al., 2004). This could be indicative of the improvement in the standard of alteplase delivery in the past decade that has resulted in shorter door-to-needle times and consequently an increase in the number of AIS patients being eligible for alteplase treatment within the 0-3 hour time-window. Furthermore, anecdotal accounts have revealed that some stroke units are already thrombolysing patients up to 4.5 hours from symptom onset following the publishing of positive results from the ECASS 3 trial in 2008 (Hacke et al., 2008) and the updated Guidelines for Stroke Management from the European Stroke Organisation in January 2009. Such practices could also have resulted in the higher than expected thrombolysis rates in AIS patients that were derived from the sales figures.

Finally, the increase in the numbers of AIS patients being treated with alteplase following the time-window extension were estimated using data from a recent study by Rudd et al. (2011). In this study of retrospective data from the National Sentinel Stroke 2008 Audit dataset, it was suggested that the percentage of thrombolysis-eligible acute stroke patients would increase from 14% to 16% following the extension of the time-window. However, it should be noted that this study had employed the time from onset of symptoms to hospital admission, and not the time from symptom onset to alteplase treatment, in order to access the eligibility of potential stroke patients for thrombolysis. It was reported by a SITS-MOST study (Wahlgren et al., 2007) that an average door-to-needle time (i.e. time from entering hospital to receiving alteplase treatment) of 68 minutes existed across all centres participating in the study. This suggests that the eligibility rate calculations by Rudd et al. should have been based on onset-of-symptoms-to-hospital-admission time-windows of 2 and 3.5 hours, instead of the 3- and 4.5-hour windows used. The adjustments made to the data from the Rudd study to include the door-to-needle times are detailed in Table 54 below.

Table 54: Estimation of the percentage increase in thrombolysis-eligible acute stroke patients as a result of the time-window extension. (Data adapted from Rudd et al., 2011)

Total Patient Population		11,262
Number of acute stroke patients admitted to the hospital within:	**2 hours**	2,118
	3 hours	2,596
	3.5 hours*	*(2,596+2,944)/2* = 2770
	4 hours	2,944
Number of acute stroke patients admitted within 3 hours that were eligible for thrombolysis *(after being subjected to other eligibility criteria, eg: age, occurrence of infarction)*		1,605
% of patients arriving within 3 hours that were eligible for thrombolysis		*1,605/2,596* = 61.8%
Number of acute stroke patients arriving within 2 hours that were eligible for thrombolysis[#]		*2,118 x 61.8%* = 1,309
Number of acute stroke patients arriving within 3.5 hours that were eligible for thrombolysis[#]		*2,770 x 61.8%* = 1,713
% of acute stroke patients eligible for thrombolysis using 0-3h OTT time-window		*1,309/11,262* = **11.6%**
% of acute stroke patients eligible for thrombolysis using 0-4.5h OTT time-window		*1,713/11,262* = **15.2%**
% increase in eligible patients after OTT time-window extension to 4.5h		*(15.2-11.6)/11.6* = **30.8%**

* calculated as the mid-point of the 3-hour and 4-hour cohorts
# assuming that 61.8% of admitted patients are eligible for thrombolysis

As shown from the calculations outlined in Table 54, the extension of the OTT time-window to 4.5 hours was estimated to result in a 30.8% increase in the current number of thrombolysis-eligible patients. This percentage increase was applied to the estimated alteplase-receiving AIS patient population under the existing licence to derive the number of thrombolysis-eligible AIS patients under the extended licence.

7.2. Assumptions made about current treatment options and uptake of technologies.

As mentioned in the response to 7.1, there have been anecdotal evidence that some stroke units are already treating acute stroke patients with alteplase up

to 4.5 hours from symptom onset. Consequently it can be expected that the budget impact of the licence extension for alteplase calculated in this document will be an overestimate.

In addition, the extension of the current 0-3 hour window to 0-4.5 hours was assumed to result in a 30.8% increase in the number of eligible patients as calculated from the data from the Rudd et al. (2011) study.

