

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL (STA)

**SPECIFICATION FOR MANUFACTURER/SPONSOR SUBMISSION OF
EVIDENCE**

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Instructions for manufacturers and sponsors

This specification for submission of evidence to the National Institute of Health and Clinical Excellence (NICE, or the Institute) as part of the single technology appraisal (STA) process is designed to indicate to manufacturers and sponsors the information required by the Institute and the format in which it should be presented. Use of the specification and completion of Appendices 9.1 to 9.3 are mandatory, and the format should be adhered to wherever possible. Reasons for not adhering to this format must be clearly stated. Sections that are not considered to be relevant should be marked 'N/A' and a justification given for this response. The specification should be completed with reference to the NICE document 'Guide to the methods of technology appraisal' (www.nice.org.uk), particularly with regard to the 'reference case'.

If a submission is based on preliminary regulatory recommendations, the manufacturer or sponsor must advise the Institute immediately of any variation between the preliminary and final approval.

A submission should be as succinct and informative as possible. It is expected that the main body of the submission will not usually exceed 75 pages. The submission should be sent to the Institute electronically in Word or a compatible format, and not as a PDF file. A list of all references must be provided, together with paper or electronic copies.

For model-based economic evaluations, a transparent and fully executable electronic copy of the model should be submitted. The Evidence Review Group should have full access to the programming code, and running of the model should be unhindered. Please ensure that the submitted versions of the model program and the content of the submission match. The model should be constructed using standard software, such as Excel or DATA. If non-standard software is required for the construction of the model, please discuss this with the Institute at the earliest opportunity in advance of submission.

The submission must be a stand-alone document. Additional appendices may only be used for supplementary explanatory information that exceeds the level of detail requested, but which is considered to be relevant to the submission.

Any additional appendices should be clearly referenced in the body of the submission and should not be used to present core information that has been requested in the specification. For example, it is not acceptable to attach a key study as an appendix and to complete the efficacy section with 'see appendix X'. Clinical trial reports and protocols should not be submitted, but must be made available on request.

Trials should be identified by the first author or trial ID rather than relying on numerical referencing alone (for example, 'Trial 123/Jones et al. ¹²⁶ found ABC' rather than 'One trial ¹²⁶ found ABC').

Manufacturers and sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to the Institute at the time of submission. There will be no subsequent opportunity to submit information unless it has been specifically requested by the Institute.

When making a submission, manufacturers and sponsors should check that:

- an electronic copy of the submission has been given to the Institute with all confidential information highlighted and underlined
- a fully executable electronic copy of the economic model has been submitted
- all key references have been made available (electronic or hard copy versions as appropriate)
- the checklist of confidential information has been completed and submitted.

Disclosure of information

To ensure that the appraisal process is as transparent as possible, the Institute considers it highly desirable that evidence pivotal to the Appraisal Committee's decisions should be publicly available. The Institute recognises, however, that because the appraisal is being undertaken close to the time of regulatory decisions, the status of information may change during the STA process. However, at the point of issuing the Final Appraisal Determination (FAD) or Appraisal Consultation Document (ACD) to consultees and

commentators, all the evidence seen by the Committee should ideally be available to all consultees and commentators.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence'). As a minimum, a structured abstract will need to be made available for public disclosure, using a recognised format such as that provided by the CONSORT statement (www.consort-statement.org).

Where data are commercial in confidence or academic in confidence, it is the manufacturer's or sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The NICE checklist of confidential information should be completed. If no checklist of confidential information is provided, the Institute will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

The manufacturer or sponsor will be requested to supply a second 'stripped' version of the submission from which any information that is to remain confidential has been removed. The confidential information should be 'blacked out' from this version, taking care to retain the original formatting as far as possible so that it is clear how much data have been removed and where they have been removed from.

The Institute will request the stripped version of the submission at least 2 weeks before the anticipated date of issue of the FAD or ACD to consultees and commentators. The stripped version will be issued to consultees and commentators along with the ACD or FAD, and made available on the Institute's website 5 days later.

It is the responsibility of the manufacturer or sponsor to ensure that the stripped version of the submission does not contain any confidential

information. **No further amendments or corrections may be made to the submission at this stage.** The NICE checklist of confidential information should be updated and submitted at the same time. The Institute will ask manufacturers and sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for the Institute to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the Evidence Review Group and the Appraisal Committee. Confidential information may be distributed to consultees with the permission of the manufacturer or sponsor. The Institute will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by the Institute that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges the Institute to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to the Institute. Information that is designated as 'commercial in confidence' may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of any information previously deemed as commercial in confidence before making any decision on disclosure.

For further information, please see the NICE website (www.nice.org.uk).

Section A

Manufacturers and sponsors will be requested to submit section A in advance of the full submission (for details on timelines, see the ‘Guide to the single technology appraisal process’ – www.nice.org.uk). A (draft) Summary of Product Characteristics (SPC) for pharmaceuticals and a (draft) technical manual for devices should be provided (see appendix 1, section 9.1).

1 Description of technology under assessment

1.1 Give the brand name, approved name and, where appropriate, therapeutic class. For devices please provide details of any different versions of the same device.

Brand name: Actilyse

Approved/Generic name: alteplase

Therapeutic class: Thrombolytic agents

ATC code B 01 A D 02

1.2 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, please give the date on which authorisation was received. If not, please state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

The Actilyse indication for the fibrinolytic treatment of acute ischaemic stroke gained a UK licence on 30th September 2002.

1.3 What are the (anticipated) indication(s) in the UK? For devices, please provide the (anticipated) CE marking, including the indication for use.

- Thrombolytic treatment in acute myocardial infarction

- Thrombolytic treatment in acute massive pulmonary embolism with haemodynamic instability
- Fibrinolytic treatment of acute ischaemic stroke

(A new product strength of Actilyse 2 mg is planned for regulatory submission. It is intended that the new strength of Actilyse will be indicated for the restoration of function to central vascular access devices)

1.4 To what extent is the technology currently being used in the NHS for the proposed indication? Include details of use in ongoing clinical trials. If the technology has not been launched, please supply the anticipated date of availability in the UK.

The national audit office (1) estimates that less than one percent of stroke patients are receiving thrombolysis annually in England (1). Up until 2005, 240 ischemic stroke patients meeting the licence requirements have been treated with alteplase in the UK, as recorded in the Safe Implementation of thrombolysis in Stroke - Monitoring Study (SITS-MOST).

The SITS-MOST study of outcomes following treatment with alteplase in acute stroke within three hours of onset is closed to recruitment after agreement with EMEA. The outstanding data are being gathered in to permit the writing of the final report which is expected in early 2007. The database of SITS-ISTR, the parent of SITS-MOST, will continue to gather worldwide outcomes data as an academic study allowing monitoring of performance at centre and national levels. Participation is voluntary. IST-3 is an outcomes trial of alteplase in patients considered unsuitable for treatment under present labelling and is being performed under the auspices of the Western General Hospital, Edinburgh – Prof. Peter Sandercock. ECASS 3 is a placebo-controlled randomized clinical trial of alteplase in acute stroke occurring 3 - 4.5 hours after stroke onset. This study is sponsored by Boehringer Ingelheim and forms part

of the present conditional approval of Actilyse within the EU and thus a commitment for the marketing authorisation holder prior to full approval.

1.5 Does the technology have regulatory approval outside the UK? If so, please provide details.

The following countries outside the UK have licensed alteplase for the fibrinolytic treatment of acute ischaemic stroke.

Albania, Argentina, Australia, Austria, Bahrain, Barbados, Belarus, Belgium, Bermuda, Botswana, Brazil, Bulgaria, Canada, Chile, China, Colombia, Croatia, Cyprus, Czech Republic, Denmark, Egypt, Estonia, Finland, France, Georgia, Germany, Greece, Hong Kong, Hungary, Iceland, India, Indonesia,

Iraq, Ireland, Israel, Italy, Jamaica, Jordan, Kazakhstan, Kenya, Korea, Kuwait, Latvia, Lebanon, Libya, Lithuania, Luxembourg, Macedonia the former Yugoslav Republic of, Madagascar, Malaysia, Malta, Mauritius, Mexico, Moldavia, Namibia, Netherlands, New Zealand, Norway, Oman, Paraguay, Peru, Philippines, Poland, Portugal, Qatar, Romania, Russian Federation, Saudi Arabia, Serbia and Montenegro, Singapore, Slovakia, South Africa, Spain, Sweden, Switzerland, Taiwan, Thailand, Tunisia, Turkey, Ukraine, United Arab Emirates, Uruguay, Venezuela, Yemen, USA.

1.6 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

Yes. The Scottish Medicines Consortium (SMC) issued advice on alteplase for the treatment of acute ischaemic stroke on March 8th 2004. The advice was as follows:

“The Scottish Medicines Consortium (SMC) has completed its assessment on the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) that alteplase is accepted

for restricted use within NHS Scotland for the treatment of acute ischaemic stroke.

Alteplase is licensed in the UK for the early treatment of acute ischaemic stroke, but there are potentially fatal risks incurred in using it. The use of alteplase is therefore confined to specialist centres with adequate resources and appropriate expertise.”

As of 2nd October 2006 we are not aware of any other health technology appraisals being undertaken for alteplase in the treatment of acute ischaemic stroke

1.7 For pharmaceuticals, what formulation(s) (for example, ampoule, vial, sustained-release tablet, strength(s) and pack size(s) will be available?

The following formulations and pack sizes of alteplase are available:

- 10 mg; 1 vial with 467 mg powder for solution for infusion ; 1 vial with 10 ml of water for injections
- 20 mg; 1 vial with 933 mg powder for solution for infusion; 1 vial with 20 ml of water for injections ; 1 transfer cannula
- 50 mg; 1 vial with 2333 mg powder for solution for infusion ; 1 vial with 50 ml of water for injections ; 1 transfer cannula

1.8 What is the proposed course of treatment? For pharmaceuticals, list the dose, dosing frequency, length of course and anticipated frequency of repeat courses of treatment.

The recommended dose is 0.9 mg alteplase/kg body weight (maximum of 90 mg) infused intravenously over 60 minutes with 10% of the total dose administered as an initial intravenous bolus. Treatment with Actilyse must be started within 3 hours of the onset of symptoms.

1.9 What is the acquisition cost of the technology (excluding VAT)? For devices, provide the list price and average selling price. If the unit

cost of the technology is not yet known, please provide details of the anticipated unit cost, including the range of possible unit costs.

The cost of alteplase, as reported in November 2006 in the Monthly Index of Medical Specialities (MIMS) are as follows¹:

10 mg pack: £135.00

20 mg pack £180.00

50mg pack: £300.00

1.10 What is the setting for the use of the technology?

The setting for the use of the alteplase is secondary care. Treatment must be performed by a physician specialised in neurological care.

1.11 For patients being treated with this technology, are there any other aspects that need to be taken into account? For example, are there additional tests or investigations needed for selection, or particular administration requirements, or is there a need for monitoring of patients over and above usual clinical practice for this condition? What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

Outcomes trials have already shown that specialist stroke units provide better results in terms of independent and partial recovery following acute ischaemic stroke compared with general medical care. Assuming that such is the accepted norm within Britain, including CT scanning to determine the nature of the stroke and therefore management of the patient, the only additional monitoring and therapeutic care that would arise would be following symptomatic intracranial haemorrhage (SICH) with neurological deterioration following the use of and attributable to alteplase. All other therapies, rehabilitation and management of risk factors, both acute and chronic, would be the same as without alteplase.

2 Statement of the decision problem

In this section the manufacturer or sponsor should specify the decision problem that the submission addresses. The decision problem should be derived from the final scope issued by NICE and should state the key parameters that the information in the Evidence Submission will address.

	Final scope issued by NICE	Decision problem addressed in the submission
Population	Adult patients with acute ischaemic stroke within 3 hours of the onset of stroke symptoms	As defined in the final scope issued by NICE
Intervention	Alteplase by intravenous infusion	As defined in the final scope issued by NICE
Comparator(s)	Standard medical and supportive management that does not include thrombolytics	As defined in the final scope issued by NICE
Outcomes	<p>The outcome measures to be considered include:</p> <ul style="list-style-type: none"> Disability Proportion of patients making good functional recovery by 3 to 6 months after treatment Neurological deficit Mental health, including anxiety & depression Survival Length of hospital stay Adverse effects of treatment, including bleeding events Health-related quality of life 	<p>If the evidence allows, the submission will assess the outcomes defined in the final scope, that is disability, proportion of patients making good functional recovery by 3 to 6 months after treatment, neurological deficit, survival, length of hospital stay, adverse effects of treatment and, health-related quality of life.</p> <p>Dementia is a long term prospect in patients suffering from recurrent stroke.</p> <p>Treatment with alteplase may be expected to reduce this by improving recovery outcome but clinical trials have not</p>

		<p>been performed to establish this. It is known that mental health and mood is poor in patients experiencing poor or dependent recovery from stroke. Improved mental health and mood may be expected from the successful use of alteplase in improving recovery especially independent recovery; however, trials have not been performed to establish this. It will therefore not be possible to assess these outcomes in this submission</p>
<p>Special considerations and other issues</p>	<p>If the evidence allows, the appraisal will attempt to identify criteria for selecting patients for whom alteplase would be particularly appropriate. Groups within this population that could be considered separately include the elderly and patients with diabetes mellitus.</p>	<p>If the evidence allows, the submission will assess the appropriateness of alteplase in the elderly (65 and 80years old) and those with diabetes mellitus</p>

Section B

3 Executive summary

Please provide an executive summary that summarises the key sections of the submission. All statements should be directly relevant to the decision problem, be evidence-based and clearly reference the relevant section of the submission. The summary should cover the following items.

- **The UK approved name, brand name, marketing status and principal pharmacological action of the proposed drug.**
- **The formulation(s), strength(s), pack size(s), maximum quantity(ies), anticipated frequency of any repeat courses of treatment and acquisition cost (see section 1.9).price.**
- **The indication(s) and any restriction(s).**
- **The recommended course of treatment.**
- **The main comparator(s).**
- **Whether the key clinical evidence in the submission comes from head to head randomised trials (RCTs), from an indirect comparison of two sets of randomised trials involving a common comparator (for example, placebo or other active therapy), or from non-randomised studies.**
- **The main clinical results of the randomised trials and any relevant non RCTs.**
- **In relation to the economic evaluation, details of:**
 - **the type of economic evaluation and justification for the approach used**
 - **the pivotal assumptions underlying the model/analysis**
 - **the incremental ratios from the evaluation.**

Key Findings:

- 1. Alteplase is indicated for the thrombolytic treatment of acute ischaemic stroke in patients (over 18 years but under 80 years) with a diagnosis of acute ischaemic stroke within 3 hours of onset of the stroke symptoms and after prior exclusion of intracranial haemorrhage.*
- 2. Thrombolysis with alteplase in acute ischaemic stroke has been tested in six randomised, placebo-controlled, phase III clinical trials in a total of 465 patients and in a number of open-label observational cohort studies (with over 6000 patients). These provide a positive evaluation of treatment with alteplase.*
- 3. The randomised control trials (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.*
- 4. The observational studies show that with strict adherence to the prescribing information for alteplase, outcomes in terms of proportion benefiting, symptomatic intracranial haemorrhage and death are at least as good as those reported in the RCTs and may even be superior. In addition, two 12 month studies have demonstrated that the shorter term benefit of alteplase appears to be maintained for up to 12 months.*
- 5. The economic evaluation robustly demonstrates the cost effectiveness of alteplase when considered in addition to standard medical and supportive management within a specialist stroke unit. The lifetime health benefits accruing to the patient cohort are estimated to be 28 QALYs per 100 patients. This equates to 16 life years gained and 144 independent life years gained per 100 patients. The probabilistic sensitivity analysis demonstrated that at a threshold of £8,000 per QALY gained, the probability that alteplase is cost –effective is 0.99.*

Alteplase is indicated for the thrombolytic treatment of acute myocardial infarction, the thrombolytic treatment of acute massive pulmonary embolism with haemodynamic instability and thrombolytic treatment of acute ischaemic stroke. The last indication gained UK marketing approval on 30th September 2002

Alteplase 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 myocardial infarction and massive pulmonary embolus is 100 mg and 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 £300¹.

Alteplase is contraindicated in the treatment of acute ischaemic stroke where symptoms of ischemic attack beginning more than 3 hours prior to initiation of treatment 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

Thrombolysis with alteplase in acute ischaemic stroke has been tested 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 largest of the observational studies, the SITS-MOST register is now in the process of data analysis and a final report on >6000 patients treated is expected in early 2007. Interim results from this register have been presented in this submission. As there are no other thrombolytic treatments licensed for use in acute ischaemic stroke patients in the UK, placebo plus usual care is the comparator used in the RCT. Observational studies have not been randomised or controlled but are capable of comparison to outcomes with the RCTs.

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. Further support for the net benefit of alteplase over risk comes from the larger scale observational cohort studies. These show that with strict adherence to the prescribing information for alteplase, outcomes in terms of proportion benefiting, SICH and death are at least as good as those coming from RCTs and may even be superior. In addition two 12 month studies have demonstrated that the shorter term benefit of alteplase appears to be maintained for up to 12 months.

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)². 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.

In particular, use has been made of the odds ratio for the 0-3 hour treatment sub-group contained in the Cochrane review³ and costs from a UK stroke burden of disease study in order to better reflect the decision problem and the NICE reference case.

This evaluation robustly demonstrates the cost effectiveness of alteplase when considered in addition to standard medical and supportive management within a specialist stroke unit. The lifetime health benefits accruing to the patient cohort are estimated to be 28 QALYs per 100 patients. This equates to 16 life years gained and 144 independent life years gained per 100 patients. The probabilistic sensitivity analysis demonstrated that at a threshold of £8,000 per QALY gained, the probability that alteplase is cost-effective is 0.99.

These sensitivity analysis also showed that even with significant improvements in standard care for the treatment and management of stroke, alteplase would still be cost-saving when considering both NHS and social service costs, and is cost-effective (ICER of £2,670 per QALY gained) when only acute costs are considered.

Shortening the modelled time horizon to 12 months, does not alter the conclusion of the analysis. The results demonstrate that alteplase, is cost-effective over a 12 month period, with an ICER of £14,026 per QALY gained.

4 Context

In this background section the manufacturer or sponsor should summarise and contextualise the evidence relating to the decision problem. The information provided will not be formally reviewed by the Evidence Review Group.

4.1 Please provide a brief overview of the disease/condition for which the technology is being used. Provide details of the treatment pathway and current treatment options at each stage.

Approximately 80% of acute strokes are ischaemic in cause, the remainder being primary 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.

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. CT scanning of the head has become the norm so as to distinguish ischaemic from haemorrhagic stroke, both for management of the acute illness and so as to determine future pharmacological interventions i.e. secondary prevention of stroke.

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 3 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. No other medications are needed at this stage.

4.2 What was the rationale for the development of the new 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.

The principle has been applied over many years to the treatment of acute myocardial infarction (also caused by thrombosis within the coronary arterial system). Similarly intravenous alteplase has been used in the treatment of massive pulmonary embolism with haemodynamic instability. In both situations thrombolysis permits the reperfusion of ischaemic tissue. Thrombolytic treatment may lead to uncontrolled haemorrhage elsewhere in the body, uncommonly intracranial haemorrhage (ICH).

In hypothesising that lysis of a thrombo-embolic clot within the cerebral circulation would allow reperfusion of the brain tissue that was ischaemic but still viable, it was evident that ICH may be a more frequent and more serious complication of treatment with a thrombolytic

agent. The overwhelming question was “would there be evidence of benefit from reperfusion of the ischaemic brain that was greater than the risk of unwanted haemorrhage caused by the drug?”

4.3 What is the principal mechanism of action of the technology?

As discussed above, alteplase is a serine protease, a glycoprotein, that by activating plasminogen to plasmin initiates the lysis of thrombus within the circulation.

4.4 What is the suggested place for this technology with respect to treatments currently available for managing the disease/condition?

Alteplase is the only drug which is licensed for the thrombolytic treatment of AIS. It is indicated in selected patients who can be treated within 3 hours of the onset of stroke symptoms. It is not suitable for unselected AIS patients e.g. beyond the 3 hour time window, severe strokes (>25 points on the NIH Stroke Scale, in uncontrolled diabetics and in severe hypertension [see SPC]).

Patients with early evidence of cerebral infarction (hypoattenuation) on CT scanning and whose infarct exceeds one third of the brain territory that is supplied by the middle cerebral artery should not be treated. It is a treatment to be administered under the guidance of experienced stroke and neuro-imaging specialists.

4.5 Describe any issues relating to current clinical practice, including any variations or uncertainty about best 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. Cardiologists have the advantage that the acutely ischaemic myocardium is more durable than the acutely ischaemic brain and have a 0-6 hour time window.

Early treatment in a 0-3 hour window will mean remarkable 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.

4.6 Provide details of any relevant guidelines or protocols.

The only protocol available for AIS patients presenting within three hours of stroke onset is strict adherence to the labelling (SPC) for Actilyse ® brand of alteplase.

Guidelines have been published as follows:

- Guidelines for the early management of patients with ischemic stroke (2005) ⁴
- Prophylaxis and treatment – information for doctors in hospitals and practice – update 2003/2004⁵

- Recommendations for stroke management (2003)⁶
- Guidelines for the early management of patients with ischemic stroke (2003)⁷
- Use of intravenous tPA for the management of acute stroke in the emergency department (2002)⁸
- Thrombolysis for acute ischemic stroke (2002)⁹
- Thrombolysis for acute ischemic stroke (2001)¹⁰
- Antithrombotic and thrombolytic therapy for ischemic stroke (2001)¹¹
- Canadian guidelines for intravenous thrombolytic treatment in acute stroke (1998)¹²

5 Clinical evidence

Manufacturers and sponsors are required to submit a systematic review of the clinical evidence that relates directly to the decision problem. Systematic and explicit methods should be used to identify, select and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review. Where appropriate, statistical methods (meta-analysis) should be used to analyse and summarise the results of the included studies. The systematic review should be presented in accordance with the QUORUM statement checklist (www.consort-statement.org/QUORUM.pdf).

The systematic review is not required to be exhaustive (that is, it is not necessary to include all evidence relating to the use of the technology), but justification needs to be provided for the exclusion of any evidence. Where manufacturers have identified a study but do not have access to the level of detail required, this should be indicated.

The Institute has a strong preference for evidence from 'head-to-head' randomised controlled trials (RCTs) that directly compare the technology and the appropriate comparator(s). Wherever such evidence is available, and includes relevant outcome evidence, this is preferred over evidence obtained from other study designs. Where no head-to-head RCTs are available, consideration will be given to indirect comparisons, subject to careful and fully described analysis and interpretation.

In the absence of valid RCT evidence, evidence from other study designs will be considered, with reference to the inherent limitation inferred by the study design. The Institute also recognises that RCT data are often limited to selected populations, short time spans and selected comparator treatments. Therefore good-quality observational studies may be submitted to supplement RCT data.

5.1 Identification of studies

Describe the strategies used to retrieve relevant clinical data both from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided.

Exact details of the search strategy used should be provided in appendix 2, section 9.2.

The databases searched for relevant clinical data were Medline-R and Medline-R in process, Embase, EBM reviews, Cochrane database of systematic reviews. For company specific data and other data sources the BILIT (Boehringer Ingelheim product literature) database was searched. Sources screened for this database include international journals, books, conference proceedings, reports and theses. For completeness of the database, external files from Medline and Embase are evaluated. Boehringer Ingelheim Operating Units contribute to the comprehensiveness by supplying copies from national journals. The turnaround time from publication to database input is generally about two weeks.

Since this is a single technology appraisal only specific studies in which the use of Actilyse (Alteplase, tPA) in acute ischaemic stroke or stroke was evaluated were searched for. These could include RCTs where the patients number greater than 50, reviews, and editorials.

The use of Actilyse in acute ischaemic stroke is dependent on availability and provision/delivery of the technology. Therefore studies investigating/evaluating service delivery/provision of the technology were also identified for review.

Since this appraisal related to the UK provision of thrombolysis for acute ischaemic stroke any study undertaken in the UK in relation to the technology was also included for review.

5.2 Study selection

5.2.1 Complete list of RCTs

Provide a list of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the assessors.

Where data from a single study have been drawn from more than one source (for example, a poster and a published report) and/or where trials are linked (for example, an open-label extension to an RCT), this should be made clear.

Since alteplase (Actilyse ®) is the only thrombolytic agent approved for the treatment of acute ischaemic stroke (AIS) all RCTs performed during the development of the indication have been placebo-controlled. The complete list is as follows:

- (i) The National Institute of Neurological Disorders and Stroke (NINDS) trials no. 1 and 2 reported by the NINDS rt-PA Stroke Study Group ¹.
- (ii) The European Cooperative Acute Stroke Study (ECASS) reported by the ECASS Study Group².
- (iii) ECASS II reported by the Second European Australasian Acute Stroke Study Investigators³.
- (iv) The ATLANTIS Study reported by the ATLANTIS Study Investigators ^{4,5}. This trial is also in 2 parts following modification of the initial protocol (A&B).

Other relevant analyses of the data have since been published as listed below:

Effects of Tissue Plasminogen Activator for Acute Ischemic Stroke at One Year. Authors Kwiatkowski TG et al. N Engl J Med 1999;340:1781-7. ⁶

Early Stroke Treatment associated with better outcome. The NINDS rt-PA Stroke Study. Authors: Marler J et al. Neurology 2000;55:1649 - 1655.⁷

Finding the most powerful measures of the effectiveness of tissue plasminogen activator in the NINDS t-PA acute stroke trial. Authors: Broderick JP et al. Stroke 2000;31:2335-2341.⁸

Atlantis Trial: Results for Patients treated within 3 hours of stroke onset. Authors: Albers GW et al. Stroke 2002;33:493-496.⁹

Better outcome with early stroke treatment: A pooled analysis of ATLANTIS, ECASS and NINDS rt-PA stroke trials. Authors: Marler JR and Hacke W for the Study Group Investigators.¹⁰

These additional five analyses are considered relevant to the STA insofar as they refine and improve the interpretation and understanding of the data from the original RCTs. (See also below, Section 5.5)

One very small pilot RCT of alteplase versus placebo has been excluded. This was reported by Haley et al¹¹ in 1993. This was a feasibility study in 27 patients with AIS, to establish whether patients could be studied within a 0 – 3 hour onset to treatment time (OTT). A total of 20 patients were randomised to receive alteplase (10) and placebo (10) were treated within 0 – 90 minutes and 7 (4 alteplase, 3 placebo) within 91 – 180 minutes. Alteplase was given as 0.85mg/kg, i.e. less than the dose ultimately used in most of the major trials. The primary endpoint was the proportions of patients improving by ≥ 4 points on the NIHSS scale at 24 hours. This endpoint was shown later in the NINDS trial to be insufficient for the demonstration of efficacy. Four patients were known to be alive but lost to follow-up and 4 patients were dead, at 3 months. From the outcomes observed the authors concluded that efficacy had not been established but that a large-scale trial was feasible.