It is further assumed that 100% of all AIS patients who meet the strict eligibility criteria will receive alteplase treatment.

7.3. Assumptions made about market share.

No assumptions were made with regard to market share as there are currently no alternative treatments to consider (although there are downstream resource savings associated with improved stroke outcomes).

7.4. Other significant costs associated with treatment

The administration costs associated with alteplase treatment were included with the acquisition costs of the drug. These are outlined in the response to question 7.5 below.

Another additional cost that was considered was that of a CT scan (£110) to determine the cause of neurological deterioration when a patient experiences an sICH. This was multiplied by the base case incremental risk of sICH in the alteplase group (2.14%) to give the incremental cost of the additional CT scan of £2.36 per patient.

7.5. Unit costs assumptions.

The unit cost of alteplase treatment comprised the direct cost of alteplase as well as the administration cost associated with the additional staffing requirements needed to administer the treatment.

Assuming a mean-body weight of 76kg for patients from the 3-4.5h cohort of the SITS-MOST Trial [Wahlgren et al., 2008], this corresponds to an average drug dosage of 68.4mg. Consequently, the incremental acquisition drug cost (including wastage) was calculated to be £480 per patient, associated with the cost of one 50mg-vial (£300) and one 20mg-vial (£180) of alteplase.

The additional staffing costs associated with the administration of alteplase treatment were based upon the resource use figures detailed by Sandercock et al. (2002). These figures were updated using PSSRU 2011 unit costs and inflated to 2012/13 levels using the Pay & Price index found in the PSSRU 2011. The derivation of these costs is detailed in Table 55.

Table 55: Extra staffing resources required to administer alteplase as outlined in Sandercock et al. (2002)

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 utilized 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)

Accordingly, the total incremental cost associated with alteplase treatment is £480 *(drug acquisition cost)* + £1,316.29 *(drug administration cost)* + £2.36 *(cost of additional CT scan associated with sICH)* = £1,798.65 per patient.

7.6. Estimates of resource savings.

As alteplase is given in addition to, rather than instead of current treatment, it is assumed that there are no immediate resource savings.

7.7. Estimated annual budget impact for the NHS in England and Wales.

The estimated annual budget impact for the NHS in England and Wales would be the costs associated with the additional patients being treated with alteplase as a result of the licence extension. These figures are detailed in Table 56.

Table 56: Estimated budget impact of extended alteplase treatment for 2012 through 2017

	2012	2013	2014	2015	2016	2017
Additional patients on alteplase as a result of licence extension	3,821	3,900	3,970	4,036	4,088	4,140
Estimated budget impact *(drug acquisition costs = £480 per patient)*	£1,834,190	£1,872,152	£1,905,827	£1,937,317	£1,962,098	£1,987,350
Estimated budget impact *(total alteplase treatment cost = £480+£1,316.29+£2.36 per patient)*	**£6,873,053**	**£7,015,306**	**£7,141,490**	**£7,259,489**	**£7,352,348**	**£7,446,974**

It should be noted that the figures in Table 56 are based upon first ever stroke events. This may be a conservative assumption given that although alteplase

is contraindicated in those with a prior stroke and concomitant diabetes and those who have had a stroke in the last 3 months, some patients witha prior AIS will receive the drug. It is noted that the NICE costing template for alteplase (0-3hrs) assumes a 33% uplift to the eligibility figures based on first ever stroke use to take into account recurrent strokes.

7.8. Other opportunities for resource savings or redirection of resources that it has not been possible to quantify.

There are significant resource savings in the long-term management of AIS patients due to the lower relative risks of death and dependency in patients receiving alteplase treatment as compared to standard treatment. These results were presented in Section 6.7 and showed that the cost savings over the lifetime of an alteplase-treated patient are likely to more than offset the initial costs of the treatment.

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Please use a recognised referencing style, such as Harvard or Vancouver.

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9. Appendices

9.1. Appendix 1

9.1.1. SPC

The product SPC can be viewed by following the link below:

http://www.medicines.org.uk/EMC/medicine/308/SPC/Actilyse/