5.2.2 Inclusion and exclusion criteria

State the inclusion and exclusion criteria that were used to identify the studies detailed in the list of relevant RCTs. If additional inclusion criteria were applied to select studies that have been included in the systematic review, these need to be listed separately.

Since alteplase given intravenously is the only thrombolytic agent to have received a Marketing Authorisation in Great Britain, all randomised controlled trials performed with alteplase have been included. Other RCTs with other agents (unapproved for Marketing) are referred to only if they provide information that may be of relevance to the use of alteplase. The Cochrane Collaboration review "Thrombolysis for acute ischaemic stroke" ¹² by Wardlaw and colleagues is included with respect to the topic of thrombolysis in acute stroke as a whole. The meta-analysis of the alteplase RCT published by the ATLANTIS, ECASS and NINDS investigators is also included ¹⁰. Studies of alteplase given intra arterially have also not been included, being an unapproved route of administration.

5.2.3 List of relevant RCTs

List all RCTs that compare the technology directly with the appropriate comparator(s) with reference to the specification of the decision problem. If there are none, state this.

Where studies have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. A flow diagram of the numbers of studies included and excluded at each stage should be provided at the end of section 5.2, as per the QUORUM statement flow diagram (www.consort-statement.org/QUORUM.pdf). The total number of studies in the QUORUM statement should equal the total number of studies listed in section 5.2.1.

Where data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or where trials are linked (for example, an open-label extension to an RCT), this should be made clear.

There are no relevant RCTs that compare the technology as licenced directly with other thrombolytic agents. No other stroke treatment/prevention therapies would be relevant comparators.

5.2.4 List of relevant non-randomised controlled trials

Provide details of any non-randomised controlled trials that are considered relevant to the decision problem. Provide justification for their inclusion.

These are listed as follows :

(i) Thrombolysis for acute ischemic stroke: results of the Canadian Alteplase for Stroke Effectiveness Study (CASES) CMAJ 2005;172 (10):1307-1312 ¹³

(ii) Intravenous Tissue-Type Plasminogen Activator for the treatment of Acute Stroke. The STARS study. JAMA 2000;283:1145-1151 ¹⁴

(iii) Early intravenous thrombolysis for acute ischemic stroke in a community-based approach. Stroke 1998;29:1544-1549 ¹⁵

(iv) Comparison of tissue plasminogen activator administration and management between Telestroke network Hospitals and Academic Stroke Centres (TEMPIS). Stroke 2006;37:1822-1827 ¹⁶

(v) Intravenous Thrombolysis for Acute Ischemic Stroke: preliminary Experience with Recombinant Tissue Plasminogen Activator in the UK. Cerebrovascular Dis 2005;20:438-442 ¹⁷

(vi) Safe implementation of treatment for stroke - monitoring study (SITS-MOST) Unpublished reports: Data on file Boehringer Ingelheim 2005/2006 ^{18,20}

There is a substantial volume of reported observational experience with alteplase in AIS from centres around the world. Those that have been selected here were mandated by regulatory authorities, e.g. Canadian, FDA and CPMP (EMEA) following the granting of licences for the marketing of alteplase in the countries/region and were monitored by marketing authorisation holders. They also represent the largest databases of alteplase treatment outcomes in the world and provide important perspectives on the implementation of thrombolysis in AIS with alteplase in medical practice. All the studies listed provide information that is important for the safe and

successful implementation of this treatment which brings both risk and benefit. In addition, all studies are analysed in such a way as to be able to compare the results with those of RCTs and particularly the NINDS trial.

Thus, the Canadian CASES study documented outcomes following the use of alteplase in more than 1100 patients across Canada in 60 hospitals. The authors concluded that their results in terms of good to excellent recovery gave credence to the generalisability of the NINDS results and the pooled results from meta-analysis. Their rate of symptomatic intracranial haemorrhage (SICH) was lower than in RCTs but they note the possibility of under-reporting and selection bias. Canada's healthcare system allows naturally the development of specialist stroke centres, important when there is also a relationship between protocol (labelling) violation which is noted as an important predictor of SICH. They recognise that their onset time to treatment (OTT) (2.5hrs) is well over the target set by NINDS of 1 hour and the low proportion of patients treated (<2%). Their data argue for more widespread infrastructural change of stroke facilities so that physicians deliver appropriate treatment appropriately.

The STARS study, mandated by the FDA, was performed in the same way in the USA and although smaller than CASES is important not only because the clinicians were able to achieve favourable outcomes and low rates of SICH in medical practice, but because concurrently in the same issue of JAMA a controversial report was published from the Cleveland area of the USA in which of 3948 patients admitted with AIS only 70 received alteplase despite 674 being admitted within 3 hrs of stroke onset and there was a 16% incidence of SICH. The in-hospital mortality for IV alteplase treated patients was significantly higher than for matched, untreated patients and the general untreated stroke population. In the Cleveland experience¹⁹ it was noted that deviation from national treatment guidelines (and, therefore, alteplase labelling) occurred in >50% of patients. The prescribing information for alteplase very clearly specifies the situations where treatment is appropriate and when it is not recommended. These data reiterate the importance of strict adherence to alteplase labelling.

The paper published by M Grond et al reports the experience from Cologne in which significant infrastructural activity allowed the direction of patients believed to be suffering from acute stroke to the one University hospital that was willing to provide treatment for AIS with alteplase. This study, although small has the shortest time to treatment of any study yet published and is important for that reason. Early and late results in the Cologne patients were slightly better than those in NINDS and comparable with the ECASS 3-hour cohort. There were differences in stroke severity and age on admission. However, the evidence from all studies is that the earlier treatment can be given, the better the outcomes. Attention to reducing the time taken to get the patient to hospital without them losing the temporal advantage gained during the arrival-to-treatment interval, is surely important.

The TEMPIS project is also interesting because it reports a solution found in rural Bavaria, Germany, which may also be applicable in Britain where significant populations may live far from equipped and established stroke units. By video camera and electronic CT scan transmission an experienced stroke physician can consult with the medical staff of community hospitals as to the diagnosis of ischaemic stroke and the advisability of alteplase treatment. The investigators report their experience on a comparative basis between patients treated on a tele-consultative basis and those treated in specialist units. The numbers, not proportions, reported as treated are the same in the community and in the specialist units. There were no statistically significant differences in mortality and SICH, although the latter was numerically more frequent in the community hospitals. Remarkably OTT in the community hospitals was identical with that in the specialist units (mean OTT 134 vs. 135 mins).

The single report of experience with alteplase in AIS in the UK is included because it demonstrates the extreme caution that has prevailed in the UK for a number of years. British participation in the alteplase RCT was almost non-existent and in those few centres who attempted to participate it proved almost impossible to comply with the protocols (ECASS I and II). With the support of Professors Ford from Newcastle and Lees from Glasgow, British

participation in SITS-MOST (see below) has improved and a number of centres have participated. However, treatment availability is far from universal.

Finally, SITS-MOST is included because it represents the largest AIS database treated with alteplase, currently, in the world. When the data from SITS-MOST (EU participation only) is merged with the data from the rest of the world, (SITS-ISTR), the latter will be the single largest dataset for outcomes following alteplase treatment. The EU approved alteplase in AIS on a conditional basis. This entailed regular, 6-monthly reports on the progress of a further placebo-controlled trial in AIS patients capable of being treated in the 3-4 hour window after onset. This was subsequently amended to 3 - 4.5hrs and remains consistent with the projected benefit described from the pooled data of ATLANTIS, ECASS and NINDS. ECASS III will not complete before 2008.

The second requirement was an observational cohort study involving principally alteplase safety and secondarily favourable outcome in centres offering alteplase treatment for AIS. The protocol stipulated comparison with the principal outcomes reported from the RCT and pooled analysis. The then CPMP mandated six-monthly reports on both studies, including cumulative analysis of the SITS-MOST cohort, of which the 6th report 18 and its prior subset, the 5th report 20 are included in this submission. The study has been closed to recruitment as a monitored study having been accepted by the CHMP as having achieved its objective, namely having demonstrated as the study name implies the safe implementation of thrombolytic treatment within the member states of the EU. A final report will be provided by the sponsor once the process of final data gathering and cleaning has been accomplished by the study monitors and the data management team, probably in early 2007. The 5th and 6th reports are both included since, notwithstanding the evidence of safe implementation of treatment, the CHMP wished to explore with the MAH an unexpected phenomenon that appeared to have arisen during the course of the study. This was that in new or relatively inexperienced stroke centres the mortality following the index ischaemic

stroke appeared to be considerably higher than in centres that were relatively experienced. This had nothing to-do with the SICH attributable to alteplase but, as shown by the analyses, was inherent in centres starting to provide thrombolytic treatment - a form of learning curve that seemed to disappear after the centre had treated some 10-15 patients. This was perhaps not altogether surprising since it might be expected that with any new major medical or surgical treatment experience would improve the performance of practitioners. The SITS-MOST data have most recently been presented by the international co-ordinator, Professor Nils-Gunnar Wahlgren in 2006 ²¹, presentation attached, with comparisons to RCTs.

Other, observational studies have not been listed since they are either too small (< 100 patients) or add nothing to the conclusions that may be drawn from the larger cohorts or are abstracts from presentations to learned societies and as such incomplete reports.

5.2.5 Ongoing studies

Provide details of relevant ongoing studies from which additional evidence is likely to be available in the next 12 months.

There are no RCTs ongoing that are expected to be reported within the next 12 months. It should be noted that there are two trials of alteplase in acute ischaemic stroke (AIS) that were required of Boehringer Ingelheim as a condition of the licence for Actilyse ® within the EU. The Marketing Authorisation (MA) for alteplase in AIS is presently conditional pending the completion of these two commitments. The first is an RCT (ECASS III) originally requested by the CPMP to assist generalisation of the previous RCT results to the European population. This trial compares alteplase with placebo in patients initially only able to receive treatment within 3-4 hours after stroke onset and more recently extended to 3-4.5 hours from onset. This study is possible because graphic representation of the decline in treatment benefit over time suggests a hypothesis of continuing benefit beyond 3 hours as late as 4.5 hours after stroke onset. ECASS III is expected to be reported in 2008. Naturally, this study will not provide additional information regarding the 0-3 hour time window. The second trial is

a monitored observational cohort study of the implementation of acute stroke treatment including the use of alteplase and is known as the Safe Implementation of Treatment for Stroke - Monitored Study (SITS-MOST). This study which has been monitored by the sponsor, Boehringer Ingelheim, was designed to report on the outcomes of treatment with alteplase in stroke centres previously or newly established throughout the EU, including latterly the new member states. in which the conditional approval of alteplase for the treatment of AIS had been granted. This important study is clinically complete and a report is expected during the early part of 2007. Interim reports are included in this STA, see below section 5.8 non-RCT evidence. This study which constitutes the largest single body of evidence presently available as to the outcomes of treatment with alteplase for AIS in the world, is compared with the outcomes seen in the RCTs considered above and provides an overview of the implementation of thrombolytic treatment with alteplase for AIS throughout the EU

5.3 Summary of methodology of relevant RCTs

As a minimum, the summary should include information on the following aspects of the RCT, but the list is not exhaustive. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (<http://www.consort-statement.org/>). The methodology should not be submitted in confidence without prior agreement with NICE. Where there is more than one RCT, the information should be tabulated.

5.3.1 Methods

Describe the RCT design (for example, duration, degree and method of blinding, and randomisation) and interventions.

The RCTs were subject to a number of minor variations one from another but had sufficient commonality with respect to patient eligibility, exclusions, end-points (efficacy and safety, short-term and longer-term [90 day outcomes]) as to make the subsequent pooled analyses possible and meaningful.

NINDS 1 and 2, ECASS I and II and ATLANTIS parts A and B were all placebo-controlled, randomized, double-blind, multicentre and conducted by stroke specialists, clinical trials performed to regulatory standards (GCP) with sponsor clinical monitoring of the data and in the cases of ECASS I / II and ATLANTIS A and B, statistical analyses following data entry were performed by the sponsors.

NINDS 1 and 2 were managed by the National Institute of Neurological Disorders and Stroke, including data management and analyses. Drug (alteplase) and matching placebo vials were provided by Genentech Inc, San Francisco USA for the North American Studies (NINDS / ATLANTIS) and by Boehringer Ingelheim, Ingelheim, Germany (ECASS trials).

Data Monitoring and Safety Boards were established for all trials including NINDS (Data and Safety monitoring Committee) so as to assess safety on a continuous basis and implement any stopping rules for each trial, (essentially harm or futility).

All trials studied a single dose of alteplase solution expressed as mg/kg and given as a 10% bolus followed by the remaining 90% as a 60-minute infusion. Placebo solution was administered the same way. The dose for all studies except ECASS I was 0.9mg/kg subject to a maximum of 90mg. ECASS I used 1.1mg/kg, maximum 100mg (the standard dose for myocardial infarction and massive pulmonary embolism).

Table 1: Randomisation

NINDS 1 / 2	ECASS I / II	ATLANTIS A / B
<p>Permuted block design, blocks of various sizes, patient stratification by centre and OTT (0-90, 90-180 mins)</p> <p>CT Scan read by staff blind to clinical information / treatment group</p>	<p>Central Randomisation Code (ECASS I)</p> <p>Independent CT reading panel blind to treatment and outcomes.</p> <p>Computer generated randomization procedure in blocks of 4 stratified by OTT (0-3, 3-6 hours) (ECASS II)</p> <p>Sealed opaque envelopes for investigators</p> <p>CT reading panel blinded to treatment and outcomes</p>	<p>Central Randomisation Code, blocked and stratified by centre ATLANTIS B used interactive voice system for randomization and drug supply management.</p> <p>Clinical examinations (ATLANTIS B) by individuals who had not been present during 1st 24 hours</p>

5.3.2 Participants

Provide details of the inclusion and exclusion criteria, and describe the patient characteristics at baseline. Highlight any differences between study groups.

All trials included patients presenting with AIS in whom ICH had been excluded by baseline CT scan. Times to treatment were as follows:

Table 2: Times to Treatment

NINDS 1/2	0 – 180 minutes dichotomised 0-90, 91-180
ECASS I / II	0 – 6 hours dichotomised as 0 – 3, 3 – 6
ATLANTIS A	0 – 6 hours dichotomised but stopped by DMSB because of safety concerns at 5-6 hours
ATLANTIS B	0 – 5 changed to 3 – 5 after NINDS report

All patients had to have a measurable neurological deficit.

NINDS

Exclusions were previous stroke or serious head trauma within 3 months, major surgery within 14 days, a history of ICH, subarachnoid haemorrhage, hypertension above 185/110 mm/Hg, rapidly improving or minor symptoms. Patients taking anticoagulants or heparin 48 hours previously and had an elevated PTT, platelet counts < 100,000 and glucose concentrations > 22.2 mmol/L were excluded as were patients needing aggressive blood pressure lowering. Patients over 80 years of age were excluded.

ECASS I and II

Patients were excluded on grounds similar to NINDS and also very severe stroke and patients with major early infarction signs on CT scan. Drugs affecting coagulation were excluded for 24 hours following which heparin could be used at discretion. ECASS II extended the CT exclusions to include brain swelling exceeding 1/3 of MCA territory.

ATLANTIS A / B

Patients were excluded on grounds similar to NINDS and ECASS I / II.

Patient characteristics at Baseline:

NINDS

Table 3: The medical histories of the patients in the study

VARIABLE	PART 1		PART 2	
	I-PA (N = 144)	PLACEBO (N = 147)	I-PA (N = 168)	PLACEBO (N = 165)
	<i>percent</i>			
Stroke	17	17	12	9
Transient ischemic attack	22	14	13	19
Aspirin therapy	41	31	40	26
Diabetes	24	21	20	20
Hypertension	66	64	67	67
Myocardial infarction	25	21	22	20
Atrial fibrillation	18	20	20	16
Angina pectoris	18	22	24	24
Congestive heart failure	14	17	16	19
Valvular heart disease	11	7	6	6
Smoking in year before stroke	43	37	27	35
No preexisting disability	90	91	95	93

*Reproduced from table 1: The medical histories of the patients in the study
NEJM 1995; 333:1581-7*

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NINDS

Table 4: Base-line characteristics of the patients in the two parts of the study, according to treatment group*

CHARACTERISTIC	PART 1		PART 2	
	I-PA (N = 144)	PLACEBO (N = 147)	I-PA (N = 168)	PLACEBO (N = 165)
Age (yr)	67±10	66±11	69±12	66±13
Race or ethnic group (%)				
White, non-Hispanic	62	61	69	66
Black	29	31	23	26
Hispanic	8	5	5	7
Asian	1	0	3	1
Other	0	3	1	1
Female sex (%)	42	40	43	42
Weight (kg)	76±15	80±18	76±16	80±21
NIHSS score				
Median	14	14	14	15
Minimum	1	1	2	2
Maximum	37	32	37	33
Stroke subtype (%)				
Small-vessel occlusive	19	11	14	9
Cardioembolic	42	44	45	44
Large-vessel occlusive	35	42	39	45
Other	3	3	2	3
Blood pressure (mm Hg)				
Systolic	155±22	153±20	153±22	152±21
Diastolic	85±12	85±13	85±14	86±15
Fibrinogen (mg/dl)	332±94	349±106	311±102	316±86
Glucose (mg/dl)†	149±76	152±78	149±66	149±78
CT findings (%)				
Edema	5	3	4	6
Mass effect	3	2	3	4

*Plus-minus values are means ± SD. Because of rounding, not all columns total 100 percent.

† To convert values for glucose to millimoles per liter, multiply by 0.05551

Reproduced from table 2: Base-line characteristics of the patients in the two parts of the study, according to treatment group* NEJM 1995; 333:1581-7

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ECASS 1

For baseline demographics of ECASS please see table 2, JAMA 1995 in Appendix 6 **Table 2: Demographics. JAMA 1995; 1017-1025**

ECASS II

Demographic and baseline features can be found in Table 1 from Lancet 1998; 352:1245-51 in Appendix 6.

ATLANTIS A

Table 5: Baseline demographics in the ITT population

	Placebo (n=71)	rtPA (n=71)	p
Age, mean \pm SD	65 \pm 12	67 \pm 13	0.56
Sex, % male	70%	66%	0.58
Race, % white	82%	86%	0.42
Weight, kg	81 \pm 15	80 \pm 23	0.75
Time to treatment	4h 27 \pm 68min	4h 24 \pm 68min	0.55
Median	4h 30min	4h 36min	
<3h, %	17	14	
3-4h, %	30	24	
4-5h, %	20	31	
>5h, %	34	31	
Baseline NIHSS score			
Mean \pm SD	13 \pm 6	13 \pm 7	0.53
Median	11	10	
<10, %	47	51	
>20, %	10	18	
Smoker, %	69	74	0.51
Cardiac disease, %	84	72	0.07
Atrial fibrillation, %	27	25	0.81
Hypertension, %	65	58	0.39
Diabetes, %	25	13	0.05

Adapted from Table 3: Baseline demographics in the ITT population. Stroke 31:811-816

ATLANTIS B

For baseline demographics of ATLANTIS please see **Table 3 JAMA 1999; 282:2019-2026** in Appendix 6.

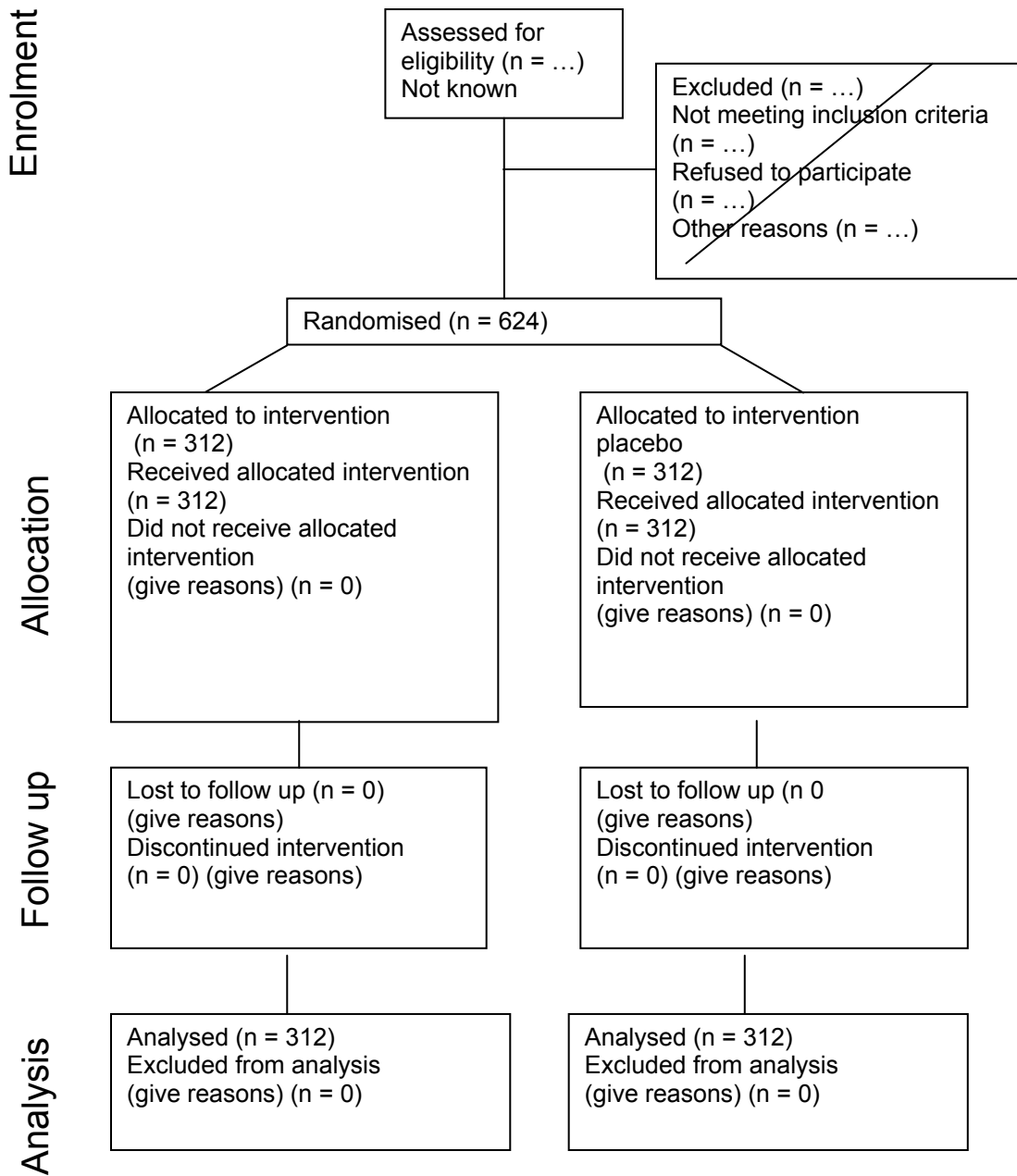
These data indicate a relatively homogeneous if selected population of AIS patients. Previous risk factors are consistent with those expected for an AIS population. Diabetes Mellitus constituted a prior stroke risk in 15-25% of patients.

5.3.3 Patient numbers

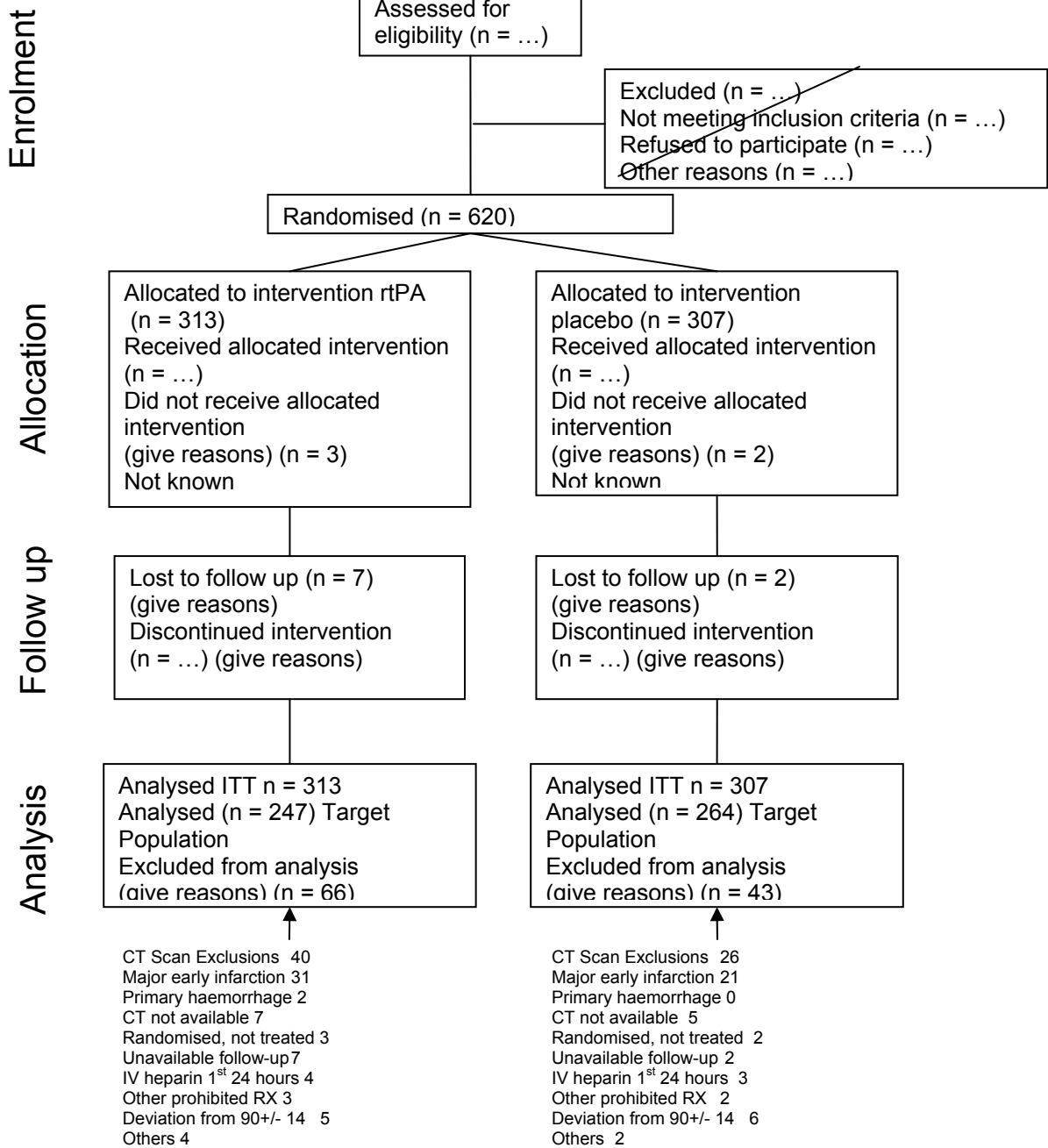
Provide details of the numbers of patients who were eligible to enter the RCT, randomised, and allocated to each treatment. Provide details of and the rationale for patients who crossed over treatment groups and/or were lost to follow up/ withdrew from the RCT. This information should be presented as a CONSORT flow chart.

See CONSORT flow charts below.

NINDS
NEJM 1995; 333:1581-1587

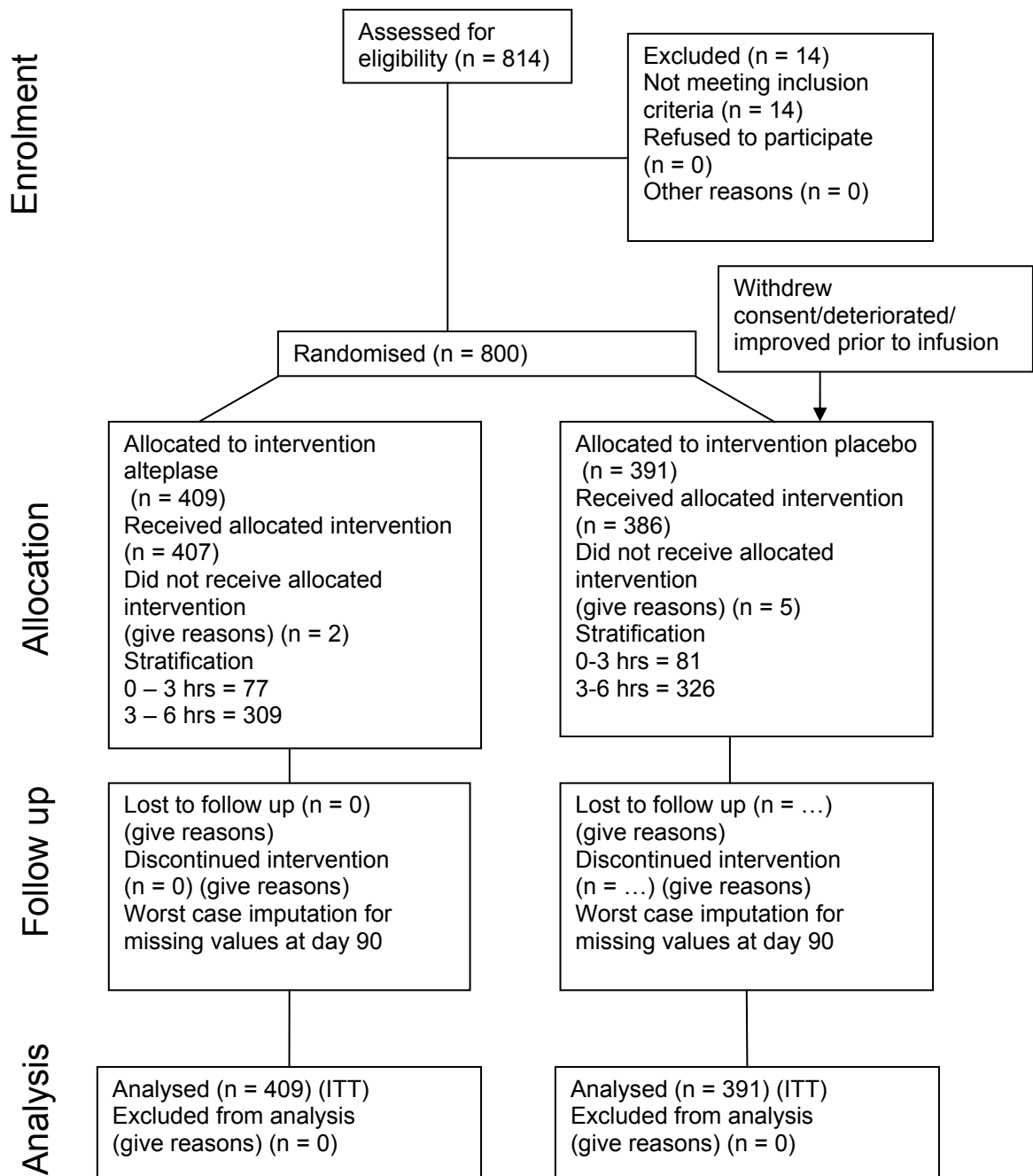


ECASS
JAMA 1995; 279:1017-1025

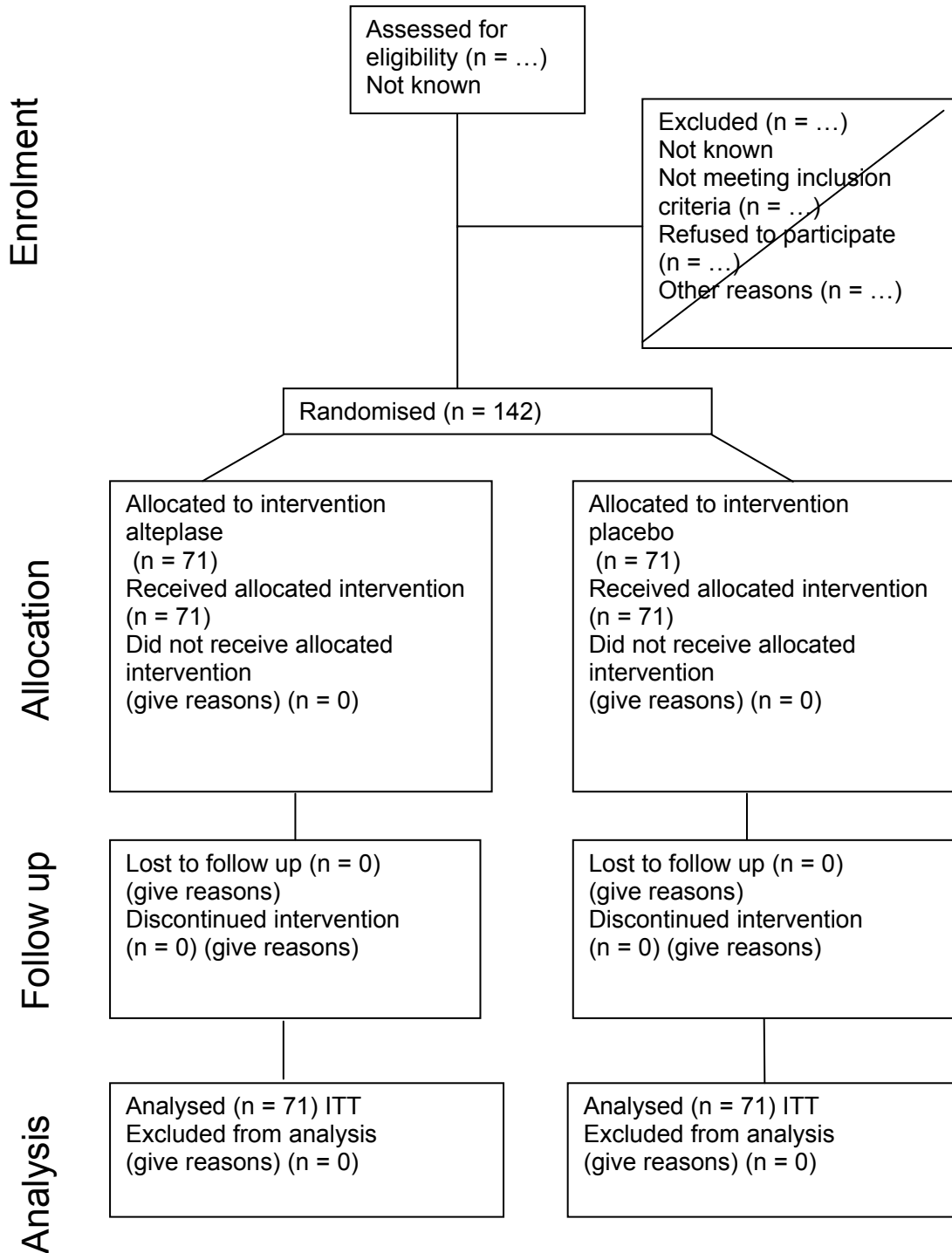


ECASS II

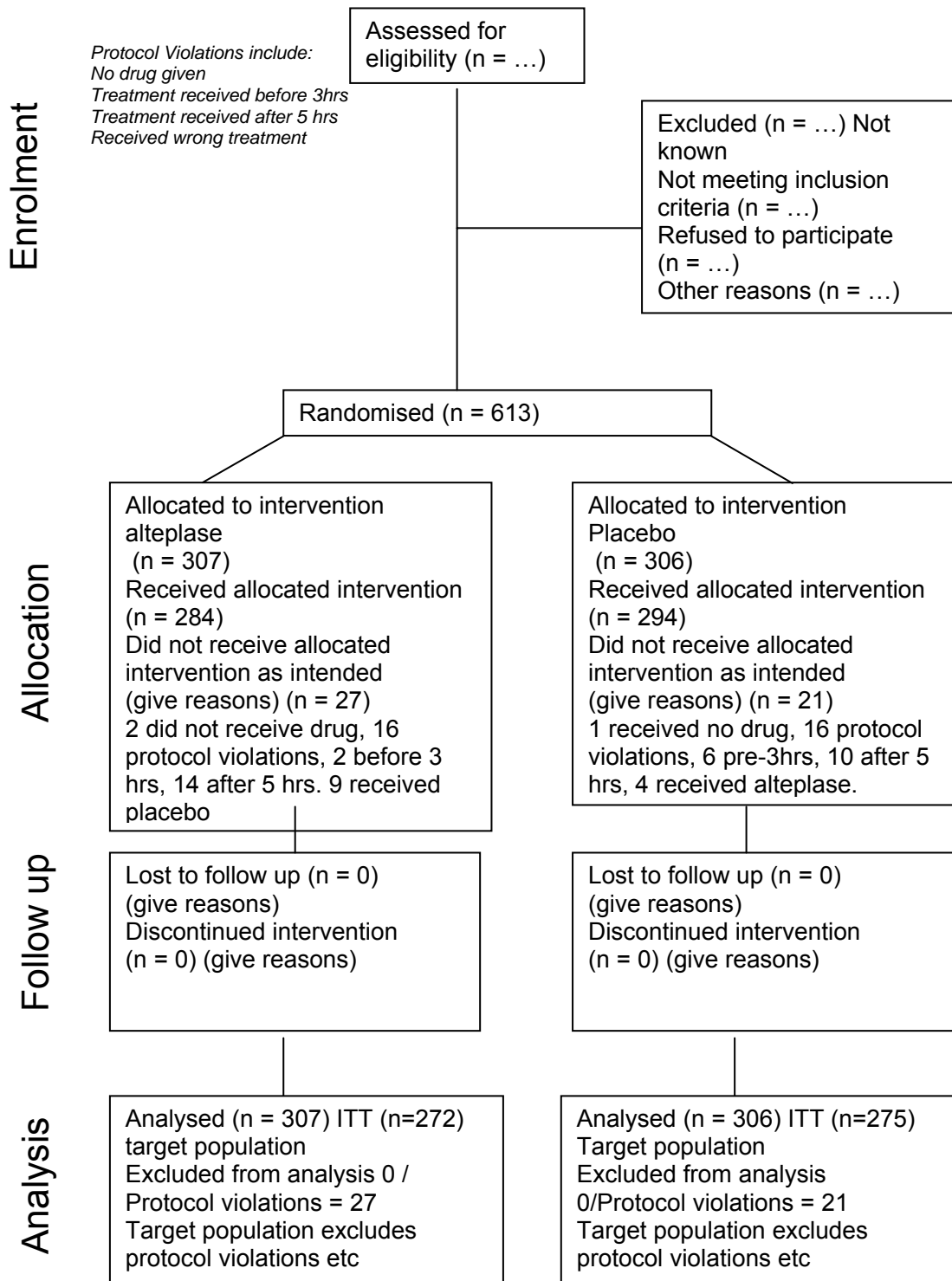
Lancet 1998; 352:1245-1251



ATLANTIS PART A
Stroke 2000; 31:811-816



ATLANTIS PART B
JAMA 1999; 282:2019-2026



5.3.4 Outcomes

Provide details of the outcomes investigated and the measures used to investigate those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the specification of the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of quality of life and social outcomes, and any arrangements to measure concordance. Data provided should be from prespecified outcomes rather than post-hoc analyses. Where appropriate, also provide details of the principal outcome measure(s), including details of length of follow-up, timing of assessments, scoring methods, evidence of reliability/validity, and current status of the measure (such as approval by professional bodies or licensing authority).

See also individual study templates in appendix 4.

Table 8: Outcomes

STUDY	OUTCOMES	INVESTIGATIONAL METHODS
NINDS Part 1	Improvement at 24 hours	Improvement from baseline National Institute of Health Stroke Scale (NIHSS) score \geq 4 points at 24 hours.
	Minimal / no deficit at 3 months	Barthel Index (BI) Modified Rankin Scale (mRS) Glasgow Outcome Scale (GOS) NIHSS scale (proposition at 0-1)
	ICH	CT Scans at 24 hours, 7-10 days and whenever clinical suspicion suggested haemorrhage
	Mortality	% OR 95 CI

Table 8 (contd)..

STUDY	OUTCOMES	INVESTIGATIONAL METHODS
NINDS Part 2	Minimal / no deficit at 3 months	As Part 1 above
	Improvement at 24 hours	As Part 1 above
	ICH	As Part 1 above
	Mortality	As Part 1 above
ECASS I	Differences in activities of daily living in global impression	Δ^* 15 points on BI Δ 1 point on mRS both at day 90
	Mortality	Terminal point on BI/mRS at day 30 Combined BI/mRS scores day 90 NIHSS scores days 1 & 90 Combined B1/mRS scores day 90 NIHSS scores day 1 & 90
	ICH / SICH	CT Scans

Table 8 (Contd)

STUDY	OUTCOMES	INVESTIGATIONAL METHODS
ECASS II	Favourable outcome in terms of function	mRS (score 0-1)
	Dependency	Post hoc mRS (0-2 = independent)
	Change in neurological deficit baseline – day 30 Neurological deficit at day 90 Duration hospital stay and quality of life at 90 days	NIHSS scores at 30 days combined BI and mRS at 90 days Scandinavian Stroke Scale (SSS) duration in days SF – 36
	Mortality at days 30 and 90 Haemorrhagic infarction Parenchymal haemorrhage SICH Other Adverse Events	All cause and haemorrhagic deaths } Clinical and CT criteria Clinical and CT criteria (any ICH plus ≤ 4 point deterioration on NIHSS score as reported)
	Clinical improvement	Δ between treatments for NIHSS scale ≥ 4 points or resolution of symptoms from baseline to 24 hours/30 days
ATLANTIS Part A	Reduction in cerebral infarction	Δ between treatments by CT scanning at 30 days
	Clinical improvement	Δ between treatments in decrease ≥ 4 points on NIHSS or resolution at 120 minutes, 7 days and 90 days
		Δ in median BI At 30/90 days
	Mortality	Δ in 30/90 day mortalities
	Asymptomatic ICH	CT scan only
	Symptomatic ICH	CT scan and deterioration in NIHSS score

Table 8 Contd

STUDY	OUTCOMES	INVESTIGATIONAL METHODS
ATLANTIS Part B	Favourable recovery	NIHSS Score 0-1 at 90 days
	Clinical progress	NIHSS scores at baseline, 120 minutes, 24 hours, 7, 30 and 90 days BI at 30/90 days mRS at 30/90 days
	ICH, infarction signs, infarction size	CT Scanning at baseline, 18-30 hours or sooner if indicated, 23-37 days
	Asymptomatic ICH	CT scan
	Symptomatic ICH	CT scan and NIHSS score worsening
	Fatal ICH	As reported
	Mortality	As reported

* Δ = difference

All neurological rating scales are well-known to neurologists and agreed by their professional associations. These are also acknowledged by regulatory authorities and accepted as clinically meaningful. Computerised Tomography (CT) scanning of the brain has been an evolving art over the period of these studies. Neuroradiology is an accepted professional discipline.

5.3.5 Statistical analysis and definition of study groups

State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were preplanned or post-hoc.

All RCTs adopted intention-to-treat (ITT) analyses. Where target populations (per-protocol analyses) were used, they were always secondary to the ITT analysis. Sample sizes were calculated on the basis of the expected/hypothesized differences from placebo. Patients lost to analysis were few since alteplase is a single one-off treatment for AIS in hospital and then the patient merely has follow-up assessments much as they might in clinical practice before and after discharge. CT scans were numerous as a routine in the US based trials but in Europe were more consistent with expected clinical practice i.e. a baseline scan to establish the diagnosis and eligibility for treatment, repeat scans only for unexpected clinical deterioration. Missing data was either imputed as worse case or based upon the last known clinical rating. Sub-group analyses were generally pre-specified and aimed at the time-window OTT. NINDS went further to distinguish 0-90 minutes and 91-180 minutes. The other trials also examined 3-6 / 3-5 hours since, at the time few patients were arriving in hospital to allow 0-3 hour treatment and it became important to assess benefit in the later OTT.

5.3.6 Critical appraisal of relevant RCTs

Each RCT should be critically appraised. If there is more than one RCT, tabulate the responses, highlighting any ‘commercial in confidence’ data. The critical appraisal will be validated by the Evidence Review Group. The following are suggested criteria for critical appraisal, but the list is not exhaustive.

- **How was allocation concealed?**
- **What randomisation technique was used?**
- **Was a justification of the sample size provided?**
- **Was follow-up adequate?**
- **Were the individuals undertaking the outcomes assessment aware of allocation?**
- **Was the design parallel-group or crossover? Indicate for each crossover trial whether a carry-over effect is likely.**

- **Was the RCT conducted in the UK (or were one or more centres of the multinational RCT located in the UK)? If not, where was the RCT conducted, and is clinical practice likely to differ from UK practice?**
- **How do the included in the RCT participants compare with patients who are likely to receive the intervention in the UK? Consider factors known to affect outcomes in the main indication, such as demographics, epidemiology, disease severity, setting.**
- **For pharmaceuticals, what dosage regimens were used in the RCT? Are they within those detailed in the Summary of Product Characteristics?**
- **Were the study groups comparable?**
- **Were the statistical analyses used appropriate?**
- **Was an intention-to-treat analysis undertaken?**
- **Were there any confounding factors that may attenuate the interpretation of the results of the RCT(s)?**

All of these RCTs were competent, well-run and monitored Phase III trials performed to GCP or equivalent in which alteplase was compared, appropriately with placebo. The ECASS trials and both ATLANTIS studies were performed to regulatory standards with clinical monitoring and data management, and analysis performed by the sponsors, NINDS was run by the National Institute for Nervous Disease and Stroke entirely apart from drug and matching placebo supplied by Genentech and was self-monitored. Allocation was concealed by drug being supplied in matching containers with solution for infusion in packs that were generally blocked and stratified to allow balanced randomization.

Randomization codes were held centrally so that investigators, patients and staff conducting the trials always remained blind to treatment. The results of NINDS part 1 were not released until part 2 had been completed. There was very restricted knowledge of treatment allocation to specifically nominated individuals and when necessary to Data Monitoring and Safety Board (DMSB) members for the purpose of advising on trial continuation e.g. ATLANTIS A and B. The blinks appear to have been conscientiously maintained, there

being generally no reason to know treatment allocations even in respect of major haemorrhage. Treatment would, in any case, have been empirical including discontinuation of the infusion if still running.

Sample sizes were always calculated on the basis of pre-specified hypotheses and follow-up was careful with patients being in hospital during the acute illness and brought back to out-patients for later follow-up. Mortality was always ascertained. Studies were all parallel-group in design. There was a criticism of bias in the NINDS trial. This arose following the publication of a statement from the American Academy of Emergency Medicine regarding the efficacy, safety and applicability of alteplase for AIS as being insufficient for its classification as a standard of care. The statement cited specific concerns regarding the risk of ICH, whether the trial results were generalisable and whether an imbalance in baseline stroke severity biased the results in favour of alteplase. A series of publications followed that were critical of the trial conduct and the subsequent development of guidelines for AIS. In response, the Institute commissioned an independent reanalysis of the trial data to address the concerns that had been raised. The independent committee found and reported²² a clinically important and statistically significant benefit of alteplase treatment despite sub-group imbalances in baseline stroke severity and an increased incidence of SICH in alteplase-treated patients (adjusted OR = 2.1 [95% CI 1.5, 2.9]). Health professionals were urged to work collaboratively to develop guidelines to ensure the appropriate use of alteplase in AIS.

There was a very small contribution from UK specialist centres to both ECASS I and II. In general centres found it extremely difficult in Britain to ensure treatment within the 6 hour time-window. However, subsequently under the leadership of Professors Kennedy Lees (Glasgow) and Gary Ford (Newcastle) and because of the development of specialist units, a slow but steady increase in the British contribution to SITS-MOST (see below section 5.7) has occurred. IST-3 is an academic clinical trial being performed in the UK and internationally in patients about whom there may be doubt as to the benefit of alteplase in an attempt to broaden the applicability of treatment.

This study is independent of Boehringer Ingelheim who made an initial donation of drug and placebo to get the study started. In the participating centres patients eligible for 0-3 hour treatment are receiving alteplase as indicated.

There is reason to believe that RCT patients would compare well (i.e. not unfavourably or favourably) with patients who are likely to receive alteplase in the UK provided that prescribing recommendations are carefully followed and variations of these are not treated outside RCTs, viz. SITS-MOST, ECASS III and IST-3. Epidemiologically, AIS is not different in Britain compared with Europe or in North America, Australia or New Zealand. Infrastructural change has been slower in the UK compared with the rest of Europe. Patient awareness, time to admission and time to treatment can only be improved by the provision of information and guidelines for treatment, the acceptance by the emergency services that AIS is a treatable medical emergency and interdisciplinary collaboration within hospitals which is essential to maximize the benefits of early treatment as suggested in the ASIST study.²³

All RCTs except ECASS I used the now recommended and approved dose of alteplase (0.9mg/kg, maximum 90mg) ECASS I used the dose (1.1mg/kg, maximum 100mg) approved for reperfusion of the infarcted heart and lungs. This dose was accepted as being too high for infarcted brain because of the excess risk of ICH. With the exception of NINDS, discussed above, all RCT had comparable study groups. NINDS studied 0-3 hours, the other trials 0-6 and 3-5 hours and had relatively few patients in the 0-3 hour time window. However the pooled analysis (see section 5.5) confirmed OR of 2.8 (68% CI 1.8, 4.5) for 0-90 minutes and 1.6 (1.1, 2.2) for 91-180 minutes. There was also evidence of benefit beyond three hours (3-4.5 hours).

Finally, statistical analyses were competent as well as consistent and appropriate. Analyses were all ITT, some analysed target population in addition. The meta analysis of NINDS, ECASS and ATLANTIS trials investigated potential confounders 10. The final logistic regression model was developed on the basis of only recorded data. The analyses with only recorded data (n = 2552) and the ITT analysis (n = 2775) gave similar results

and therefore the ITT results were used. Interaction between OTT and treatment remained significant ($p = 0.005$) in the final multivariable model, in which benefit increased as OTT decreased. The results of OR for favourable outcome at 3 months, the same by OTT and NIHSS category and the model estimating OR for favourable outcome at 3 months in alteplase-treated patients compared with controls by OTT are shown in Table 1 The Lancet 2004; 363:770, Figure 2, Lancet 2004; 363:768-774 and Figure 3, Lancet 2004; 363:768-774 (see appendix 6). Measurements on the mRS scale by OTT for both treatments are shown in Figure 4, Lancet 2004; 363:768-774 (see appendix 6).

Thus, because of concerns expressed not only by clinicians but also regulators around the world, the outcomes of the RCT for alteplase versus placebo in AIS both beneficial and hazardous have been subjected to the most rigorous scrutiny and analysis. As a result, the EU-SPC contains very specific recommendations as to the population to be treated and the adherence of stroke specialists to these recommendations has been confirmed in the major published observational studies of outcome. Violation of these recommendations merely increases the risk.

5.4 Results of the relevant comparative RCTs

Provide the results for all relevant outcome measure(s) pertinent to the decision problem. If there is more than one RCT, tabulate the responses, highlighting any 'commercial in confidence' data. The information may be presented graphically to supplement text and tabulated data. Data from intention-to-treat analyses should be presented wherever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given.

For each outcome for each included RCT the following information should be provided.

- **The unit of measurement.**

- **The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic. Both absolute and relative data should be presented.**
- **A 95% confidence interval.**
- **The number of patients included in the analysis.**
- **The median follow-up time of analysis**
- **State whether intention-to-treat was used for the analysis and how data were imputed if necessary.**
- **Discuss and justify definitions of any clinically important differences.**
- **Where interim RCT data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that RCT. Analytical adjustments should be described to cater for the interim nature of the data.**
- **If the RCT measures a number of outcomes, discuss whether and how an adjustment was made for multiple comparisons in the analysis.**
- **Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.**

In the 1990s when the relevant RCTs of alteplase were being performed the methodology was still to a certain extent evolving as was the art of neuroradiology and the reading of CT scans. Thus a number of neurological assessment scales were available to clinicians investigating acute stroke treatment and some or all of these were used in the alteplase RCTs. There is, in addition, enough commonality of assessment in each of the studies to permit pooled assessment of the results of all trials. See below 5.5 Meta Analysis. In addition the data have lent themselves to the reassessment of the most relevant outcomes e.g. NIHSS 0-1 as excellent outcome, mRS 0-1, minimal or no disability vs mRS 0-2, independent recovery. Finally 1-year follow-up of the first RCT – NINDS – has been

published⁶ together with the non-randomised experience of the Cologne Group²⁵ included below (section 5.8) which compares their outcomes with the 1 year outcomes of NINDS. These additional issues will be considered at the end of this section in so far as they relate to the original data.

Each RCT included patients in whom AIS had occurred and was treated with alteplase or placebo within 0-3, 0-6 or 3-5 hours previously. Patients were assessed and observed for recovery and/or adverse reactions during their in-hospital period and assessed for recovery at 90 days/3 months. The results are tabulated elsewhere. (See Section 5.3).

NINDS

The NINDS study (parts 1 and 2) found a benefit in intravenous alteplase therapy for patients with AIS when treatment was initiated within three hours of the onset of symptoms. When compared with patients given placebo, patients treated with alteplase were at least 30% more likely to have minimal or no disability at three months, as measured by the outcome scales (absolute increase in favourable outcome, 11-13%). This benefit was not associated with any increase in mortality but is a benefit associated with early treatment (approximately 50% of patients treated within 90 minutes). SICH occurred in 6.4% of alteplase-treated patients compared with 0.6% of placebo-treated patients. Mortality at 90 days was 17% (alteplase) and 21% (placebo further analysis of the OTT – treatment interaction showed a confounder-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. No effect of OTT on ICH was detected in the alteplase group. NINDS required agreement across rating scales in the primary outcome of benefit at 90 days as well as early changes in NIHSS at 24 hours or baseline to 24 hours. A post hoc analysis⁸ was performed to identify the most

powerful binary measures of the alteplase treatment effect. The best overall single outcome measure for early activity of alteplase was NIHSS score ≤ 2 at 24 hours which provided an OR of 5.4 (2.4, 12.1). The second and third best measures for detecting longer-term efficacy of alteplase also involved the NIHSS score (NIHSS $\leq 0-1$) with mRS scores of 0-1 at 3 months the next most powerful outcome measure. These have since been used to assess data from other trials.

The follow-up study of NINDS patients at 1 year now published ⁶ lists an ITT analysis for the combined results of the two parts of the trial. The global statistic for a 6 and 12 month favourable outcome favoured alteplase, 6 months OR 1.7 (1.3, 2.3), 12 months OR 1.7 (1.2, 2.3). Alteplase-treated patients were at least 30% more likely to have minimal/no disability at 12 months than the placebo-treated patients (absolute increase 11-13%), with no significant difference in mortality. The shorter term benefit detected initially appears to be maintained.

ECASS I

ECASS I included 620 patients with AIS in a placebo-controlled trial of alteplase given at a slightly higher dose than NINDS (1.1mg/kg, max 100mg) being the recommended dose for thrombolytic treatment of myocardial infarction. A total of 109 patients were considered major protocol violations. Among these were signs of CT scanning of major early infarction, considered to be a serious risk of poor outcome and/or ICH. Protocol violations also favoured placebo, i.e. less of them, 66 vs 43 patients. As a result the data were analysed both by ITT analysis and by Target Population (TP). Apart from the violations the population was demographically well-balanced. Of the primary end-points the BI showed no difference between treatment for either the ITT and the TP. As to mRS, at 90 days the median value was equal for both treatments (ITT) but statistically significantly improved for the TP, ($p = 0.035$). In the ITT analysis 29.3% of patients on placebo and 35.7% of patients on alteplase

had Rankin Scores better than 2 at 90 days. The OR for independent recovery was 1.15 (0.98, 1.35) in ITT for alteplase and percentages for the TP were 29.2% (placebo) and 40.9% (alteplase) respectively. OR for asymptomatic or independent recovery for the alteplase group was 1.29 (1.09, 1.54) and for asymptomatic recovery was 1.47 (1.05, 2.05) for ITT and 1.54 (1.28, 2.85) for TP, for alteplase. Of the secondary end-points the Scandinavian Stroke Scale (SSS) (long-term score) at day 90 was not different for the ITT analysis but was significantly in favour of alteplase in the TP analysis ($p = 0.03$). Using the combined BI/RS end-point both ITT and TP were significantly in favour of alteplase for surviving patients, as per protocol.

Mortality at 30 days was not significantly different between groups in either analysis but rates were higher in the alteplase-treated group, ITT 39 patients (12.7%; 9.4%, 17.2%) on placebo and for alteplase, 56 patients (17.9%; 14.1%, 22.9%), ($p = 0.08$). The RR was 1.20 (0.98, 1.46). In the TP, 31 patients (11.7%; 8.2%, 16.4%) died on placebo and 36 patients on alteplase (14.6%; 10.5%, 19.7%) within 30 days. The OR was 1.13 (0.88, 1.44).

Other measures of efficacy included neurological change within the early course of the disease with significant improvement in SSS score in favour of alteplase at all times points (2 hours, 8 hours, 1 day, 7 days) in both ITT and TP analysis. Duration of hospital stay for surviving patients was significantly shorter for alteplase-treated patients (both ITT and TP analyses) and NIHSS at 24 hours and 90 days showed medians that were significant in both TP analyses and for ITT as well, only at 24 hours. Total 90 day mortality was 117 (18.9%), 69 alteplase and 48 placebo patients (log rank test $p = 0.04$). The difference was not significant in the TP analysis (log rank test $p = 0.17$). The mortality among protocol violations was 20 vs 9, alteplase and placebo respectively, with major early infarction signs on CT predominantly in alteplase patients.

Haemorrhagic events of any degree numbered 247 patients (39.8%) in total; 134 patients with alteplase and 113 with placebo; not significantly

different (ITT) and in the TP analysis 205 (40.1%), 108 on alteplase and 97 placebo. Parenchymal haemorrhage was more frequent in alteplase treated patients and haemorrhagic infarction in placebo treated patients. There was no difference in the occurrence of serious adverse events other than ICH.

The authors concluded that thrombolytic therapy was effective in improving some functional and neurological measures in the sub group of stroke patients with moderate to severe neurological deficit and without extended infarction signs on the initial CT scan. However, these did not outweigh the higher mortality at 30 days in the alteplase treated patients and the significant increase in Parenchymal haemorrhage. Treating the wrong patients leads to unacceptably high complication rates and excluding patients known to be at high risk is essential. Selecting patients likely to respond positively and avoiding an unselected population is recommended.

ECASS II

ECASS II was performed within the EU, Australia and New Zealand. Alteplase (n = 409) and placebo (n = 391) were randomly assigned with stratification for time since symptom onset (OTT 0-3 hour or 3-6 hour). The primary end-point was the modified Rankin Score at 90 days, dichotomised for favourable (mRS 0-1) and unfavourable (mRS 2-6). Analyses were by ITT. The dose of alteplase was 0.9mg/kg to a maximum of 90mg given as a 10% bolus followed by the remaining 90% as a 1 hour infusion. At baseline 341 (42.6%) had no signs of infarction on the initial CT scan, 414 had hypodensity of 33% or less of the middle cerebral artery territory and 37 had hypodensity of that territory greater than 33%. The CT scans of 8 patients were not available or were unreadable due to poor quality. Protocol violations numbered 72, 34 in the alteplase group and 38 in the placebo group. A favourable outcome (mRS 0-1) was seen in 165 (40.3%; 35.6%, 45.4%) alteplase patients and 143 (36.6%; 31.8%, 41.6%)

placebo patients, an absolute difference of 3.7% ($p = 0.277$), OR 1.17 (0.9, 1.6). Post hoc analysis of independent recovery (mRS 0-2) showed 222 (54.3%; 49.5%, 59.5%) alteplase patients and 180 (46.0%; 41.1%, 50.9%) placebo patients, an 8.3% absolute difference in favour of alteplase that was significant ($p = 0.024$ Fisher's exact test). Of the remaining secondary and other end-points only the NIHSS from baseline to 30 days showed a significant difference ($p = 0.035$). 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 placebo response was unexpectedly high, similar to active treatment in NINDS, ECASS I. Mortality was 85 patients ((10.6%) during the 90 +/- 14 days with no difference in the 30 day and 90 day mortalities by treatment group, 43 alteplase and 42 placebo patients. Of these, 45 patients died before day 7, 25 (6.1%) following alteplase and 6 (8%) after placebo.

Haemorrhagic infarction did not differ between treatment groups but parenchymal haemorrhage of any kind was more common following alteplase (11.8 vs 3.1% respectively). SICH showed a 2.5 fold excess with alteplase.

The authors considered that alteplase should be part of the routine management of AIS within 3 hours of symptom onset at the dose used of 0.9mg/kg subject to a maximum of 90mg. A secondary analysis of ECASS II 29 looked at risk factors for severe haemorrhagic transformation in ischemic stroke patients treated with alteplase. The analysis confirmed the importance of hypoattenuation in the CT scan as a risk factor for severe haemorrhagic transformation. The findings also suggest that increasing age and prior aspirin use before stroke also increase the risk of severe haemorrhagic transformation.

ATLANTIS A AND B

ATLANTIS parts A and B were randomized, double-blind, placebo-controlled, multicentre studies performed in the USA. The study became two because the original 0-6 hour trial of alteplase was stopped after 142 patients had been treated and the DMSB had safety concerns in the 5-6 hour subgroup, namely that SICH, 30 and 90 day mortalities were higher with alteplase than with placebo and higher than the corresponding rates with alteplase in other time windows. However, there was confounding by stroke severity with more patients with NIHSS scores at baseline >20. The trial, having been stopped, was reported separately from part B (see below). The ITT analysis of 0-6 hours did not show benefit for alteplase for any endpoint apart from NIHSS score ≥ 4 point improvement at 24 hours, lost at 7 days and beyond. However, a favourable recovery was seen at day 30, ($p = 0.04$) post hoc analysis. Symptomatic ICH was significantly different for alteplase from placebo, 8 vs 0 respectively ($p = 0.003$). Mortality was also significantly increased in alteplase patients at 30 and 90 days.

Part B of ATLANTIS was resumed with a reduction in the time window to a maximum of 5 hours and later, in view of the NINDS outcome to a minimum of 3 hours. A total of 613 AIS patients were randomized, 547 within 3-5 hours, 39 within 3 hours, 24 more than 5 hours and 3 received no drug. Thus 272 received alteplase and 275 placebo according to protocol. Both ITT and Target Population analyses were performed. The study did not find a benefit for alteplase in the 3-5 hour window from stroke onset in either the TP or ITT analysis. The proportion of patients experiencing a substantial (11 point) improvement in NIHSS at 90 days was significantly in favour of alteplase. All other end-points showed no difference, including mRS 0-2 day 90. SICH at 7% following alteplase was not more than that seen in the NINDS trial (6%) and there was no difference between groups as to mortality.

In the Target Population in this trial, 80% of patients were treated within 4-5 hours of stroke onset and the numbers of patients treated within 3-4 hours were too few to evaluate. The baseline NIHSS score was low at

median 10 compared with 14 in NINDS possibly contributing to the rate of placebo recovery.

Albers et al⁹ have reported on the 0-3 hour subset of patients treated in ATLANTIS. This analysis includes only 61 patients, 23 on alteplase and 38 on placebo. Encouraging was the proportion achieving NIHSS ≤ 1 at 90 days, 60.9% on alteplase and 26.3% on placebo. The OR was 4.4 (1.4, 13.2; $p = 0.01$). The alteplase strokes were more severe than the placebo strokes at baseline. Not all 90 day outcome data were collected for all patients. SICH was 13% (2.8, 33.6) in the alteplase group. All three noted were fatal. The subset though small was considered to provide support for the NINDS result.

These results coupled with the pooled analysis (see section 5.5) form the basis of the regulatory approvals for alteplase in AIS 0-3 hours after stroke onset despite the conditional nature of such approval within the European Union.

5.5 *Meta-analysis*

Where more than one study is available and the methodology is comparable, a meta-analysis should be undertaken. If a meta-analysis is not considered appropriate, the rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal. If any of the relevant RCTs listed in response to section 5.2.3 are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored. The following steps should be used as a minimum.

- Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.**

- **Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).**
- **Provide an adequate description of the methods of statistical combination and justify their choice.**
- **Undertake sensitivity analysis where appropriate.**
- **Tabulate and/or graphically display the individual and combined results.**

A Cochrane Review ¹², an overall meta-analysis of thrombolysis for AIS has been published for the Cochrane Collaboration, in the form of a review in 2003 by Wardlaw, del Zoppo, Yamaguchi and Berge. Both efficacy and safety of thrombolytic treatment are included. While the trials tested urokinase (UK), streptokinase (SK), alteplase or pro-urokinase (PUK), approximately 50% of the data relate to trials of alteplase. The total number of patients randomised was 5727 (data available on 5721).

The meta-analysis sought to determine whether:

1. Thrombolytic therapy
 - (a) increases the risk of death within the first two weeks and
 - (b) reduces the risk of death at long-term follow-up.
2. Thrombolytic therapy increases the risk of early symptomatic or fatal ICH.
3. Thrombolysis reduces the proportion of patients alive but dependent at long-term follow-up in spite of any early hazard, so that there is an overall net benefit and a reduction in the proportion with a poor outcome (i.e. dead or dependent).
4. By exploratory analyses:
 - (a) thrombolytic therapy interacts with antithrombotic therapy to increase the hazard;
 - (b) the balance of risk and benefit with thrombolytic therapy may vary with the severity of the stroke;
 - (c) the therapeutic time window extends beyond three hours.

The authors give their criteria for considering studies for the review, including types of studies, types of participating patients, types of intervention and types of outcome measures. They also describe their search methods in detail as well as their methods of the review. Odds

ratios were calculated for each outcome and heterogeneity between trial results tested by standard Chi squared test. Odds ratios were calculated using the Peto-fixed effects method and the random effects method when significant heterogeneity existed between trials. Methodology is also given for the calculation of absolute events avoided (or caused) per 1000 patients treated and differences in outcomes between clinically important subgroups. All randomised controlled trials of alteplase listed above (section 5.3) were included in this analysis.

In discussion the authors confirm that despite a significant excess of deaths within the first 7-10 days and SICH, including fatalities as well as deaths by the end of follow-up, there was a reduction in disability in survivors and therefore an overall net benefit. For every 1000 patients treated with thrombolytic agents, 43 avoided death or dependency. For every 1000 patients treated with alteplase 55 patients avoided death or dependency if treated within 6 hours of stroke onset. However, there was significant heterogeneity between trials at the end of follow-up and for alteplase trials too.

Their conclusions are two-fold, implications for practice and implications for clinical research. These can only be quoted in their entirety as follows:

"Implications for practice

(a) taken overall, in patients given thrombolysis in the acute phase of ischaemic stroke, there appears to be a net benefit of a significant reduction in the proportion who are dead or dependent at the end of follow-up, ie significantly more patients are alive and independent. The data available however are limited.

(b) There is, overall, reasonable proof of an excess risk of fatal intracranial haemorrhage and death from all causes with thrombolytic therapy.

(c) despite the overall net benefit, the available data do not provide sufficient evidence to determine the magnitude of treatment effect for the individual patient, including: the duration of the therapeutic time window,

the optimum agent (or dose or route of administration) or the clinical or radiological features which identify the patients most likely to be benefited (or harmed), the age of the patient, and when and if antithrombotic treatment may be safely used around the time of thrombolysis.

(d) the greatest amount of data are available for intravenous rt-PA (alteplase), which was associated with fewer deaths and more patients avoiding death or dependent survival than was intravenous SK (there are fewer data for intravenous UK, and the P-UK data were from intra-arterial trials).

(e) in the light of these considerations, some clinicians may wish to use thrombolytic therapy in highly selected patients under licence conditions; others who are concerned about the definite risks may choose not to use the treatment at all, or only in the context of a randomised trial.

Implications for research

These limited data leave uncertainties which suggest that further large-scale randomised trials comparing thrombolytic therapy with control in patients with acute ischaemic stroke are needed:

(a) to identify which categories of patient are most likely to benefit (and which are harmed), especially the elderly (age >75) in whom the data on the effects of thrombolysis are very sparse.

(b) to determine reliably the effects on long-term survival (i.e. one year and beyond).

(c) to confirm whether the advantage to thrombolytic therapy in terms of the reduction in death and dependency at three months does indeed persist to six months and beyond, as suggested by one trial.

(d) to identify means of minimising the hazard without reducing the benefit.

(e) to provide clearer evidence that when used in a wider range of hospitals, thrombolytic therapy is associated with a definite net benefit.

In future trials, it would be helpful if data could be collected in such a way as to be compatible with the simple and fundamental outcome assessments analysed in this review. This would (a) help to address the problem in the present review of between trial heterogeneity (which may be exacerbated by missing data), and (b) facilitate future meta-analysis."

It should be noted that since the publication of this review at least some of the research implications are being met. Alteplase is approved for patients up to the age of 80 years. There are now a number of abstracts/reports in the very elderly which suggest that while there is an increase in risk (ICH) and unfavourable outcome, there are very favourable results too. All authors conclude that age alone should not be a reason to deny treatment with alteplase. References are not provided since beyond 80 years of age alteplase is not approved. There are now two reports of outcome at 12 months which suggest that benefit accruing at 90 days is carried forward to one year. The first of these relates to the NINDS RCT⁶ and the second a review of the Cologne experience²⁴ with alteplase also discussed in this STA. Comparisons are made with the NINDS data. The NINDS data show a sustained benefit over twelve months for those patients within 3 hours of stroke onset, OR 1.7, (95% CI 1.2, 2.3). Alteplase treated patients were at least 30% more likely to have minimal or no disability at 12 months than placebo-treated patients (absolute increase 11-13%). The Cologne experience with comparable patients to NINDS except for a younger age and lower mean baseline NIHSS score, showed an identical minimal or no disability rating (mRS 0-1) at 41%. Independent recovery (mRS 0-2) was 52% and functional independence (BI 95-100) was 51%. A total of 150 patients treated with alteplase were assessed. Mortality in Cologne at 1 year was 15% compared with NINDs 24%. Age may have played a part in this. Thus the authors also conclude that the benefit seen at 90 days is maintained at 12 months in the 0-3 hour patients treated with alteplase.

An issue not raised in the Cochrane review concerns the possibility of patient selection for benefit in the 3-6 hours treatment window (unlicensed for alteplase). ECASS III as already noted is examining the 3 - 4.5 hour window even though the earlier RCTs have shown no benefit for alteplase beyond three hours. This may be a function of the limitations of CT imaging technology. CT scanning is the standard for the majority of hospitals capable of assessing patients with AIS. However, more advanced techniques (Magnetic Resonance Imaging, MRI) are also being used to try to detect patients who may still have viable penumbral brain around the infarct and thus who may yet benefit from later reperfusion treatment. These reports are not included with a view to recommending later treatment than 0-3 hours for alteplase but to alert reviewers to the fact that later arrival in specialist units may not preclude the possibility of benefit from thrombolysis. Desmoteplase is a thrombolytic agent derived from the vampire bat saliva. Studies 25 in patients whose ischaemic stroke had been assessed as showing viable penumbra by MRI-scanning at 3-9 hours after symptomatic onset showed an improved rate of reperfusion and clinical outcome than those treated with placebo. Initial dosing was too high with unacceptable levels of SICH (26.2%), but lower doses were found that were acceptable in safety terms for Phase III trials.

There are two reports of treatment with alteplase that bear consideration. Ribo et al ²⁶ had a two stage protocol for patients with acute middle cerebral artery stroke. Patients from 0-3 hours after onset were treated with alteplase according to standard CT criteria. Patients who could only receive treatment from 3-6 hours after stroke onset were assessed by multi-modal Trans-cranial Doppler and by multiparametric MRI-scanning. This allows localisation of the thrombus on the one hand and Diffusion-weighted/Perfusion-weighted imaging on the other. The one determines the territory of vascular occlusion, the other the amount of penumbral brain that could reasonably be reperfused. CT Scanning provides the best information regarding haemorrhage. A total of 122 patients was A (0-3hrs)

n=79 and B (3-6hrs) n=43. Median OTT for A was 136 minutes and for B was 223 mins. NIHSS scores were the same (17) and proximal MCA occlusion location was comparable. Recanalisation rates at 2hrs were similar (A 49.3%, B 55.2%) as were haemorrhagic transformation rates (asymptomatic A 18.7%, B 26.6%; symptomatic A 3.75%, B 2.3%). Improvement at discharge was similar in both groups (NIHSS reduction 6.3 points for A, 6.1 points for B. The number of patients benefiting from treatment was somewhat higher in the 3-6 hour group (A = 58.2%, B = 76.2%, p=0.05), while the patients worsening were the same for both groups. At 3 months independent recovery was A = 42% vs. B = 38%. The authors conclude that the technology permits "later" successful patient treatment.

A second report²⁷ also compared outcome and SICH in alteplase treated patients within 6 hours of stroke onset in MRI-selected patients with acute MCA infarction, with the pooled data of the randomised placebo-controlled trials of alteplase. Perfusion- and diffusion-weighted imaging \leq 6 hours was performed in all patients. In patients treated within 0-3 hours treatment was per ECASSII criteria. Patients between 3-6 hours received alteplase treatment based on MRI findings. Favourable outcome was assessed after 90 days using dichotomised mRS 0-1. ICH was assessed on MRI or CT scanning. The data were compared with the pooled placebo and pooled alteplase patients of the ATLANTIS, ECASS and NINDS alteplase trials. Of 174 MRI-selected alteplase patients 108 (62%) were treated in \leq 3 hours and 66 (38%) within 3-6 hours. Favourable outcome was more frequent in MRI-selected alteplase patients (48% [95% CI, 39, 54]) compared with pooled placebo (33% [95% CI, 31, 36]); p< 0.001) and pooled alteplase patients (40% [95% CI, 37, 42]; p = 0.46). OR were comparably greater for the MRI-selected alteplase group 1.82 (1.32, 2.51) compared with pooled placebo, and the pooled alteplase group 1.39 (1.01, 1.92). SICH was 3% (MRI-selected) and lower than pooled alteplase, 8% (CT-selected), as well as comparable to the pooled placebo group (2%).

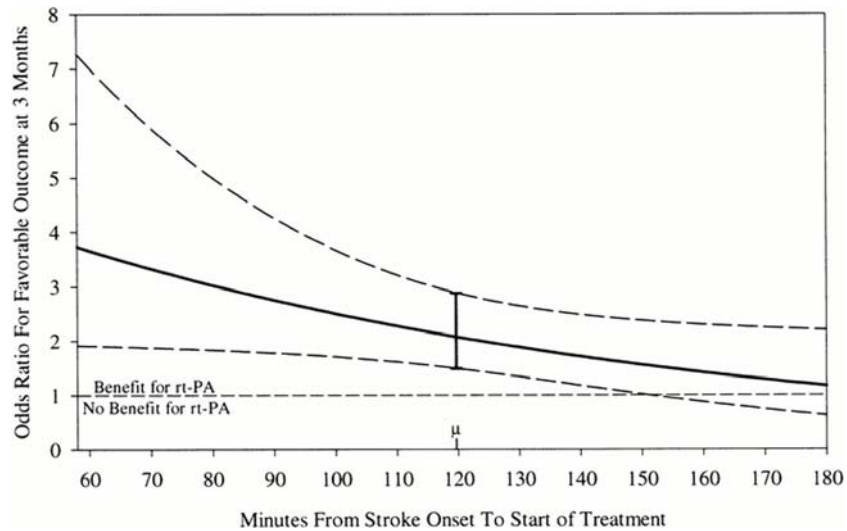
Again this suggested the possibility of benefit from treatment to imaging-selected MCA stroke patients for up to 6 hours. It is emphasised that treatment beyond three hours OTT is not licensed for alteplase.

Pooled analysis of ATLANTIS, ECASS and NINDS studies ¹⁰

In addition, the ATLANTIS, ECASS and NINDS rt-PA study group investigators have performed a pooled analysis of ATLANTIS parts A and B, ECASS and ECASS II and NINDS parts 1 and 2, (see below, this section) and therefore Boehringer Ingelheim has not performed a separate or repeat analysis of the data. It should be noted that Boehringer Ingelheim provided the data from ECASS and ECASS II and statisticians undertaking the combined analysis of the data from all six trials.

In the 5 of the 6 multi-centre, randomised, placebo-controlled trials of alteplase the benefits of treatment were tested for AIS within 6 hours of onset. While similar doses of alteplase were used and common outcome measure employed the maximum time allowed to start alteplase infusion ranged from 3 - 6 hours. Marler et al ⁷ in showing from the NINDS trial that early treatment was associated with better outcome had shown graphically their estimates of Odds Ratios (OR) for favourable outcome at three months in alteplase-treated patients compared with those in patients receiving placebo, by time from stroke onset to treatment.

Figure 1: Odds Ratio for Favourable Outcome



Graph of model estimating OR for favourable outcome at 3 months in recombinant tissue-type plasminogen activator (rt-PA) treated patients compared to placebo treated patients by time from stroke onset to treatment (onset-to-treatment time [OTT]) with 95% confidence intervals, adjusting for the baseline NIH Stroke Scale. OR > 1 indicates greater odds that rt-PA treated patients will have a favourable outcome at 3 months compared to the placebo treated patients. Range of OTT was 58 to 180 minutes with mean (μ) of 119.7 minutes. **Reproduced from *Neurology* 2000;55:1649-55**

The ATLANTIS, ECASS and NINDS study group investigators, by pooling the individual patient data from the 6 trials, have extended this analysis to 6 hours and sought to determine whether time-to-treatment with intravenous thrombolytic therapy (alteplase) is a critical predictor of therapeutic benefit. They excluded a small randomised pilot feasibility trial (n = 27) because different end-points were used.¹¹ The trials had previously been identified in an independent ongoing cumulative meta-analysis published by Wardlaw et al²⁸. For this combined analysis a neuro-radiologist assessed the CT scans of patients with symptomatic or asymptomatic haemorrhage within 36 hours so as to standardise the definition of ICH across trials. In all 6 trials inclusion was based on a

clinical diagnosis of ischaemic stroke determined by a focal neurological deficit measurable on either the NIHSS (NINDS, ATLANTIS, ECASS II) or the Scandinavian Stroke Scale (ECASS), a clearly defined time of stroke onset and CT scans of the head that excluded haemorrhage. As confirmed in the Cochrane review the time allowed from stroke onset to treatment varied. Thus, NINDS allowed 180 minutes from OTT with half to be less than 90 minutes, in ECASS/ECASS II patients should be treated within 360 minutes, ATLANTIS A 0-360 mins, B 0-360, later narrowed to 180-300 minutes. Exclusion criteria were designed to restrict the risk of bleeding. Although, NINDS had no upper age limits, the two ECASS trials and ATLANTIS trials excluded patients over 80 years. The studies had important differences in exclusion of patients with mild or severe stroke. All excluded patients who were rapidly improving. Patients without significant deficit were excluded from NINDS 1 and 2, but there were no upper/lower limits of baseline NIHSS scores. In ECASS and ATLANTIS minor stroke was excluded as were patients with severe stroke in ECASS/ECASSII. ECASS/ECASS II and ATLANTIS B excluded patients with signs of severe and extensive early infarction of the brain on CT scanning. ECASS used a total dose of 1.1mg/kg alteplase (100mg maximum) while the other trials all used 0.9mg/kg. While all trials allowed inclusion of patients who had taken prior antiplatelet agents, oral and intravenous anti-coagulants and antiplatelet agents were precluded for the first 24 hours after alteplase treatment.

The trials were similar as to outcome measures. In all studies NIHSS, modified Rankin Scale and Barthel Index were assessed at 90 days, mortality was calculated and the occurrence of ICH with CT was carefully determined. Glasgow Outcome and Scandinavian Stroke Scales were not used in all trials and were excluded from analysis. There were substantial differences between trials as to definitions of ICH and in specific outcome scales and definitions of favourable outcomes that had been chosen. These are all clearly expressed in the published report.

For the pooled analysis the investigators focussed primarily on the 3-month favourable outcome defined by three neurological function scores, modified Rankin Scale (mRS 0 or 1), Barthel Index (95 or 100) and NIHSS (0 or 1). These represent minimal or no post-stroke disability. Interaction by Onset to Treatment Time (OTT) and treatment, by means of a global statistical test. OR were calculated with 95% CI and p values. since all trials were missing one or more of these outcome measures at 90 days for some patients, a conservative algorithm assigning outcomes based on earlier measurements was developed and applied to all investigations. This allowed all patients with known OTT to be included in the final ITT analysis. Patients missing 1 or more outcomes at 3 months based on the ITT algorithm were given the worst outcomes. To maximise the study power to establish whether benefit from alteplase changes with OTT statistical methodology is described, including that for potential confounding influences.

The ITT analysis included 2775 patients treated in more than 300 hospitals from 18 countries. Median baseline NIHSS score was 11 and median OTT was 243 minutes (1847 patients [67%] were treated beyond 3 hours). A total of 928 patients were treated within 3 hours.

In creating the multivariable model of favourable outcome a variety of potential factors were included as well as 15 potential confounders related to outcome and OTT or treatment. Interaction between OTT and treatment remained significant ($p = 0.005$) in the final model, in which benefit from treatment increased as OTT decreased.

Figure 3 in the Lancet 2004; 363:768-774 (see appendix 6) redefines OTT by treatment interaction through estimation of global OR at different times from stroke onset. This graph demonstrates the justification for ECASS III.

Figure 4 in the Lancet 2004; 363:768-774 (see appendix 6) shows the Modified Rankin Scale measurement at day 90.

Table 2 page 772 Lancet 2004; 363:768-774 (see appendix 6) shows the frequency of parenchymal haematoma broken down by OTT. In addition the proportion of alteplase patients with parenchymal haematoma, including haemorrhagic infarct conversion between 0-360 minutes exceeded those receiving placebo, but the incidences were not more than 6.9% at maximum and for 0 - 90 minutes were only 3.1% (95% CI 1.6 - 5.6). These figures compare with the overall incidence of haemorrhage reported earlier by Wardlaw et al (Cochrane) of 8.6%; 6.1, 11.1).

The authors conclude that their results confirm the strong association between rapid treatment and favourable outcome. Although less effective their results confirm a potential benefit after 3 hours. A next step will be to identify patients presenting after 3 hours who are likely to benefit.

These data are included because there is evidence that patients beyond 3 hours can respond to thrombolysis favourably. ECASS III may confirm this but if not it will then be for more sophisticated methods of imaging to determine those patients who may benefit^{25, 26, 27}. The alteplase license does not include patients from 3-6 hours after stroke onset but the data are included because stroke centres with MRI imaging may perceive that they can treat selected patients from the 3 - 6 hour time window.

5.6 Indirect/mixed treatment comparisons

In circumstances where there are no RCTs that directly compare the technology with the comparator(s) of interest, consideration should be given to using indirect/mixed treatment comparisons. This analysis indirectly compares the proposed technology with the main comparator by comparing one set of RCTs in which participants were randomised to the intervention/common reference with another set of RCTs in which participants were randomised to the main comparator/common reference. The common reference is often placebo, but may be an alternative technology.

Before comparing the proposed technology with the main comparator, the comparability of the two sets of RCTs must be established. If the RCTs have not been described in the previous sections the methodology and results from the RCTs included in the analysis should be summarised using the format described in sections 5.3 and 5.4 Highlight any potential sources of heterogeneity between the RCTs included in the analysis.

Give a full description of the methodology used and provide a justification for the approach.

There are none that are relevant

5.7 Safety

This section should provide information on the safety of the technology in relation to the decision problem. Evidence from comparative RCTs and regulatory summaries is preferred; however, findings from non-comparative trials may sometimes be relevant. For example, they may demonstrate that the technology shows a relative lack of adverse effects commonly associated with the comparator, or the occurrence of adverse effects not significantly associated with other treatments.

If any of the main trials are designed primarily to assess a safety outcome (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse effect), these should be reported here in the same detail as described in the previous sections relating to the efficacy trials.

Give a brief overview of the safety of the technology in relation to the decision problem.. Give incidence rates of adverse effects if appropriate.

Alteplase (Actilyse ®) has been available for many years for the thrombolytic treatment of acute myocardial infarction and massive pulmonary embolism. The principal adverse reaction which may be severe and even fatal is haemorrhage. Infrequently anaphylactic reactions have been observed. The

latter are usually mild but can be life-threatening in rare cases. Their frequency is uncommon. Haemorrhage, which may be serious, includes intracranial haemorrhage (ICH). With respect to other organ systems gastrointestinal haemorrhage has the frequency classification as common. The Company Core Data Sheet and the EU SPC are consistent with respect to potential system haemorrhage and other adverse reactions. In the indication of acute ischaemic stroke the incidence of ICH is different, being classified as common, insofar as haemorrhagic transformation of an acute cerebral infarct may occur as well as remote parenchymal haemorrhage. ICH is not always associated with symptomatic neurological deterioration and the RCTs and observational studies make it clear that symptomatic ICH (SICH) is considered important in defining serious adverse reactions to alteplase, this being determined by the presence of bleeding as shown by imaging together with a deterioration of ≥ 4 points on the NIHSS stroke scale. Haemorrhage in other organ systems beyond ICH is uncommon in stroke patients and consistent with that seen in the other approved indications. Non-haemorrhagic adverse reactions include decreased blood pressure (very common $> 1:10$), body temperature increased (common $>1:100$, $<1:10$), fat embolisation (rare $>1:10,000$, $<1:1000$).

ICH is increased in frequency in patients being treated with alteplase for AIS, compared with patients being treated for acute myocardial infarction or massive pulmonary embolism (uncommon $>1:1000$, $,1:100$). The frequency in AIS is common ($>1:100$, $,1:10$) and includes cerebral haemorrhage, cerebral haematoma, haemorrhagic stroke, haemorrhagic transformation of stroke, intracranial haematoma, subarachnoid haemorrhage. ICH has not been shown to increase overall mortality although, of course, ICH can be fatal.

Larrue *et al*²⁹ have analysed ECASS II to detect risk factors in AIS patients treated with alteplase. These include alteplase itself, extent of hypo-attenuation on baseline CT, congestive heart failure, increasing age and baseline systolic blood pressure. Prior aspirin also appears to increase the risk of SICH.

Table 2 on page 772 Lancet 2004; 363:768-774 shows the frequency of parenchymal haematoma between 0 and 360 min after treatment including haemorrhagic conversion for the pooled analysis of the alteplase placebo-controlled trials¹⁰, dichotomised for the various time-windows investigated.

The frequencies reported in the non-RCTs included in this STA are consistent with or less frequent than that reported for all RCTs in the Cochrane review, (8.6%, 95% CI 6.1 – 11.1). It should be noted that in SITS-MOST, the largest single outcomes database available today, the comparable SICH frequency is 64/4481 (1.4%, 95% CI 1.1, 1.8) as reported in the 6th report (final report still awaited). The other (RCT) definition of SICH includes any haemorrhage plus NIHSS score deterioration ≥ 4 points has a frequency in SITS-MOST of 229/4381 (5.2%, 95% CI 4.6, 5.9).

The EU-SPC section on side effects is currently up to date according to the most recent periodic safety update report and spontaneous reports of adverse events and Actilyse brand of alteplase has had its marketing authorisation renewed in 2004. It should be noted that for the central venous access device thrombotic occlusion indication for which regulatory approval is to be sought in the coming weeks, treatment with alteplase (2mg) has not been associated with ICH.

Of interest with respect to in-hospital mortality in patients with AIS treated with alteplase is a report from Heuschmann PU *et al*³⁰ of a prospective, observation cohort from 225 German hospitals collaborating with the German Stroke Registers Study Group. Of 1658 AIS patients admitted between 2000 – 2002 and treated with alteplase, 166 (10%) died during hospitalisation. Factors predicting hospital death after alteplase were older age and altered level of consciousness. SICH was 7.1% and increased with age. An inverse relationship between the number of patients treated with alteplase in the respective hospital and the risk of in-hospital death, was observed (adjusted). OR 0.97, 95% CI 0.96, 0.99 for each additional patient treated with alteplase/year). The findings are consistent with the observation in SITS-MOST (see above section 5.5) of increased mortality from the index AIS

treatment with alteplase for the first 10-15 patients. Such deaths are not caused by SICH.

5.8 Non-RCT evidence

In the absence of valid RCT evidence, evidence from other study designs will be considered, with reference to the inherent limitation inferred by the study design. The level of detail provided should be the same as for RCTs and where possible more than one independent source of data should be examined to explore the validity of any conclusions. Inferences about relative treatment effects drawn from observational evidence will necessarily be more circumspect from those from RCTs.

In North America and Europe after alteplase was approved as thrombolytic treatment in AIS a number of important observation cohort studies were performed, so as to examine the implementation of this treatment in hospitals accustomed to receiving and treating stroke patients. Such studies that have been cited for this STA are included on the basis that substantial numbers of patients have been included in the treatment cohorts, that there was evidence of competent data collection, that observations with regard to safety are relatively complete and that outcomes can be considered with reference to the evidence from RCTs.

Thus, in the EU, initially 15 member states and then 25 upon expansion of the Union, alteplase was approved upon two conditions, that the MAH performed a further placebo-controlled investigation into the 3-4.5 hour time window, ECASS III, (see above section 5.2.5) and secondly that patients receiving treatment within the EU according to the alteplase labelling of 0-3 hours from stroke onset be documented as to outcomes in a monitored observational cohort study (SITS-MOST). This study, now closed to recruitment upon agreement with the CHMP, is now in the process of data collection, cleaning and entry and a final report on >6000 patients treated is expected in early

2007. This will represent the largest available single body of data regarding the use of alteplase in the treatment of AIS in the world at present.

Centres participating in SITS-MOST will continue to report their treatment outcomes into the academic parent of SITS-MOST, namely Safe Implementation of Treatment of Stroke – International Stroke Treatment Registry (SITS-ISTR) which is presently collecting outcomes data on stroke treatment with alteplase from centres in countries where alteplase is approved outside North America and the EU. SITS-MOST has been monitored by representatives of the sponsor, Boehringer Ingelheim. For the purposes of the STA the 5th and 6th SITS-MOST reports, the former being a subset of the latter, both filed with the CHMP at their request are provided.

The 5th report reference covers 3180 patients treated in 222 centres, while the 6th report reference covers 4543 patients from 259 centres. Both reports are provided because of a finding from centres previously inexperienced in managing acute stroke patients with alteplase was found to have higher mortality from the initial ischaemic event. This was explored at the request from the CHMP as a post-hoc analysis and confirmed in the 6th report, following which the CHMP agreed that SITS-MOST had served its original purpose and that the study might be concluded.

The finding demonstrates a message that may be considered important for the purposes of this STA that new stroke centres intending to offer thrombolytic treatment of AIS with alteplase to need to understand the importance of training and experience as well as inter-disciplinary collaboration both prior to and after arrival in the stroke unit, given that treatment must be initiated as early as possible and before the expiry of the 3-hour window from stroke onset. The finding was clearly not related to intracranial haemorrhage rates in the inexperienced units, which are the same as with experienced units.

Two North American cohorts have been included; the STARS 'trial' because the study demonstrated the importance of adherence to alteplase labelling and the avoidance of protocol violation if poor overall outcomes are to be

avoided and the CASES reference trial reported from Canada where strict adherence to protocol/labelling was shown to provide the expected favourable results.

In the Boehringer Ingelheim literature database there are many abstracts and full reports of small cohorts from different hospital centres around the world but most are too small to be of additional value. However, the Cologne experience is of interest not just because the authors compared their own performance with the outcomes reported in RCT, but because the one hospital prepared to offer thrombolysis in AIS went to exceptional lengths in the public awareness arena as well as the ambulance service so as to direct events considered possibly to be acute stroke urgently to the stroke unit and as a result have the shortest onset – and door-to-needle treatment times currently reported. This is important not only for improving beneficial outcomes but also in increasing the proportion of patients who can be treated.

Experience of telephone/video film/electronic transmission of CT scans and neurological support in the management of AIS in a rural area of Germany (Bavaria) by the Telemedic Pilot Project for Interactive Stroke Care (TEMPIS) has shown in an initial report the feasibility of remote, specialised neurological stroke consultation allowing the early administration of alteplase in local hospitals without stroke units, with promising early results. The project is ongoing.

Finally, a small UK cohort is included from Glasgow and from Newcastle. This report shows how cautious the UK has been with respect to thrombolysis in AIS. The fact is that there was virtually no contribution from the UK to RCTs of alteplase. Those centres who tried to contribute to the ECASS trials simply found themselves unable to comply with the protocols, even to treat within 6 hours of onset. Professors Ford and Lees have led the way in the UK and since these early experiences they have been responsible for a contribution to SITS-MOST of 240 patients from 20 centres (6th report).

5.8.1 Summary of methodology of relevant non-RCTs

All are open-label observational cohort studies in the absence of relevant comparators. Placebo is no longer appropriate in terms of ethics and there are no other approved thrombolytic agents that can be used. Other agents are being studied but cannot be used as comparators being experimental. Aspirin and/or heparin have been considered as possible comparators or given alone or as well as alteplase. However neither agent has thrombolytic properties and both are considered to add to the risk of ICH when given concurrently with alteplase.

The studies included are either large cohorts or raise issues relating to the availability of treatment for patients capable of being treated within three hours and have generally been compared in terms of outcomes with the results of RCTs. All are published with the exception of SITS-MOST for which the 5th and 6th unpublished reports are included, written by representatives of the MAH for regulatory purposes in the EU and from which the most recent interim results have been presented at the European Stroke Conference 2006 by the international coordinators – Professor Nils Gunnar-Wahlgren ²¹ (presentation attached)

5.8.2 Critical appraisal of relevant non-RCTs

The three largest studies including some 6000 patient outcomes were performed and monitored by the sponsors, Genentech Inc in the USA; Hofmann La Roche in Canada and Boehringer Ingelheim in the EU; and as such, are considered to have been performed to accepted standards of GCP. While they are open-label observational cohorts they represent a larger database of patient outcomes than that of the RCTs and the results have been compared with those of the RCTs. In addition they have been monitored by the MAH's clinical monitors

All were performed with the intention of assessing the implementation of thrombolytic treatment of AIS within medical practice and all have shown that when patients are carefully selected according to the approved alteplase labelling and treated by experienced stroke specialists in acute stroke units then both safety results (SICH, Mortality) and favourable outcome proportions

are consistent with, if not better than those outcomes in RCTs. As such the studies included are considered relevant to this STA. It should be noted that a final report on SITS-MOST now closed to patient entry, is expected in early 2007 and may be available as an addendum to this submission.

5.8.3 Results of the relevant non- RCTs

5.8.3.1 CASES¹³

A total of 1135 patients enrolled at 60 centres in all major hospitals across Canada, provided data on the outcomes of treatment with alteplase within the terms of the product labelling, over some 2.5 years. The registry is believed to have collected data for an estimated 84% of all alteplase-treated ischaemic stroke patients in the country. An excellent clinical outcome (mRS 0-1) was documented in 37% of patients. SICH was reported in only 4.6% of patients (95% CI 3.4, 6.0%). The outcomes were considered commensurate with the results of RCTs.

5.8.3.2 STARS Study¹⁴

STARS enrolled 389 patients from medical centres in the USA. Median OTT was 2 hours 44 minutes, median baseline NIHSS score was 13. The 30-day mortality was 13%. At 30 days, 35% of patients had a very favourable outcome (mRS 0-1) and 43% were functionally independent (mRS 0-2). SICH numbered 13 (3.3%) including 7 fatalities. Protocol violations were 32.6%, usually breaches of labelling recommendations. These outcomes were considered consistent with the results of RCT as well as acceptable.

5.8.3.3 Cologne Experience¹⁵

Of 453 patients referred with a presumed diagnosis of ischaemic stroke by means of a direct referral system for eligible patients throughout the city, 22% (100) were treated with IV alteplase at labelled dosage, 26 within 90 minutes. The mean time from stroke onset to arrival was 78 minutes and arrival to treatment 48 minutes. Total mean OTT = 126 minutes (the lowest recorded to date). At 90 days 53% were recovered to fully independent function. The

rates of total, symptomatic and fatal ICH were 11%, 5% and 1% respectively. Overall mortality was 12%. The results were considered at least comparable to those of RCTs.

5.8.3.4 TEMPIS Project¹⁶

All systemic thrombolyses in patients with AIS admitted to 12 regional (rural) clinics and two specialist stroke centres were recorded prospectively in Bavaria, Germany. Of 4725 stroke/TIA patients; 115 (2.4%) in the community hospitals and 110 of 1889 in the stroke centres (5.8%) received thrombolysis with alteplase at recommended doses. Neurologist supervision was maintained by electronic communications between the community hospitals and the specialist centres, by video-links, electronic CT transmission and telephone. Mean time to treatment was identical for the community hospitals and the stroke centres, notwithstanding the consultation time for the former. SICH (7.8%) was higher in the community centres than in the stroke centres (2.7%), ($P=0.14$), but both were within the NINDS Range. Mortality was low at 3.5% (community hospitals) and 4.5% (stroke centres). The study is considered to show the feasibility of thrombolytic treatment in rural areas under the electronic/telephone supervision of stroke specialists.

5.8.3.5 The UK Experience¹⁷

This initial report of UK experience confirms the very cautious approach taken in the UK before and after the regulatory approval of alteplase. The authors concluded that the cohort included more severely affected patients than in other published series but that the outcomes and complications were consistent with experience elsewhere. Mean NIHSS score was 17, OTT was 139 minutes; 5/16 episodes of ICH were SICH. 31% achieved mRS 0-1 at 90n days. The UK experience has increased thanks to participation in SITS-MOST (see below). It should be noted that in December 2005 (5th report) the UK contribution into SITS-MOST was 240 patients from 20 centres.

5.8.3.6 SITS-MOST^{18, 20}

SITS-MOST is the largest observational cohort study of alteplase to be performed to date. It was mandated by the CHMP as one of two conditions upon which the conditional approval of alteplase was granted within the EU and interim results have been reported by the MAH (Boehringer Ingelheim) on a six-monthly basis since initiation. The study is derived from an academic registry based in Sweden; SITS-ISTR and now that SITS-MOST has been closed to recruitment (final report expected early 2007) the participants will continue to report treatment outcomes into SITS-ISTR along with country input from outside the EU. SITS-MOST has been monitored by Boehringer Ingelheim staff who receive the data from Sweden by electronic transfer and who have written the reports for the CHMP. The most recent full interim report (the 6th) is included together with its prior subset (the 5th).

The reason for this is that following the CHMP review of the 4th report in which there was a suggestion of higher initial stroke mortality in less experienced stroke units. The authority requested post hoc analyses of the data in order to determine a reason for this. The 5th report suggested that the issue was simply a result of centres learning to manage AIS patients and not a result of thrombolytic treatment. The 6th report has confirmed the findings and in the view of the MAH, confirmed the cause. Namely in setting up to manage AIS patients on an acute emergency basis there is an inevitable “learning curve” in managing these patients efficiently and that the price of offering treatment is inevitably associated with less good/management initially followed by outcomes which improve to become consistent with those obtained in experienced units.

Close consultation with experienced units is strongly recommended for new/inexperienced units so as to speed the patient efficiently through diagnosis and assessment to treatment and expectation of response.

The results of SITS-MOST (6th report) are as follows: the status overview by country shows a broad base of treatment uptake, with still relatively few treatment centres in some countries. A total of 4543 patients have been

enrolled in 259 centres in 14 countries in Europe. Of these 4517 have been confirmed as receiving treatment with alteplase. Demographic data confirm the evidence from other trials. A total of 20 patients were treated at age >80 years. The medical histories are consistent with other studies including RCTs, hypertension \leq 60%, diabetes \leq 16%, hyperlipidaemia 30%. Mean alteplase dose was 68.8mg, OTT was 136 minutes and patients enrolled but not treated were only 5. Mean baseline NIHSS score was 12.9 and that at 7 days was 6.5. There was only a small and non-significant difference in NIHSS score between more experienced and less experienced centres (mean 12.7 vs 13.0).

Improvement in NIHSS score from baseline at 7 days (\geq 4 points) was seen in 2588 patients (68.4%), worsening in 176 (4.6%). Mean NIHSS data at baseline for all centres (12.9) improved to 6.5 at 7 days (median 13.0-4.0). Global outcome 24 hours to 7 days was much better/better at 63.3% and 72.4% respectively.

Any haemorrhage according to ECASS trials criteria is shown in table 7.1 [SITS-MOST tables] below, (41 = HI = haemorrhagic infarction, PH = Parenchymal Haemorrhage, PHr = Parenchymal Haemorrhage remote from infarct site; 1 = minor, not considered space-occupying, 2 = considered space-occupying). Cerebral Oedema while present in some 27% of patients is considered to occur less frequently and less severely in treated as opposed to untreated patients (table 7.3 SITS-MOST 6th report). SICH according to protocol definition (grade 2 haemorrhage plus \geq 4 points NIHSS score deterioration) at 7 days was 5.2% with 1.0% uncertain (6.2% worst case). There was no evidence of increased SICH attributable to alteplase by site experience.

Mortality at 90 days was known for 3609 patients. Clearly mortality would not be known for those patients whose data were not yet entered or who had not reached 90 days. The 90-day mortality was 12.9%, with independent recovery (mRS 0-2) 52.8%. Mortality in relatively inexperienced centres was 123/706 (17.4%) although independent recovery (mRS 0 - 2) was as good (52.3%) as in the most experienced centres (54.4%).

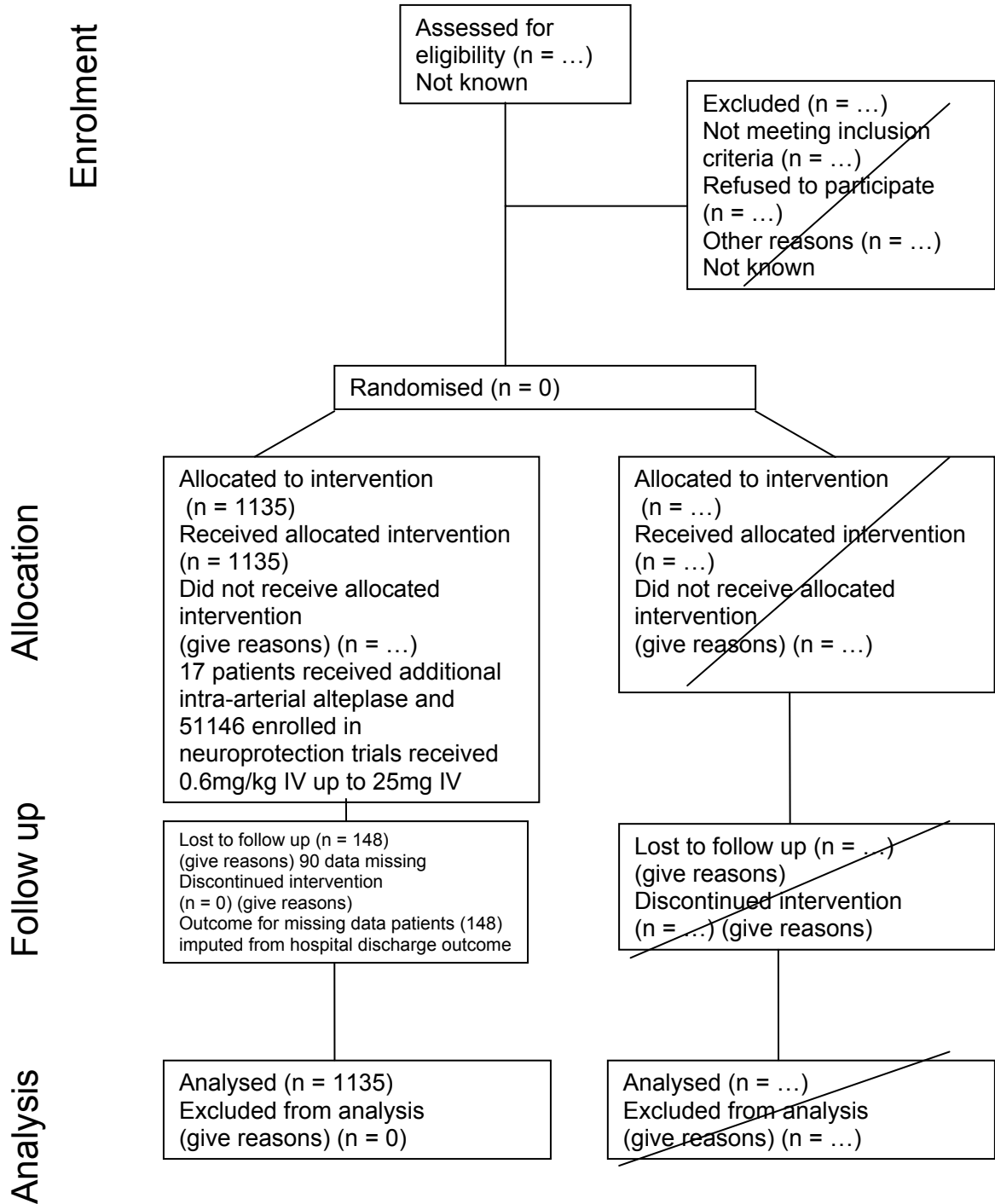
Confidence intervals (95%) for the very experienced centres for mortality was 9.7-12.6% and for the very inexperienced was 14.8-20.4%. The figures for independent recovery are 52.1-56.7% (very experienced) and 49.1-53.6% (very inexperienced). The data plotted over time shows that plateaus have been reached and that the proportions are very stable. Primary causes of death (table 8.10) show that the index stroke was responsible in more than 50% of patients dying. ICH and haemorrhagic transformation account for < 18% of deaths. Finally mRS at 90 days outcome (n = 3609) is 0-1 = 38.2% and 0-2 = 52.9%.

The explanatory analysis for higher mortality in inexperienced centres was explored according to those who participated in the two ECASS trials vs those who had treated at least 5 patients prior to entering SITS-MOST vs those centres who had treated < 5 patients prior to joining the study, notwithstanding training and advice from the national study coordinators. All the evidence points to the fact that any “new” centre will need to treat at least 10-15 patients so as to refine the efficiency and effectiveness with which they manage their patients. This appears to be a price to be paid for introducing thrombolysis in AIS into the community of medical practice. Training and support from experienced colleagues and centres will be important. There is no difference between centres with respect to the ICH risk attributable to alteplase in AIS patients. A report published independently³⁰ seems to confirm this.

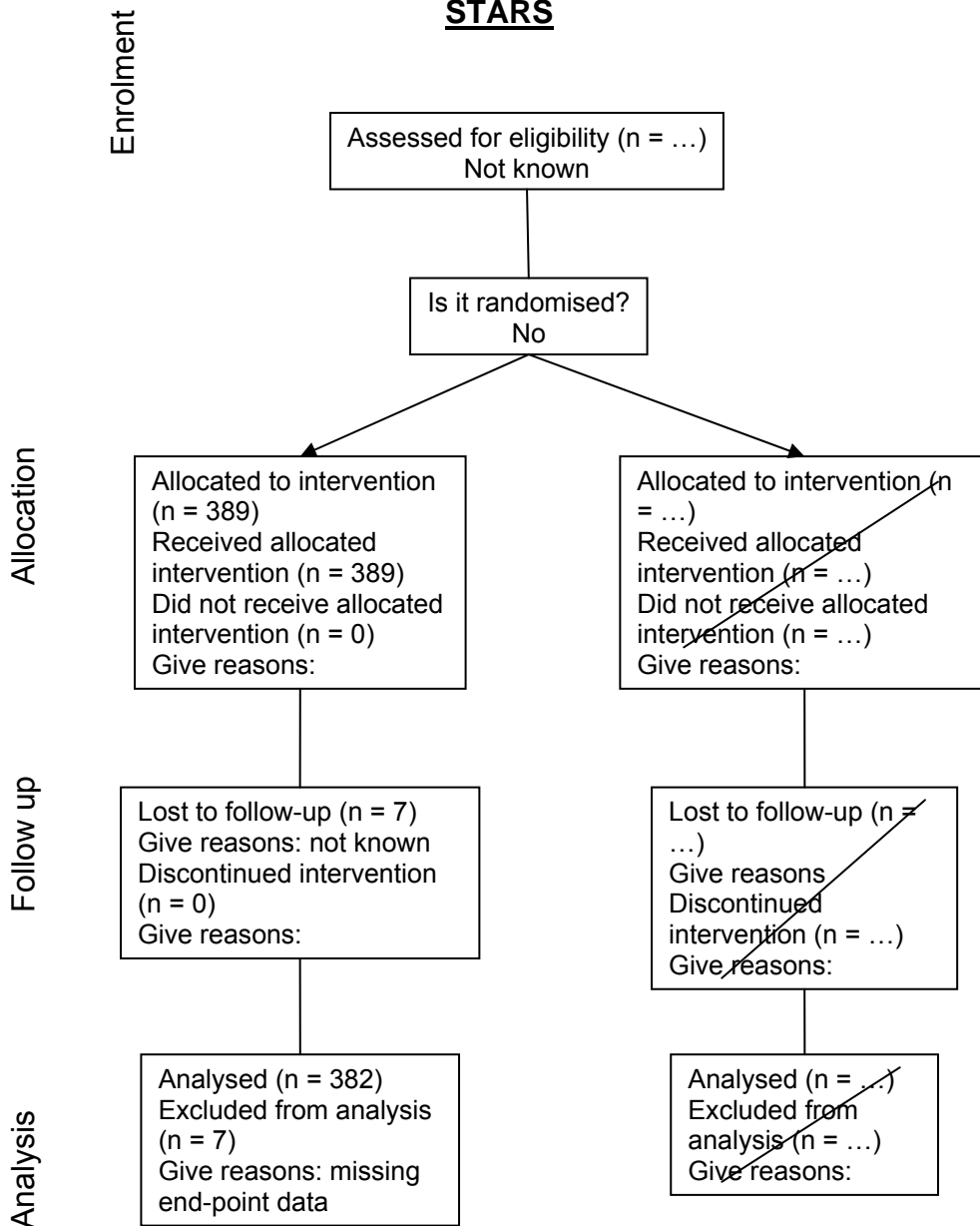
Finally the presentation made most recently to the European Stroke Conference in 2006 is attached²¹. Professor Wahlgren makes particular reference to the outcome comparisons with RCTs. Thrombolysis for acute Ischaemic stroke: main outcome results for 2003-2005 of SITS-MOST in Europe. It should also be noted that the CHMP has agreed that SITS-MOST has meet its objectives of “safe implementation”.

Overleaf are the consort flow charts for the non-RCT studies:

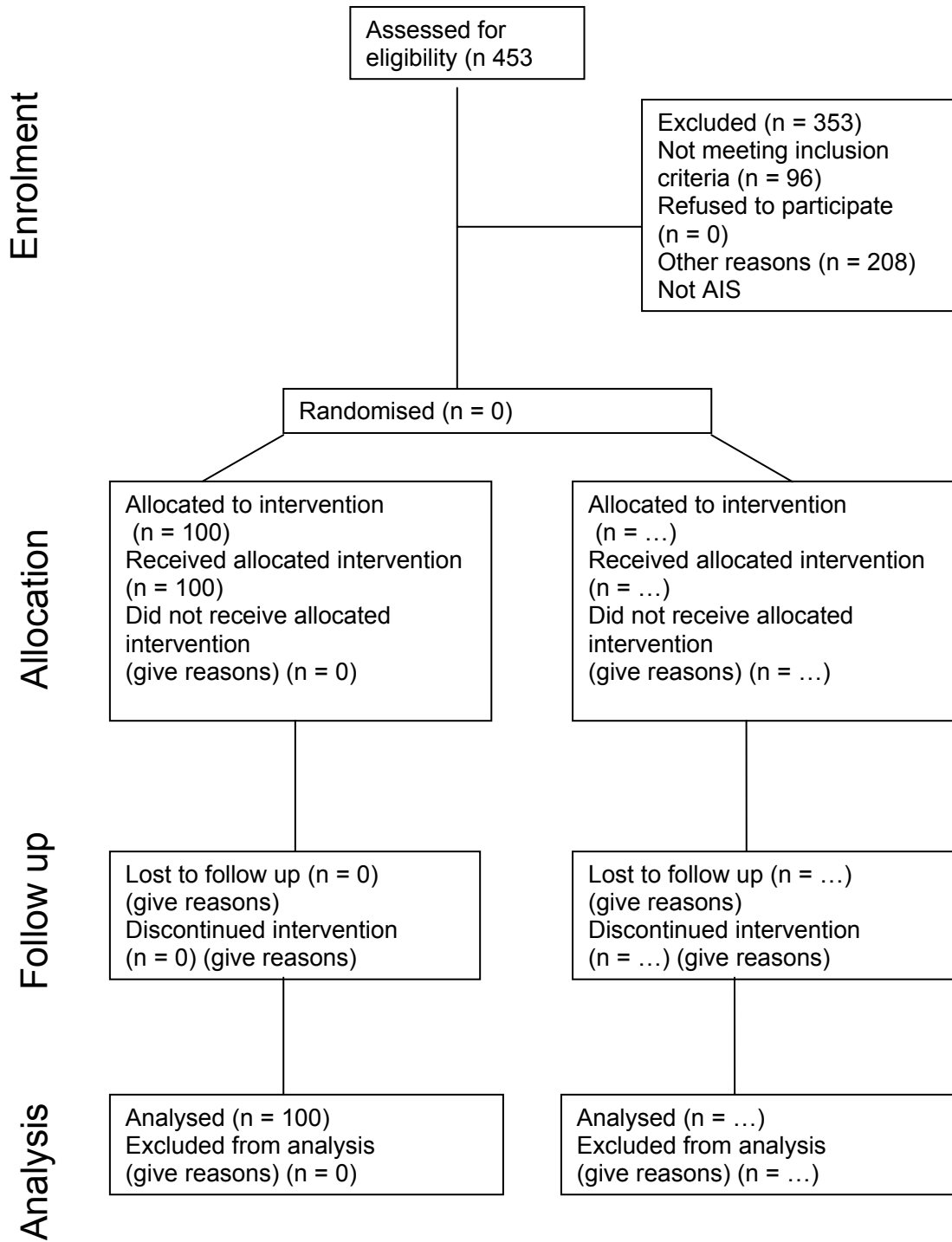
CASES

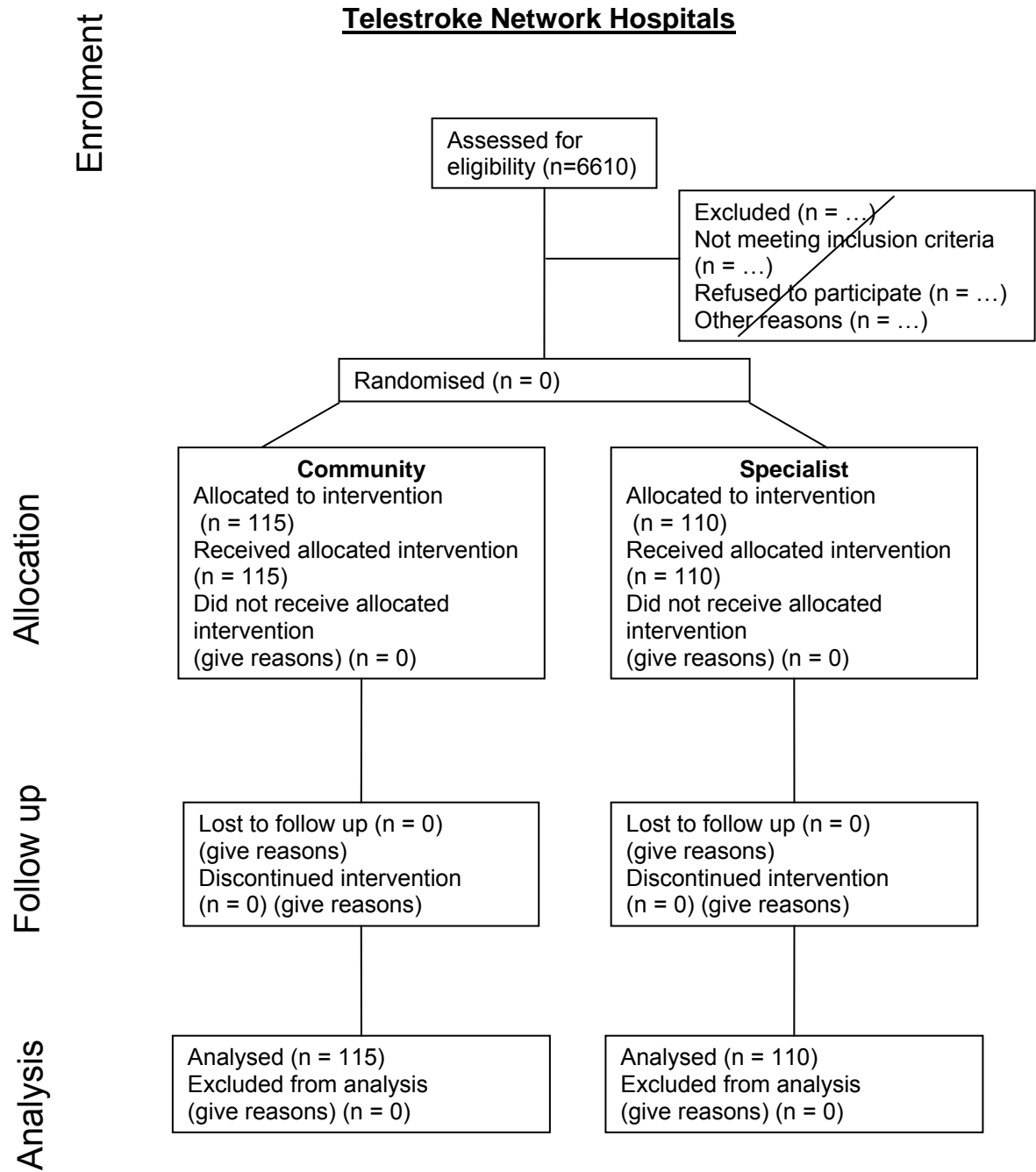


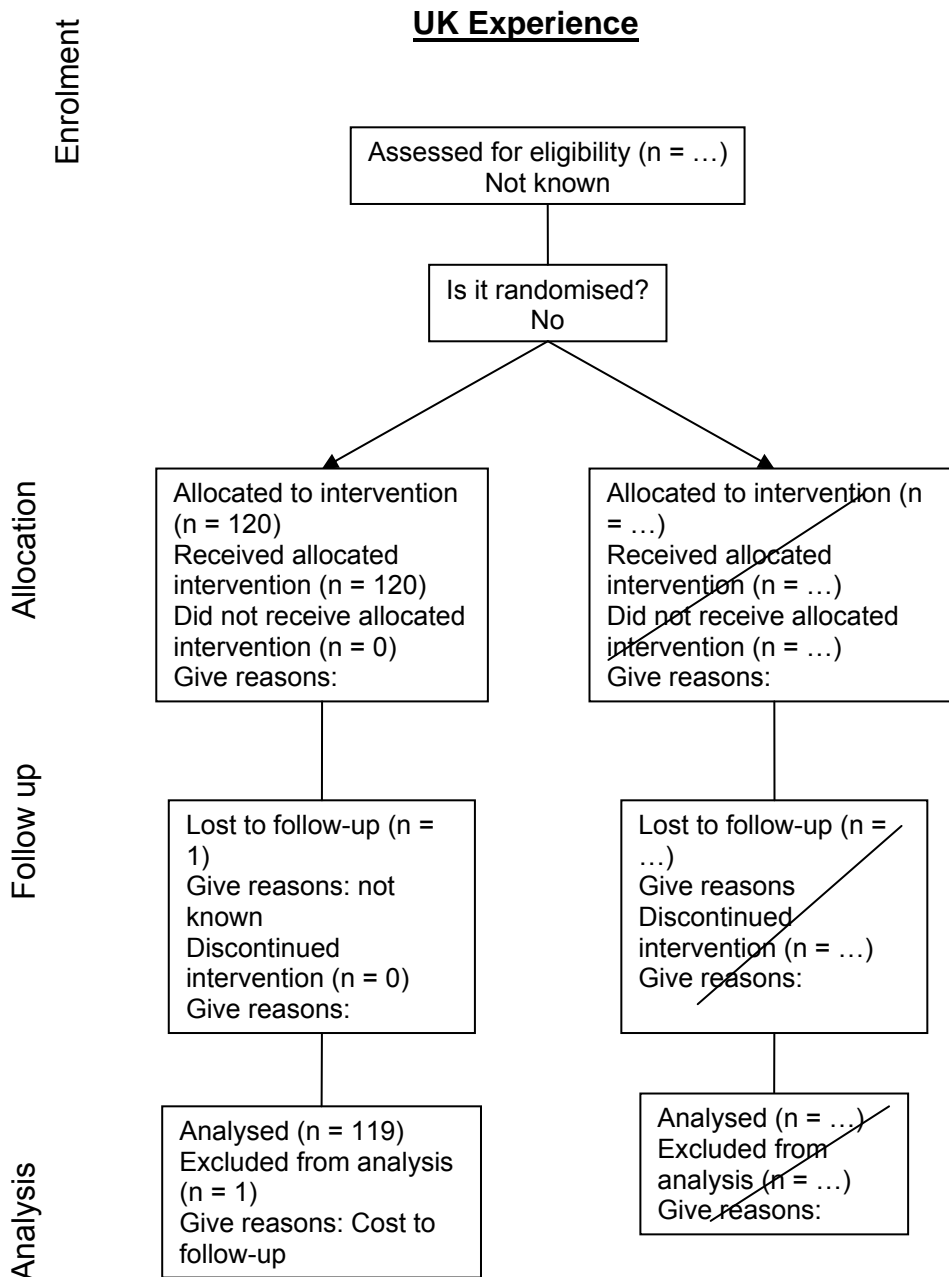
STARS



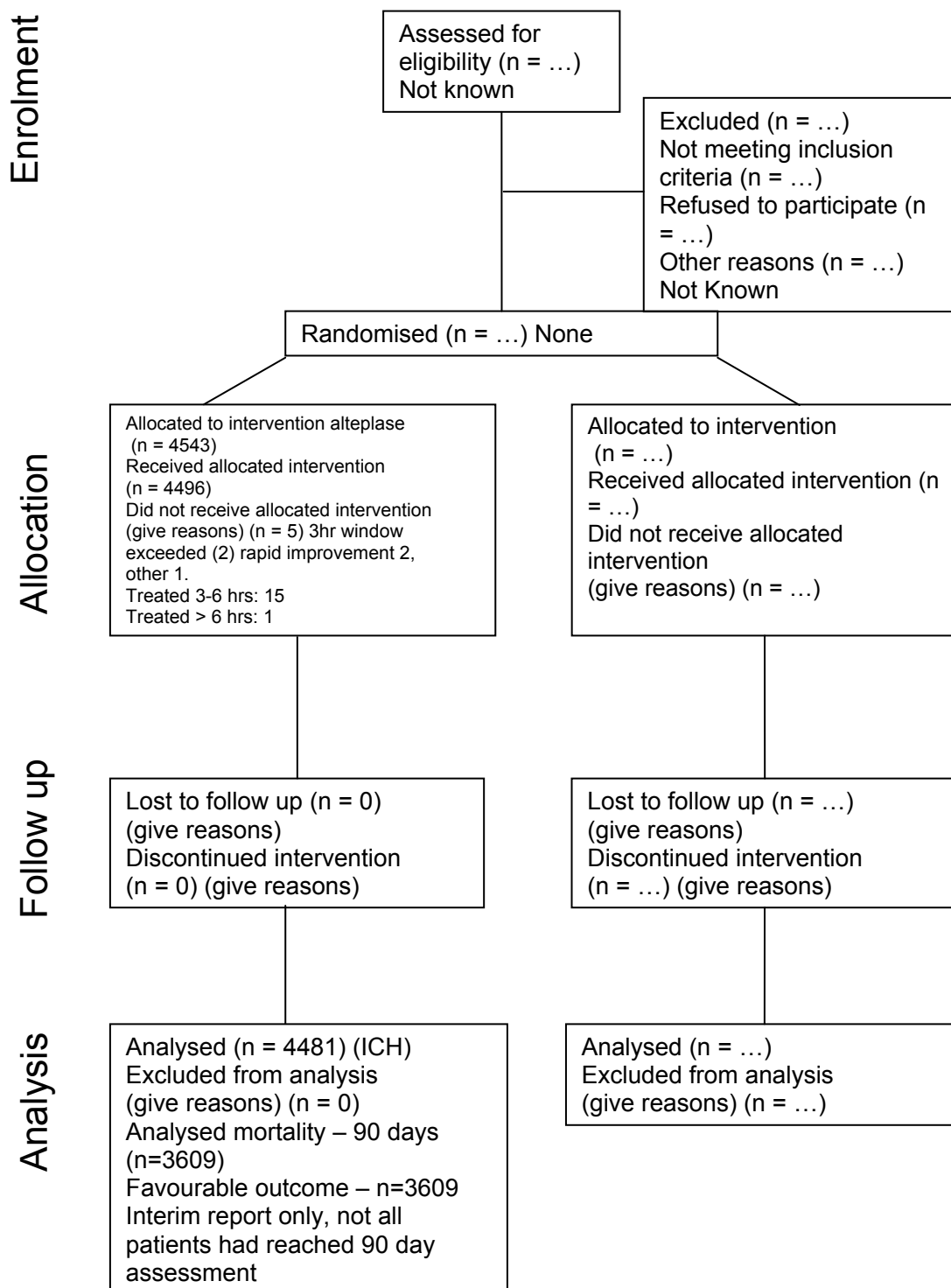
COLOGNE







SITS-MOST



5.9 Interpretation of clinical evidence

5.9.1 Provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

The active ingredient of Actilyse® is alteplase, a recombinant human tissue-type plasminogen activator, a glycoprotein, which activates plasminogen directly to plasmin. When administered, alteplase remains relatively inactive in the circulation. Once bound to fibrin, it is activated, inducing the conversion of plasminogen leading to the dissolution of the fibrin clot. Alteplase was first developed for the thrombolytic treatment of acute myocardial infarction within 6 hours of symptom onset and has proven to reduce 30 day mortality in patients with acute MI. The drug is also approved for the thrombolytic treatment of massive pulmonary embolism with haemodynamic instability and now most recently for the thrombolytic treatment of acute ischaemic stroke (AIS) within 3 hours of the onset of stroke symptoms and after exclusion of ICH by appropriate imaging techniques such as CT scanning of the head.

The approved dose in AIS is 0.9mg/kg IV subject to a maximum of 90mg given by 10% bolus followed by infusion of the remaining solution over 1 hour. This is less than the approved dose (1.1mg/kg, maximum 100mg) for acute MI and massive pulmonary embolism.

The clinical evidence supporting this regulatory approval comes from double-blind, placebo-controlled RCT conducted in North America, Europe, Australia and New Zealand, from meta-analyses including a Cochrane systematic review and the pooled analysis of the alteplase RCTs, as well as a number of open-label observational cohort studies which lend themselves to comparison with the outcomes of the RCTs and one of which, mandated by the CHMP in Europe, constitutes the largest single outcomes database following the treatment of AIS with alteplase.

Proof of clinical benefit for alteplase when compared with placebo relies principally on the outcome of the NINDS RCT of alteplase versus placebo in

the 0 -3 hour time-window after onset of stroke symptoms and on the 0 -3 hour dichotomised windows from the 0 -6 hour ECASS I and II trials and the (originally) 0-6 hour ATLANTIS trials A and B. The pooled analysis of all RCTs confirms the benefit of treatment both early and at 90 days. The 1 year follow-up of the NINDS trial patients confirms that the benefit seen at 90 days persists for 12 months. The Cochrane review of all trials of thrombolytic drugs confirms a net benefit of a significant reduction in the proportion who are dead or dependent at the end of follow-up i.e. significantly more patients alive and independent at 3-6 months.

The Cochrane data also confirm a significant excess risk of treatment with alteplase (and other similar drugs), namely fatal intracranial haemorrhage and death from all causes with thrombolytic therapy. The pooled alteplase data show the hazard ratio for death adjusted for baseline NIHSS score was not different from 1.0 for the 0 - 4.5 hour times to treatment. ICH was seen in 82 (5.9%) alteplase patients and 15 (1.1%) controls ($p < 0.0001$). ICH was not associated with OTT but was with alteplase treatment ($p = 0.0001$) and age ($p = 0.0002$).

Further support for the net benefit of alteplase over risk comes from the larger scale observational cohort studies several of which were required by regulatory authorities to assess the implementation of treatment into medical practice, principally in Europe, Canada and the USA. These show that with strict adherence to the prescribing information (SPC) for alteplase outcomes in terms of proportion benefiting, SICH and death are at least as good as those coming from RCTs and may even be superior. The alteplase labelling contains very specific dosing recommendations, contra-indications and precautions/warnings to be followed. While these limit the number of patients for whom treatment with alteplase can be provided the emphasis is particularly on getting patients with AIS urgently to centres where eligibility for treatment can be established rapidly.

5.9.2 Identify any factors that may influence the applicability of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of

the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select suitable patients based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the Summary of Product Characteristics?

SITS-MOST including the contribution from the United Kingdom has demonstrated that treatment with alteplase for AIS according to the prescribing information for Actilyse® (SPC) is feasible and achieves the same or somewhat better outcomes than did RCTs. However, the mean time from onset to treatment with few exceptions is relatively late within the 0 - 3 hour window. The evidence shows that early treatment is associated with better outcomes. In order to achieve this there needs to be better understanding by patients and their families as to what constitutes a stroke, acceptance by the emergency services that ischaemic stroke diagnosed early is a treatable emergency and the interdisciplinary efficiency within hospitals effectively minimises delay from “door-to-needle”. Reducing the OTT should be a priority for specialist stroke units intending to provide treatment with alteplase. Once units are trained and experienced the evidence is strong that consistently beneficial results can be achieved.

The criteria for patient selection are clearly listed in the SPC for Actilyse® and all of these have emerged from the RCT development programme for alteplase. Apart from excluding prior ICH, severe stroke (NIHSS score >20) should not be treated, nor should minor degrees of disability or rapidly improving stroke scale scores. Severe hypertension should be managed, as should hyperglycaemia. CT exclusions are important since failure to comply with the recommendations is associated with increased risk of ICH and unfavourable outcome.

The SPC dose of alteplase (0.9mg/kg subject to a maximum of 90mg) given by 10% bolus injection followed by a 60 – minute infusion of the remaining 90 % of solution, was used in 5 of the 6 RCT described in this STA.

6 Cost effectiveness

6.1 *Published cost-effectiveness evaluations*

6.1.1 Identification of studies

Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided in appendix 3, section 9.3.

In order to evaluate the extent of need for a modelled economic evaluation, a comprehensive literature review was undertaken to identify any existing studies that have attempted to estimate the cost-effectiveness of alteplase in acute ischaemic stroke. The literature review encompassed the following databases:

- EMBASE
- MEDLINE
- MEDLINE IN-PROCESS
- COCHRANE
- NHS EED
- HEED

In addition, a search was performed on Boehringer Ingelheim's internal database of product-related studies, BILIT. Please refer to Appendix 3, Section 9.3 for a full description of the search strategies employed for each database.

Table 6 outlines the retrieval results, including primary reason for exclusion and identified studies across all databases. A record was excluded if it was readily obvious from the title and/or abstract that one or more of the following pragmatic exclusion criteria applied to the article:

- Did not relate to acute ischaemic stroke
- Was not an economic evaluation
- Did not relate to alteplase
- Was not English language
- Was either recorded in duplicate or had been already identified in a previous database
- Was conference proceedings not a published article

No other exclusion criteria were applied.

Table 6 Literature review retrieval results

Exclusion criteria	Number of studies
None	353
Not relating to acute ischaemic stroke	83
Not an economic evaluation	198
Not relating to alteplase	25
Not English language	0
Duplicate or already included	31
Conference proceedings	8
Total excluded	345
Total identified	8

In addition, a review of the bibliographies of the identified studies was performed. One further study that was not reported in any of the above database searches was identified from this review. All of the identified studies are listed and discussed in the following section.

6.1.2 Description of identified studies

Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. Where studies have been identified and not included, justification for this should be provided.

The nine identified studies are as follows:

1. Demaerschalk and Yip, (2005)¹

Aim: To determine the economic impact of increasing alteplase use in the United States.

Methods: The study examined the cost of stroke care and the potential savings from extended use of alteplase. No health outcomes are considered.

Results: More than \$7m can be saved in the US for every 2% increase in alteplase treated patients.

Relevance: This study is not a cost-effectiveness analysis but rather a budget impact analysis in a US setting.

2. Mar et al., (2005)².

Aim: To use a probabilistic model to assess the cost-effectiveness of the use of thrombolytic therapy in stroke treatment.

Methods: A Markov model of stroke care and disease pathway comparing alteplase administered within the 3-hour time window with current practice. The outcomes associated with current practice were based on Spanish survey of stroke patients. Disability post-stroke was defined as autonomous or disabled based on the Barthel Index and QALYs were derived from local survey.

Results: Alteplase dominated current practice when societal costs were included, and was associated with an incremental cost of less than €4,000 per QALY gained when they were not.

Relevance: This study addresses the correct decision problem but is based on a Spanish setting.

3. Moodie *et al.*, (2004)³

Aim: To trial the use of the intervention module of the MORUCOS model to evaluate two different treatment strategies for acute ischaemic stroke, including alteplase given within the 3-hour treatment window.

Methods: An existing stroke model was used to simulate the costs and outcomes for patients using the different interventions, compared to current practice. US cost estimates and Dutch DALY weights were used.

Results: Alteplase was estimated to dominate current practice in those patients eligible to receive it.

Relevance: This study addresses the correct decision problem but is based on an Australian setting, used US cost estimates and DALYs rather than QALYs.

4. Sandercock *et al.*, (2004)⁴.

Aim: To model the health economic impact of limited use of thrombolytic therapy and to assess whether it was likely to be cost-effective when used more widely in the NHS.

Methods: A Markov model of stroke care and disease pathway comparing alteplase administered within the 6-hour time window with current standard care. Survival post-stroke was stratified by dependent/independent health states and also considered risk of recurrent stroke.

Results: At 12 months, alteplase was associated with an incremental cost of £13,581 per QALY gained compared to current practice. When lifetime assumptions were applied, alteplase dominated current practice.

Relevance: This study examines the correct decision problem in the appropriate setting with only one exception in that it considers a 6-hour treatment window, as opposed to the 3-hour window in the licensed indication for alteplase.

5. Stahl *et al.*, (2003)¹⁸.

Aim: To evaluate the potential cost-effectiveness of alteplase compared to current practice in the framework of a NINDS compliant strategy.

Methods: A discrete event simulation of stroke care comparing current care with alteplase administered within 1 hour of presentation. A detailed treatment and disease pathway is utilised. Post-stroke outcomes are stratified by all categories of the Rankin scale and utilities applied as per Fagan *et al.*, (1998).

Results: In the base case analysis, alteplase dominated current strategy.

Relevance: This study addresses the correct decision problem but is based on a US setting.

6. Chambers *et al.*, (2002)²⁰ (this study was not identified via any of the database searches).

Aim: To use a modelling approach to measure the long-term impact of new interventions in stroke care. The model is adapted to four different country settings: France, Germany, UK and US.

Methods: A decision-analytic model represented the acute care phase with a Markov component to estimate the long-term management of stroke survivors. Patients are stratified as disable or non-disabled according to the Rankin scale. For the UK, resource use was based on panel estimates.

Results: In the base case analysis, alteplase dominated current therapy.

Relevance: This study examines the correct decision problem in the appropriate setting with only one exception in that it considers a 6-hour treatment window, as opposed to the 3-hour window in the licensed indication for alteplase.

7. Sandercock *et al.*, (2002)⁸

This paper refers to the full study report of Sandercock *et al.*, (2004) above.

8. Sinclair *et al.*, (2001)¹⁹.

Aim: To compare clinical and economic outcomes of alteplase versus current practice.

Methods: A Markov model of the natural lifetime course following an acute ischaemic stroke. Post-stroke health states were stratified by disability according to the Rankin scale. Resource use of alteplase patients derived from local hospital experience.

Results: In the base case analysis, alteplase dominated current practice.

Relevance: This study addresses the correct decision problem but is based on a Canadian setting.

9. Fagan *et al.*, (1998)¹⁶.

Aim: To estimate the health and economic impact of alteplase for acute ischaemic stroke.

Methods: A Markov model comparing the costs of 1,000 patients eligible for t-PA with 1,000 untreated patients. Six post-stroke health states stratified by disability severity according to the Rankin scale, assigned utility values as Solomon *et al.*, (1994)⁵. Intracerebral haemorrhage (ICH) included as a cost element of the model only.

Results: The use of alteplase is cost-saving in the long-term due to reduced follow-up care costs. Alteplase is also superior in terms of health outcomes due to reduced disability and less mortality. In the base case analysis therefore, alteplase dominated current practice.

Relevance: This study addresses the correct decision problem but is based on a US setting.

Following FDA approval of alteplase for the treatment of acute ischaemic stroke in June 1996, the 1998 study by Fagan *et al.* (1998)¹⁶ was the initial published economic evaluation of alteplase in this indication, and all subsequent works have commonly used it as a reference point. The general pattern of the identified studies is extremely similar with regards to the model structures and sources of clinical data, with cost data adapted for the local setting. The results of the studies are almost unanimous that alteplase

dominates current practice if one considers the longer-term cost savings and health benefits associated with reduced disability.

There are only two studies (Sandercock *et al.*, (2002 and 2004)^{8,4} and Chambers *et al.*, (2002)²⁰) that base their economic evaluations on a UK setting. Although the comparators in each study are appropriate neither of these studies consider the treatment time window as set out in the licensed indication. Both studies allow for alteplase treatment up to 6 hours from onset. However, it was believed that Sandercock *et al.*, (2002)⁸ better reflected the decision problem and the NICE reference case as the Chambers *et al.*, (2002)²⁰ paper did into evaluate specifically the cost effectiveness of alteplase in acute ischaemic stroke.

Whilst there is no single study in the published literature that would serve as an appropriate economic evaluation for this submission, the identified studies will be useful for comparison and validation. It is evident therefore that there is a clear gap in the published literature of an economic evaluation that considers both the UK setting and the strict 3-hour treatment window. With this in mind, there is a definite need for a *de novo* modelled economic evaluation to accompany this submission.

6.2 *De novo economic evaluation(s)*

In the absence of a relevant published economic evaluation, manufacturers or sponsors should submit their own economic evaluation. When estimating cost effectiveness, particular emphasis should be given to adhering to the 'reference case' (see the NICE document 'Guide to the methods of technology appraisal'). Reasons for deviating from the reference case should be clearly explained. Particularly important features of the reference case include those listed in the table below.

Attribute	Reference case	Section in 'Guide to the methods of technology appraisal'
Comparator(s)	The comparator that has been specified in the decision problem	5.3.2
Perspective costs	NHS and Personal Social Services	5.3.3
Perspective benefits	All health effects on individuals	5.3.3
Form of economic evaluation	Cost-effectiveness analysis	5.3.4
Time horizon	Sufficient to capture differences in costs and outcomes	5.3.5
Synthesis of evidence	Systematic review	5.4.1
Outcome measure	Quality-adjusted life years (QALYs)	5.5
Health states for QALY measurement	Described using a standardised and validated instrument	5.5
Benefit valuation	Time trade-off or standard gamble	5.5
Source of preference data	Sample of public	5.5
Discount rate	Health benefits and costs – both 3.5%	5.7.2
Equity	No additional weighting to QALYs	5.9.7
Sensitivity analysis	Probabilistic sensitivity analysis	5.9.3

6.2.1 Technology

How is the technology (assumed to be) used within the economic evaluation? For example, give indications, and list concomitant treatments, doses, frequency and duration of use. The description should also include assumptions about continuation and cessation of the technology.

The economic evaluation assumes that alteplase is used exactly in line with its licensed indication. That is, “adult patients (over 18 years but under 80 years) with a diagnosis of acute ischaemic stroke within 3 hours of onset of the stroke symptoms and after prior exclusion of intracranial haemorrhage (ICH)⁶

It is assumed that CT scanning to determine the nature of the stroke is part of standard management of stroke. Therefore the economic evaluation assumes that the only additional monitoring and therapeutic care that would arise, in comparison to the “comparator technology”, would occur following a symptomatic intracranial haemorrhage (SICH) with neurological deterioration attributable to the use of alteplase. All other therapies, rehabilitation and management of risk factors, both acute and chronic, are assumed to be the same with as without alteplase.

The recommended dose of 0.9 mg alteplase/kg body weight (maximum of 90 mg), infused intravenously over 60 minutes with 10% of the total dose administered as an initial intravenous bolus, is assumed throughout the economic evaluation⁶

Treatment with alteplase must be started within 3 hours of the onset of symptoms, and consists of a one-off administration. No further alteplase treatment occurs after the initial dose.

6.2.2 Patients

6.2.2.1 What group(s) of patients is/are included in the economic evaluation? Do they reflect the licensed indication? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem?

The patient group included in the economic evaluation is in line with the licensed indication⁶. That is, adult patients (over 18 years but under 80 years) with a diagnosis of acute ischaemic stroke within 3 hours of onset of the stroke symptoms and after prior exclusion of ICH.

6.2.2.2 Was the analysis carried out for any subgroups of patients? If so, how were these subgroups identified, what clinical information is there to support the biological plausibility of this approach, and how was the statistical analysis undertaken?

No subgroup analysis was carried out.

6.2.2.3 Were any obvious subgroups not considered? If so, which ones, and why were they not considered?

A subgroup analysis on the elderly (aged between 65 and 80 years old), and patients with diabetes mellitus (as requested in the final scope) was not carried out due to a lack of evidence evaluating the impact of alteplase. This analysis would be possible following the completion of the SITS-MOST study. However there is no evidence to suggest that a subgroup analysis of patients who meet the licensed criteria for treatment with alteplase would be required.

Diabetic patient and patients less than 80 years of age are eligible for alteplase, so long as they meet the requirements defined by the product's licence.

6.2.2.4 At what points do patients 'enter' and 'exit' the evaluation? Do these points differ between treatment regimens? If so, how and why?

All patients enter the evaluation at the same point. That is, patients who meet the licenced criteria for treatment with alteplase on admission to hospital. The base case model has a lifetime timeframe, therefore all patients exit the evaluation when entering the "dead" health state.

6.2.3 Comparator technology

What comparator(s) was/were used and why was it/were they chosen? The choice of comparator should be consistent with the summary of the decision problem (Section A).

In line with the decision problem outlined in section A and the final scope, the comparator treatment is standard medical and supportive management that does not include thrombolytics (standard treatment) in patients that would potentially be eligible for treatment with alteplase. It has been assumed that standard medical and supportive management of stroke in the UK is within a specialist stroke unit, as defined in the National Service Framework (NSF) for older people⁷.

As reported in Sandercock *et al.*, (2002)⁸. Patients with confirmed ischaemic stroke who do not receive thrombolysis would be given aspirin immediately, whereas those treated with thrombolysis would receive aspirin about 24 hours later. The benefits of aspirin, whether started within 24 hours or between 24

and 48 hours of stroke onset have been shown to be comparable, Sandercock *et al.*, (2002)⁸ conclude that there is no material difference in outcome attributed to the delay in starting aspirin among patients given thrombolysis. It is therefore reasonable to assume that the comparator in this evaluation is standard care without thrombolytics.

As there are no other thrombolytic treatment licensed in the UK for use in acute ischaemic stroke patients it has been assumed that alteplase is given in addition to standard medical treatment and supportive management.

6.2.4 Study perspective

If the perspective of the study did not reflect NICE's reference case, provide further details and a justification for the approach chosen.

The study takes the perspective of the NHS and Personal Social Services as per the NICE reference case.

6.2.5 Time horizon

What time horizon was used in the analysis, and what was the justification for this choice?

The sequelae of acute ischaemic stroke can result in serious long-term disability to the patient. Therefore to reliably compare the treatment strategies, it is essential that the economic evaluation has a timeframe sufficient to account for the health effects and costs of treatment caused by long-term disability. The base case analysis is life-time, however as short-term recurrence, disability and mortality results are often of interest output is presented for a 12-month follow-up from the initial stroke event.

6.2.6 Framework

The purpose of this section is to provide details of the framework of the analysis. Section a) below relates to model-based evaluations, and section b) below relates to evaluations conducted alongside clinical trials. Please complete the section(s) relevant to the analysis.

a) Model-based evaluations

6.2.6.1 Please provide the following.

- **A description of the model type.**

A Markov Model was constructed to perform the economic evaluation. The analytic technique used was a cost-utility analysis (CUA) utilising 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 thrombolytic therapy by Sandercock *et al.*, (2002)⁸. The model has been replicated using the same structure and inputs described in the text of the published appraisal, with parameters updated where possible with up-to-date data on costs and effects. In particular the economic evaluation extends the Sandercock⁸ study further by:

- Incorporating the odds ratio for the 0-3 hour treatment window subgroup contained in the Cochrane review by Wardlaw *et al.*, (2006)⁹. Use of the odds ratios for this treatment window enables the effectiveness estimate to reflect the product licence and intended use.
- Incorporating the costs of long-term rehabilitation accruing to the Social Services budget and short term acute care costs associated with death, independence and dependence as reported in the Health Technology Appraisal of clopidogrel and dipyridamole¹⁰.

- In addition, unit costs have also been applied to the expected impact on staffing resources associated with alteplase treatment outlined in Sandercock *et al.*, (2002)⁸.
- **A schematic of the model. For models based on health states, direction(s) of travel should be indicated on the schematic on all transition pathways.**

Figure 2 presents an illustration of the model structure.

Patients begin the model at the point of treatment where they receive either alteplase or standard care. Dependent on the outcome of treatment at 6 months, patients enter one of three health states:

- Dependent
- Independent
- Dead

The dependent health state is defined as a modified Rankin score (mRS) of $\geq 3-5$, while the independent health state is defined as a score of $0 < 3$.

The distribution of patients across these three health states at 6 months after treatment with alteplase are derived from the alteplase randomised control trials (RCTs) reported in the Cochrane review by Wardlaw *et al.*, (2006)⁹. The probability of entering each of these three health states at 6 months following standard treatment were taken from patients in the Lothian Stroke Register (LSR)⁸.

At 12 months following standard treatment or treatment with alteplase, movement between the independent and dependent health states is permissible as is movement from independent and dependent to the dead health state. This captures the probability of deterioration (due to the index-

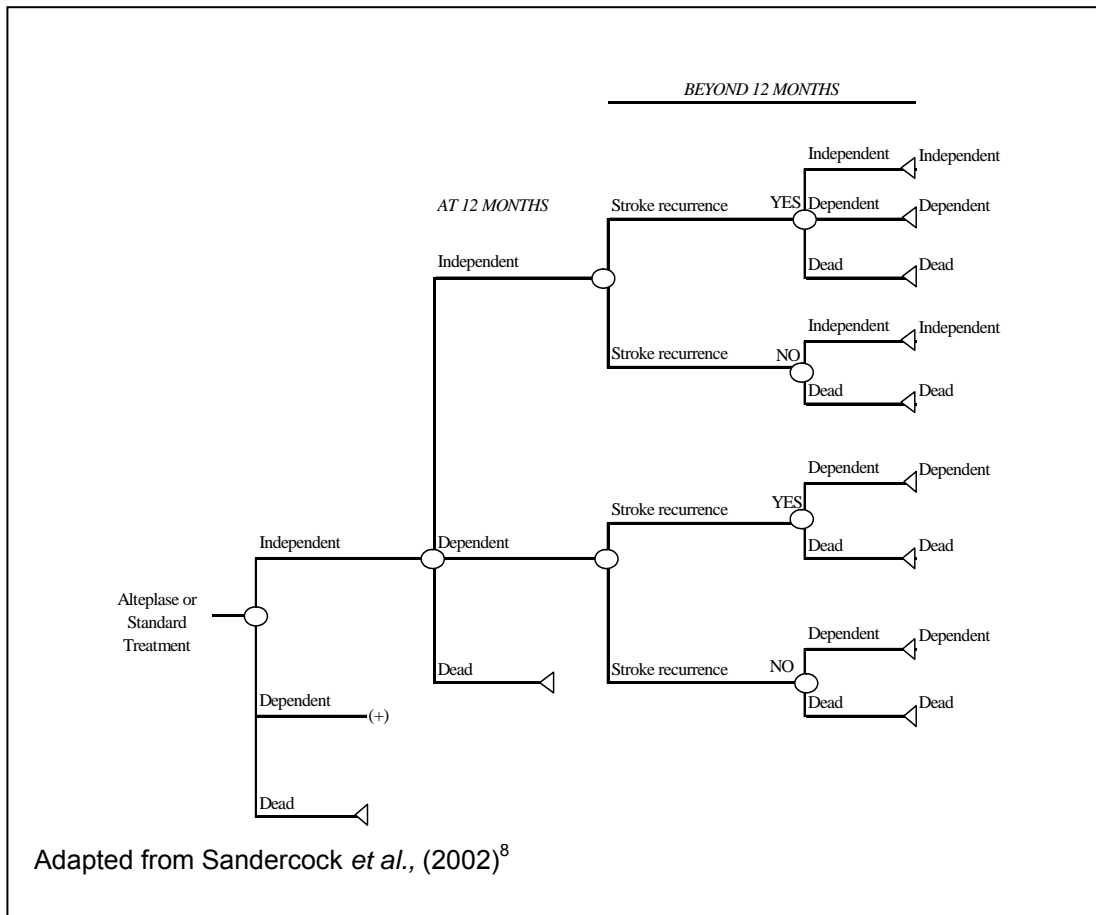
stroke or recurrent-stroke) or recovery in the 12months following a stroke event.

12 months following the index stroke, surviving patients have an annual probability of a stroke recurrence. Following a recurrent stroke, patients in the independent health state, can either remain in the independent health state or transition to the dead or dependent states. Dependent patients who experience a recurrent stroke can either remain in the dependent health state or transition to the dead health state. A death rate of 0.25 in patients who experience recurrent stroke is applied. This is in addition to the annual probability of death applied to the entire stroke cohort.

Independent and dependent patients who do not experience a recurrent stroke can only transition into dead health state. 40 yearly cycles capture the annual probability of all cause death in addition to death associated with recurrent stroke.

Please see sections 6.2.7, 6.2.8 and 6.2.9 for further details regarding transition probabilities and sources of parameter valuations.

Figure 2: Model Schematic



A list of all variables that includes their value, range (distribution) and source.

Table 7 through to Table 11 present the variables input into the economic model by category.

Table 7: Clinical (efficacy and safety) variables

	Model Parameter	Base-case value	Plausible range (95% CI)	Source/comments
	Odds Ratio for death or dependency at 6 months following stroke event	0.64	(0.50 – 0.83)	Wardlaw <i>et al.</i> , (2006) ⁹
	Odds ratio for Death at 6 months following stroke event	0.97	(0.69 – 1.36)	Wardlaw <i>et al.</i> , (2006) ⁹
	Haemorrhage probability: standard treatment at 6 months following stroke event	0.006	-	meta-analysis of the NINDS, ECASS and ATLANTIS trials ¹¹
	Haemorrhage probability: alteplase at 6 months following stroke event	0.048	-	meta-analysis of the NINDS, ECASS and ATLANTIS trials. ¹¹
Probability of different outcomes at 6 months following standard treatment	Independent	0.3953	-	Sandercock <i>et al.</i> , (2002). ⁸
	Dependant	0.3256	-	Sandercock <i>et al.</i> , (2002). ⁸
	Dead	0.2791	-	Sandercock <i>et al.</i> , (2002) ⁸
Probability of different functional outcomes at 12 months. (Transition probabilities at 6 months cycle) in the alteplase and standard treatment cohorts	Independent to independent heath state	0.8750	-	Sandercock <i>et al.</i> , (2002). ⁸
	Independent to dependent heath state	0.0938	-	Sandercock <i>et al.</i> , (2002). ⁸
	Independent to dead heath state	0.0313	-	Sandercock <i>et al.</i> , (2002). ⁸
	Dependent to dependent heath state	0.7407	-	Sandercock <i>et al.</i> , (2002). ⁸
	Dependent to independent heath state	0.1111	-	Sandercock <i>et al.</i> , (2002). ⁸
	Dependent to dead heath state	0.1481	-	Sandercock <i>et al.</i> , (2002). ⁸
	Dead state to dead state	1.00	-	Sandercock <i>et al.</i> , (2002). ⁸

Table 8: Survival and stroke recurrence variables

Model Parameter	Base-case value	Plausible range (95% CI)	Source/comments
Multiplier age-specific mortality after among stroke survivors, 12 months of initial stroke event.	2.5	-	Assumption as described in Sandercock <i>et al.</i> , (2002). ⁸
Annual risk of stroke recurrence at 1 year stroke	0.05	-	Estimated from the LSR as described in Sandercock <i>et al.</i> , (2002). ⁸
Annual stroke mortality among patients with recurrent stroke	0.25	-	Estimated from the LSR as described in Sandercock <i>et al.</i> , (2002). ⁸

Table 9: Utility variables

Model Parameter	Base-case value	Plausible range (95% CI)	Source/comments
Utility of the "Dependent" health state	0.38	(0.29-0.47)	Sandercock <i>et al.</i> , (2002) ⁸ Health Technology Appraisal of clopidogrel and dipyridamole ¹⁰
Utility of the "Independent" health state	0.74	(0.69-0.79)	Sandercock <i>et al.</i> , (2002) ⁸ Health Technology Appraisal of clopidogrel and dipyridamole ¹⁰
Utility of the "Dead" health state	0		Sandercock <i>et al.</i> , (2002) ⁸ Health Technology Appraisal of clopidogrel and dipyridamole ¹⁰

Table 10: Cost and resource variables

Model Parameter	Base-case value	Plausible range (95% CI)	Source/comments
Cost of alteplase	£480	£600	Base case value: The mean dose of alteplase as reported in the 6th report of the SITS-MOST registry is 68.79mg ¹² . This equates a cost of £480 (one 50mg pack at £300 and one 20mg pack at £180) Plausible range: The maximum licensed dose is 90mg. This equates to a cost of £600 (two 50mg packs at £300) ⁶
Cost of staff time to deliver agent	£628	-	PSSRU costs ¹³ have been applied to the estimated extra resources required to deliver thrombolytic therapy as outlined in the Sandercock <i>et al.</i> , (2002) ⁸ .
CT scan to determine the nature of the neurological deterioration	£69	£56-£102	2005 NHS Reference costs ²¹
Cost of independent stroke year 1	£6,531 (NHS and Personal Social Services) £5,404 (Acute care costs only)	-	Health Technology Appraisal of clopidogrel and dipyridamole ⁶ . Youman <i>et al.</i> , (2003) ¹⁴
Cost of independent stroke post-year 1	£1,504	-	Health Technology Appraisal of clopidogrel and dipyridamole ¹⁰ . Youman <i>et al.</i> , (2003) ⁶
Cost of dependent stroke year 1	£14,851 (NHS and Personal Social Services) £11,562 (Acute care cost only)	-	Health Technology Appraisal of clopidogrel and dipyridamole ¹⁰ . Youman <i>et al.</i> , (2003) ¹⁴
Cost of dependent stroke post-year 1	£4,385	-	Health Technology Appraisal of clopidogrel and dipyridamole. ¹⁰ Youman <i>et al.</i> , (2003) ¹⁴
Cost of acute event fatal stroke	£7,428	(£5,963-£10,813)	Youman <i>et al.</i> , (2003) ¹⁴

Table 11: Other Variables

Model Parameter	Base-case value	Plausible range (95% CI)	Source/comments
Mean age of stroke occurrence	66 years	-	SITS-MOST 6 th report ¹²
Proportion of female	40%	-	SITS-MOST 6 th report ¹²
Discount rate for future costs	3.5%	-	Reference case ¹⁵
Discount rate for future outcomes	3.5%	-	Reference case ¹⁵

- **A separate list of all assumptions and a justification for each assumption.**

Assumptions as described in the Health Technology assessment of alteplase by Sandercock et al., (2002)⁸:

1. The baseline clinical outcome data for the 'standard treatment' group were taken from patients in the Lothian Stroke Register. The baseline group included all stroke patients admitted to hospital less than 6 hours after onset, without contraindications and who received a CT scan within this time window. It was assumed that patients presenting in the 0-3 hour time window, receiving standard treatment, had the same outcomes. The clinical outcomes used are based on the assessed modified Rankin Scale at 6 months and 12 months.

Justification: The Lothian Stroke register is a robust source of UK stroke patient data. It is reasonably assumed that the registry population is representative of the UK population in general. However, it could be argued that patients presenting in 0-3 hours would have a marginal improvement in outcomes over patients presenting within the 0-6 hour window. This was tested in the sensitivity analysis.

2. It was assumed that that the overall death rate (for patients suffering an initial or recurrent stroke) after the first year was 2.5 times the age-adjusted mortality of the England population.

Justification: This is in line with other published cost-effectiveness evaluations¹⁶

3. It was assumed that after the first year, deaths occurred at an equal rate in dependent and independent survivors.

Justification: While it is reasonable to assume an equal death rate amongst independent and dependent survivors, it could be argued that death-rates amongst dependent survivors would be higher than independent survivors. The impact of this assumption was tested in the sensitivity-analysis by varying the mortality rates amongst the survivors.

4. It was assumed that the risk of a recurrent stroke and death due to a recurrent stroke was equal in dependent and independent patients.

Justification: It is reasonable to assume that the probability of a recurrent stroke is equal in both independent and dependent patients, and that the risk of death is dependent on the severity and location of the infarct, rather than a patient's disability status.

5. It was assumed that patients in the dependent health state 12 months after the index stroke event could only recycle into the dependent health state or transition to the death health state.

Justification: Most functional recovery in stroke patients occurs within the first 2 months. There is less functional recovery at 4 to 5 months post-stroke and after 6 months little further functional recovery can be expected¹⁷. It is therefore reasonable to assume limited functional recovery after 12 months of a stroke event.

6. It was assumed that independent patients suffering a recurrent stroke, who did not enter the death state, had an equal chance of transitioning to either the independent and dependent states.

Justification: It is reasonable to assume that the risk of death and disability is dependent on the severity and location of the infarct, rather a patient's disability status.

7. It is assumed that alteplase is not prescribed in patients in subsequent strokes

Justification: While alteplase can be given to patients with recurrent stroke, the probability of this happening is low given the 0-3 hour treatment window and the contraindication for the product such as (known history of or suspected intracranial haemorrhage, and a stroke in the previous 3 months, over 80 years of age). The impact of this assumption on results was tested in the sensitivity analysis by varying the probability of recurrent stroke.

Assumptions relating to the extended model:

8. As described in the Health Technology Appraisal of clopidogrel and dipyridamole¹⁰, it was assumed that the costs reported by Youman *et al.*, (2003)¹⁴ for mild and moderate strokes describe the cost of independent stroke survivors, and that severe stroke describe the cost of dependent stroke survivors.

Justification: It is a fair assumption that the resource utilisation associated with severe stroke is reflective of dependent patients and the resource use associated with mild or moderate stroke is reflective of independent patients.

6.2.6.2 Why was this particular type of model used?

Following the evaluation of cost-effectiveness studies described in section 6.1 the published economic evaluation of thrombolytic therapy by Sandercock *et al.*, (2002)⁸ was identified as meeting most of the reference case and scope requirements. Therefore the Sandercock model was adapted with the data inputs refreshed where possible as described in section 6.2.6.1

6.2.6.3 What was the justification for the chosen structure? How was the course of the disease/condition represented? Please state why any possible other structures were rejected.

As described above, with the exception of the 0-3 hours treatment window, the published economic evaluation by Sandercock *et al.*, (2002)⁸ is a robust and thorough examination of the relevant decision problem within a UK setting. There was no compelling reason to change the model structure.

Stahl *et al.*, (2003)¹⁸, Sinclair *et al.*, (2001)¹⁹, and Fagan *et al.*, (1998)¹⁶, mapped a similar course of disease as that described by Sandercock *et al.*, (2002)⁸. However unlike Sandercock *et al.*, (2002)⁸ these studies did not aggregate outcomes into independent (0-<3) or dependent (mRS \geq 3-5), and reported utilities for each mRS score. However none of these publications were from a UK perspective, nor did they incorporate utility values derived exclusively from a UK population. In addition, given the long-term effects of stroke and the low probability of long-term improvement in functionality¹⁷, it is fair to state that the Sandercock *et al.*, (2002)⁸ model fully captures the disutility associated with ischemic stroke.

Sinclair *et al.*, (2001)¹⁹, and Fagan *et al.*, (1998)¹⁶, Chambers *et al.*, (2002)²⁰ disaggregated the deaths associated with 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) study⁸ by the proportion of patients who enter the dead, dependent and independent health states.

However, in order to conservatively estimate the cost of an SICH it was assumed that the cost of CT scans to determine the cause neurological deterioration associated with SICH was not included in the Youman *et al.*, (2003)¹⁴ costing of acute stroke care. The cost of CT scanning was therefore incorporated into the adapted Sandercock⁸ model.

Chambers *et al.*, (2002)²⁰ also modelled the cost-effectiveness of various stroke recurrence prevention measures, which is outside the scope of this economic evaluation.

6.2.6.4 What were the sources of information used to develop and inform the structure of the model?

Clinical variables were sourced from Wardlaw *et al.*, (2006)⁹ and the meta-analysis of the NINDS, ECASS and ATLANTIS trials¹¹. Transition variables were sourced from Sandercock *et al.*, (2002)⁸ and Wardlaw *et al.*, (2006)⁹ and cost variables were sourced from PSSRU costs¹³ and NHS reference costs²¹ and a UK stroke burden of disease study¹⁴. For a full list of variables and sources see section 6.2.6.1.

6.2.6.5 Does the model structure reflect all essential features of the condition that are relevant to the decision problem? If not, why not?

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

As outlined in section A, the impact of stroke on mental health has not been evaluated in this analysis due to the absence of trial data evaluating the impact of alteplase in this area.

Resource use and the cost of current stroke management was derived from the published study by Youman *et al.*, (2003)^{14,10}. While the cost of hospitalisations was included in the costs presented in the Youman *et al.*, (2003) study¹⁴, given the level of data dis-aggregation it was not possible to evaluate within the health economic model the length of hospitalisations separately from acute and long term resource utilisation. However results of the ECASS II study suggests that there is a reduction in hospital stay associated with alteplase. In this study the mean duration of hospital stay amongst surviving placebo patients was 21 days while for alteplase treated patients it was 17 day $p=0.002$)³³.

6.2.6.6 For discrete time models, what was the model's cycle length, and why was this length chosen? Does this length reflect a minimum time over which the pathology or symptoms of a disease could differ? If not, why not?

In order to fully examine the initial impact of the two treatment strategies and best reflect the available clinical data, the model begins with two cycle lengths of six months each (see section 6.2.6.1 for more detail). Following the first year, the model reverts to yearly cycles. Movement between states has been described in section 6.2.6.1.

The Markov process was repeated until the end of the cohort life-time, and totals were computed for the accumulated health outcomes and costs. The

Markov model used age-specific mortality, risk of recurrent stroke, and stroke-specific case fatality to estimate the probabilities of being dead, dependent, and independent in each Markov cycle.

6.2.6.7 Was a half-cycle correction used in the model? If not, why not?

Yes a half –cycle correction was used in the model

6.2.6.8 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer-term difference in effectiveness between the technology and its comparator?

Odds ratios for death and dependence at 6 months were calculated from outcomes measured at 90 days following a stroke event. As described in section 6.2.6.1, beyond 12 months movement between states is dependent on stroke recurrence and age-specific mortality. The distribution of these outcomes at 12 months in the alteplase and standard treatment group was calculated by applying transition probabilities calculated from the 12 month follow-up data in the Lothian Stroke Registry as reported in Sandercock *et al.*, (2002)⁸. A 12 month follow up study²² of patients within the NINDS trial indicated a sustained benefit of alteplase over a 12 month period.

b) Non-model-based economic evaluations

6.2.6.9 Was the evaluation based on patient-level economic data from a clinical trial or trials?

No.

6.2.6.10 Provide details of the clinical trial, including the rationale for its selection.

Not applicable.

6.2.6.11 Were data complete for all patients included in the trial? If not, what were the methods employed for dealing with missing data for costs and health outcomes?

Not applicable.

6.2.6.12 Were all relevant economic data collected for all patients in the trial? If some data (for example, resource-use or health-related utility data) were collected for a subgroup of patients in the trial, was this subgroup prespecified and how was it identified? How do the baseline characteristics and effectiveness results of the subgroup differ from those of the full trial population? How were the data extrapolated to a full trial sample?

Not applicable.

6.2.6.13 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about any longer-term differences in effectiveness between the technology and its comparator?

Not applicable.

6.2.7 Clinical evidence

Where relevant, answers to the following questions should be derived from, and consistent with, the clinical evidence section of the submission (section 5). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided and a justification for the approach provided.

**6.2.7.1 How was the baseline risk of disease progression estimated?
Also state which treatment strategy represents the baseline.**

Treatment strategy representing the baseline:

The treatment strategy representing baseline is standard medical and supportive management that does not include thrombolytics (standard treatment). It has been assumed that standard medical and supportive management of stroke in the UK is within a specialist stroke unit, as defined in the National Service Framework (NSF) for older people⁷.

Estimation of baseline risk of disease progression:

The baseline clinical outcome data for the 'standard treatment' group were taken from patients in the Lothian Stroke Register potentially eligible for treatment as reported in Sandercock *et al.*, (2002)⁸. The baseline group included all stroke patients admitted to hospital less than 6 hours after onset, without contraindications and who received a CT scan within this time window. For patients receiving alteplase, it was assumed that patients presenting in the 0-3 hour time window had the same outcomes at 6 months post treatment. The distribution of outcomes at 12 months in the standard treatment and alteplase cohorts was calculated by applying transition probabilities calculated from the 12 month follow-up patient data in the LSR.

For values used see section 6.2.6.1.

6.2.7.2 How were the relative risks of disease progression estimated?

The approach taken in Sandercock *et al.*, (2002)⁸ makes use of the odds ratios reported in the 2003 Cochrane systematic review (meta-analysis)⁹ for 'death' and 'death or dependency' in order to calculate the distribution of outcomes in the alteplase treated population. This review published odds ratios for alteplase versus placebo in patients presenting less than 3 hours from treatment onset. These odds ratios are applied to an existing patient outcome distribution ('standard treatment' group described above) which enables the calculation of the distribution of outcomes in the alteplase treated patient cohort at 6 months. The distribution of outcomes at 12 months in the alteplase and standard treatment group was calculated by applying transition probabilities calculated from the 12 month follow-up data in the LSR. The RCT contributing to these odd ratios were the NINDS³², ECASS 1²³, ECASS II³³, ATLANTIS A³⁰, ATLANTIS B³¹ and Haley *et al.*, (1993)²⁴ studies

6.2.7.3 Were intermediate outcome measures linked to final outcomes (such as patient survival and quality-adjusted life years)

[QALYs])? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

Patient health-related quality of life (HRQoL) is quantified in the economic model by applying health state utility values to each Markov health state, allowing the calculation of QALYs. Patient utility values for the dependent and independent states are based on the responses to the EuroQoL quality of life questionnaire of a sample of 147 Lothian Stroke Register patients as described in Sandercock *et al.*, (2002)⁸ and the Health Technology Appraisal of clopidogrel and dipyridamole¹⁰. These patients had also been assessed by standard measures of dependence, allowing relative preferences for the three different health states to be assigned: 0.74 for independence, 0.38 for dependence, and 0.00 for death.

6.2.7.4 Were the health effects or adverse effects associated with the technology included in the economic evaluation? If not, would their inclusion increase or decrease the estimated cost-effectiveness of this technology?

As discussed in section 5, thrombolytic therapy administered up to three hours after acute ischaemic stroke, significantly reduced the proportion of patients who were dead or dependent at 3-6 month follow-up.

In the population treated up to 3 hours, adverse events and serious adverse events were comparable between alteplase and placebo with one relevant exception: bleeding complications were significantly higher following treatment with alteplase. The most clinically relevant events in this difference between the strategies are ICH. ICH with a fatal outcome is approximately 5-fold higher following treatment with alteplase compared to placebo. This adverse effect of alteplase is accounted for by the economic model.

Explicitly, the costs and outcomes associated with death, dependence and independence have been included in the economic evaluation. The proportion of patients entering the dead, dependent and independent health states due to the occurrence of an ICH have been incorporated into the transition probabilities used to model outcomes associated with both standard treatment and alteplase. The costs and outcomes of ICH associated with standard treatment and alteplase have also been captured by the proportion of patients entering the dependent, independent and death states.

6.2.7.5 Was expert opinion used to estimate any clinical parameters? If so, how were the experts identified, to which variables did this apply, and what was the method of elicitation used?

No expert opinion was used to estimate clinical parameters. Clinical parameters were measured using well established rating scales commonly used by stroke physicians.

6.2.7.6 What remaining assumptions regarding clinical evidence were made? Why are they considered to be reasonable?

Please see section 6.2.6.1 for a full list of assumptions and justifications

6.2.8 Measurement and valuation of health effects

6.2.8.1 Which health effects were measured and how was this undertaken? Health effects include both those that have a positive impact and those with a negative impact, such as adverse events.

Relative effectiveness of the two treatment strategies was measured in terms of death and disability following stroke. Independence was defined as a modified Rankin Scale score of 0- <3 and dependence as a modified Rankin Scale score of $\geq 3-5$, measured at 6 months follow-up in the Lothian Stroke Register and at 90 days in the alteplase clinical trials. The full modified Rankin Scale can be found in appendix 5. The health effects of ICH were captured by the proportion of those patients entering the dead, dependent and independent states at 6 months following treatment.

Standard Treatment: The baseline clinical outcome data for the 'standard treatment' group were taken from patients in the Lothian Stroke Register potentially eligible for treatment as reported in Sandercock *et al.*, (2002)⁸. The baseline group included all stroke patients admitted to hospital less than 6 hours after onset, without contraindications and who received a CT scan within this time window. It was assumed that patients presenting in the 0-3 hour time window had the same outcomes. The clinical outcomes used are based on the assessed modified Rankin Scale at 6 months and 12 months. For values used see section 6.2.6.1.

Survival was measured as described in section 6.2.8.2

6.2.8.2 Which health effects were valued? If taken from the published literature, how and why were these values selected? What other values could have been used instead? If valued directly, how was this undertaken?

Death & Disability (dependent and independent states)

Alteplase: The source of the death and disability estimates for alteplase, are the 2003 Cochrane systematic review meta-analysis⁹. This review published odds ratios (OR) for alteplase versus placebo in patients presenting less than 3 hours from treatment onset. Trials included in the OR calculations were

NINDS³², ECASS 1²³, ECASS II³³, ATLANTIS A³⁰, ATLANTIS B³¹ and Haley *et al.*, (1993)²⁴ studies

For values used see section 6.2.6.1

Standard Treatment: The baseline clinical outcome data for the 'standard treatment' group were taken from patients in the Lothian Stroke Register potentially eligible for treatment as reported in Sandercock *et al.*, (2002)⁸

Utility values

Patient utility values for dependent and independent states are based on the responses to the EuroQoL quality of life questionnaire of a sample of 147 Lothian Stroke Register patients as described in Sandercock *et al.*, (2002)⁸ and the Health Technology Appraisal of clopidogrel and dipyridamole¹⁰. Utility values from this study are applied directly to the relevant health states in the economic model.

Adverse Events (ICH and SICH)

The health effects of ICH were captured by the proportion of those patients entering the dead, dependent and independent states at 6 months following treatment.

The rate of parenchymal haematoma (including haemorrhagic infraction) together with evidence of neurological deterioration (defined as a change on the NHISS scale equal or greater than 4 points) as reported in a meta-analysis of the NINDS, ECASS and ATLANTIS trials¹¹ was used to estimate the rate of SICH in both standard treatment and alteplase.

As discussed above potential sources of safety data identified in the literature search (see appendix 2) are the SITS-MOST trial, CASES trial²⁵ and STARS trial²⁶. As discussed in the medical (section 5.8.3), the results of these studies are consistent with or better than those seen in the randomised placebo controlled trials.

Recurrent Stroke

Assumptions and rates regarding stroke recurrence were as reported in Sandercock *et al.*, (2002)⁸ that is:

1. Among patients who had a recurrent stroke, after the first year, fatalities were calculated from patients with recurrent stroke in the LSR.
2. It was assumed that the risk of death due to a recurrent stroke was equal in dependent and independent patients.
3. It was assumed that dependent patients who suffered a recurrent stroke either entered the death state or remained in the dependent state.
4. It was assumed that independent patients suffering a recurrent stroke, who did not enter the death state, had an equal chance of transitioning to either the independent and dependent states.

Survival after 1 year

Survival rates and assumptions are as reported in the Sandercock *et al.*, (2002)⁸ that is:

1. It was assumed that after the first year, deaths occurred at an equal rate in dependent and independent survivors.
2. It was assumed that that the overall death rate (for patients suffering an initial or recurrent stroke) after the first year was 2.5 times the age-adjusted mortality of the England population.

The model assumes patients get life years from model entry until death. Based on interim results reported from the SITS-MOST registry, it is assumed that the average starting age of patients in the model is 66 years and that 40% of patients are female.

Results of systematic literature review

A systematic literature did not identify any further RCTs, outside of those reported in the Cochrane review⁹ that assessed the safety (death rates, or ICH rate) or efficacy (measured by the mRS) in patients treated within 3 hours of onset of stroke symptoms.

Other potential sources of efficacy data are the SITS-MOST trial, CASES trial²⁵ and STARS trial²⁶. As discussed in the medical section (section 5.8.3), the results of these studies are consistent with or better than those seen in the alteplase randomised control trials.

6.2.8.3 Were health effects measured and valued in a manner that was consistent with NICE's reference case? If not, which approach was used?

Utilities and QALYs were measured and valued utilising the EuroQoL as per the NICE reference case, which values HRQoL using general population weights. For a further description see section 6.2.8.2.

6.2.8.4 Were any health effects excluded from the analysis? If so, why were they excluded?

Please refer to section 6.2.6.5

6.2.8.5 If health effects were not expressed using QALYs, what health outcome measure was used and what was the justification for this approach?

Not applicable.

6.2.9 Resource identification, measurement and valuation

6.2.9.1 What resources were included in the evaluation? (The list should be comprehensive and as disaggregated as possible.)

The resource use and costs associated with administering alteplase, and the management and rehabilitation cost of stroke and ICH are outlined below.

Cost of administering and acquiring alteplase

Table 12 describes the extra staffing requirements, needed to administer alteplase as outlined in Sandercock *et al.*, (2002)⁸, PSSRU¹³ unit costs were then applied to estimate the value of additional staffing costs associated with administering alteplase.

It was assumed that CT scanning to determine the nature of the stroke is a routine part of standard management of stroke and therefore is not an additional cost associated with the administration of alteplase.

Table 12: Extra staffing resource required to administer alteplase as outlined in Sandercock *et al.*, (2002)⁸

Extra staffing requirements	Cost per hour	Unit cost	Source /comments
5min additional nurse time	£46	£3.83	PSSRU 2005 (staff nurse 24hr ward) ¹³
190 min Registrar time	£46	£145.67	PSSRU 2005 (specialist registrar costs) ¹³
50min consultant time	£107	£89.17	PSSRU 2005 (Medical consultant costs) ¹³
5min routine observation by senior nurse in place of more junior nurse	£18/ hour (£64-£46)	£1.5	It has been assumed that observations are carried out by a senior nurse, and that each observation takes 5 mins PSSRU 2005 (ward manager 24hr ward and staff nurse 24hr ward) ¹³
12 additional sets of observations at 5 min each	64	£64	It has been assumed that routine observations take 5 mins to be carried out PSSRU 2005 (ward manager 24hr ward) ¹³
Senior nurse requires 1:1 care for 5 hours	£64	£320.00	PSSRU 2005 (ward manager 24hr ward) ¹³
10 min overnight junior staff review	£25	£4.17	PSSRU 2005 p181 Pre-registration house officer ¹³

Table 13 presents the estimated acquisition cost of alteplase applied to the economic model.

Table 13: Estimated acquisition cost of alteplase

Model Parameter	Base-case value	Plausible range	Source/comments
Cost of alteplase	£480	£600	Base case value: The mean dose of alteplase as reported in the 6th report of the SITS-MOST registry is 68.79mg. This equates a cost of £480 (one 50mg pack at £300 and one 20mg pack at £180) ^{12, 27} Plausible range: The maximum licensed dose is 90mg. This equates to a cost of £600 (two 50mg packs at £300) ⁶

Cost of ICH management and rehabilitation

Both acute and long term costs of ICH associated with standard treatment and alteplase have been captured by the proportion of patients entering the dependent, independent and death states. The only additional cost not captured by these states is the requirement for a CT scan to determine the cause of neurological deterioration and confirm that this is not due to a SICH (Table 14).

Table 14: Unit cost of CT scanning

Model Parameter	Base-case value	Plausible range	Source/comments
CT scan to determine the nature of the neurological deterioration	£69	£56-£102	2005 NHS Reference costs ²¹

Cost of stroke management and rehabilitation

The annual cost of stroke has been taken from the Health Technology Appraisal of clopidogrel and dipyridamole¹⁰. This HTA identified a large, randomised, prospective trial of stroke care in the UK²⁸, which recorded resource use in hospital, primary care, healthcare contacts, and utilisation of social services over a period of 1 year following stroke. These data were then used in a study describing the economic burden of stroke to the UK¹⁴. This study applied national unit costs to the resource use data to calculate the 3-month cost of acute events and long-term care, according to the severity of the stroke, and which also reported the probabilities of incurring each event. Stroke was divided into mild, moderate and severe events, defined by the Barthel Index. For the purpose of the model the HTA assumed that mild and moderate strokes described the costs of independent stroke survivors, and that severe stroke described the cost of dependent stroke survivors.

Table 15 describes the data used to calculate the annual cost of stroke care. These were subsequently indexed to the current price year.

Table 15: Data used to calculate the annual cost of stroke care as reported in Youman *et al.*, (2003) and Karla *et al.*, (2005)^{14,28}

Parameter	Value	95% confidence interval
3 month cost of ongoing care at home (including accommodation)	£326	£195 to £457
3 month cost of ongoing care in an institution (including accommodation)	£3,872	£3,669 to £4,865
Cost of stroke fatality	£6,781	-
Mild stroke		
3 month cost of acute event	£5,099	£4,558 to £5,636
Percentage discharged home	100%	Not Applicable
Percentage discharged to an institution	0%	Not Applicable
Percentage dead	0%	Not Applicable
Moderate stroke		
3 month cost of acute event	£4,816	£4,406 to £5,225
Percentage discharged home	95.9%	Not Applicable
Percentage discharged to an institution	0.8%	Not Applicable
Percentage dead	3.3%	Not Applicable
Severe stroke		
3 month cost of acute event	£10,555	£9,575 to £11,535
Percentage discharged home	73.2%	Not Applicable
Percentage discharged to an institution	17.2%	Not Applicable
Percentage dead	9.6%	Not Applicable
Proportion of mild stroke patients amongst independent patients	0.413	Not Applicable
Proportion of moderate stroke patients amongst independent patients	0.587	Not Applicable
Proportion of moderate stroke patients amongst dependent patients	1.0	Not Applicable
<i>Calculated cost of independent stroke after 1 year</i>	$0.413*(£5099 + 3*£326) + 0.587*(£4816 + 3*(0.959/(1-0.033)*£326 + 0.0081/(1-0.033)*£3872)) = \mathbf{£5963}$	
<i>Calculated cost of independent stroke post year 1</i>	$0.413*4*£326 + 0.587*4*(0.959/(1-0.033)*£326 + 0.008/(1-0.033)*£3872) = \mathbf{£1373}$	
<i>Calculated cost of dependent stroke after 1 year</i>	$£10555 + 3*(0.732/(1-0.096)*£326 + 0.172/(1-0.096)*£3872) = \mathbf{£13557}$	
<i>Calculated cost of dependent stroke post year 1</i>	$4*(0.732/(1-0.096)*£326 + 0.172/(1-0.096)*£3872) = \mathbf{£4003}$	

6.2.9.2 How were the resources measured?

Please refer to section 6.2.9.1 for details of how resource use was measured

6.2.9.3 Were the resources measured using the same source(s) of evidence as the baseline and relative risks of disease progression?

No. Please refer to sections 6.2.9.1 and section 6.2.8.2 for more detail.

6.2.9.4 Were resources used to treat the disease/condition included for all relevant years (including those following the initial treatment period)? Provide details and a justification for any assumptions that were made (for example, assumptions regarding types of subsequent treatment).

Yes. Resource use was assigned to each of the three health states in the model, dead, independent, dependent. The annual cost of stroke (management and rehabilitation) in the year following the stroke event (initial or recurrent stroke) was taken from the Health Technology Appraisal of clopidogrel and dipyridamole¹⁰. 12 months after the stroke event, annual rehabilitation costs are accrued by patients in the independent and dependent states. The annual rehabilitation cost was assumed to remain constant in each subsequent year that a patient survives. These rehabilitation costs have also been taken from the Health Technology Appraisal of clopidogrel and dipyridamole.

Please refer to section 6.2.9.1 for more details.

6.2.9.5 What source(s) of information were used to value the resources?

Please refer to section 6.2.9.1 for details on the unit costs used in the economic model.

6.2.9.6 What is the unit cost (excluding VAT) of the intervention(s) included in the analysis? Does this differ from the (anticipated) acquisition cost reported in section 1?

See Table 13 in section 6.2.9.1 for details of unit cost. The unit cost does not differ from the acquisition cost outlined in section 1.

6.2.9.7 Were the resources measured and valued in a manner consistent with the reference case? If not, how and why do the approaches differ?

Yes, the resources measured are those under the control of the NHS and/or PSS. The unit costs used to value the resources are from standard established UK sources.

6.2.9.8 Were resource values indexed to the current price year?

Values that were not based on 2006 costs were indexed to the current price year.

6.2.9.9 Provide details of and a justification for any assumptions that were made in the estimation of resource measurement and valuation.

- It is assumed that CT scanning to determine the nature of the stroke is part of standard management of stroke and therefore is not an additional cost over standard treatment associated with the administration of alteplase.

Justification: This is in line with recommendations on the acute management of stroke by the Royal Collage of Physicians which states that brain imaging should be undertaken as soon as possible in all patients, within 24 hours at most, of onset unless there are good clinical reasons for not doing so²⁹.

- Assumptions regarding the cost of stroke management and rehabilitation are as reported Health Technology Appraisal of clopidogrel and dipyridamole¹⁰. See sections 6.2.9.1 and 6.2.9.4 for more detail.
- The resource use required to administer alteplase were based on Sandercock et al., (2002)⁸. The only parameter not provided was time required of staff to carry out routine observations. It was conservatively assumed that clinical observations take 5 minutes to complete

6.2.9.10 Time preferences

Were costs and health benefits discounted at the rates specified in NICE's reference case?

Both costs and outcomes are discounted to present value at a rate of 3.5% per annum as per the NICE reference case.

6.2.10 Sensitivity analysis

Sensitivity analysis should be used to deal with sources of main uncertainty other than that related to the precision of the parameter estimates.

For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

6.2.10.1 Which variables were subject to sensitivity analysis? How were they varied and what was the rationale for this?

In addition to the probabilistic sensitivity analysis, key variables for the base-case (life time) model parameters were subject to a simple one-way sensitivity analysis within plausible ranges. Where plausible ranges, confidence intervals (CI) or minimum or maximum values were not reported, values were doubled or halved.

Table 16 summaries the how parameters were varied in the one-way sensitivity analysis. The results of these sensitivity analyses are presented and discussed in section 6.3.

The cost on the acute care costs alone in the life time model is examined through sensitivity analysis as is a shorter time horizon of 12 months

Table 16: Values attached to parameters tested in the one-way sensitivity analysis

Variable	Sensitivity analysis value and rationale
Alteplase Efficacy	
OR for death and dependency	increased to 0.83 (higher 95% CI)
OR for death and dependency	decreased to 0.5 (lower 95% CI)
OR for death	increased to 1.36 (higher 95% CI)
OR for death	decreased to 0.69 (higher 95% CI)
Utility Values	
Dependent state	Decreased to 0.29. Lower plausible estimate for utility as reported in Sandercock et al., (2002) study ⁸
Dependent state	Increased to 0.47. Higher plausible estimate for utility as reported in Sandercock et al., (2002) study ⁸
Independent state	Decreased to 0.69. Lower plausible estimate for utility as reported in Sandercock et al., (2002) study ⁸
Independent state	Increased to 0.79. Higher plausible estimate for utility as reported in Sandercock et al., (2002) study ⁸
Cost of alteplase treatment and administration	
Cost of alteplase £480 to £600	£600. The maximum licensed dose is 90mg. This equates to a cost of £600 (two 50mg packs at £300) ⁶
Staff costs	Doubled from £628 to £1256
Cost of independent stroke year 1	Halved to £3,266 (NHS and social service costs)
Cost of independent stroke year 1	Doubled to £13,063 (NHS and social service costs)
Cost of independent stroke post-year 1	Halved to £752 (NHS and social service costs)
Cost of independent stroke post-year 1	Doubled to £3,008 (NHS and social service costs)
Cost of dependent stroke year 1	Halved to £7,425 (NHS and social service costs)
Cost of dependent stroke year 1	Doubled to £29,701 (NHS and social service costs)
Cost of dependent stroke post-year 1	Halved to £2,192

Variable	Sensitivity analysis value and rationale
Cost of dependent stroke post-year 1	Doubled to £8,769
Cost of acute event fatal stroke	Reduced to £5,963 (based on the 95% CI reported in Youman <i>et al.</i> , (2003) ¹⁴
Cost of acute event fatal stroke	Increased to £10,813 (based on the 95% CI reported in Youman <i>et al.</i> , (2003) ¹⁴
Survival and stroke recurrence rates	
Multiplier age-specific mortality after among stroke survivors, 12 months after the initial stroke event	Halved to 1.25
Multiplier age-specific mortality after among stroke survivors, 12 months after the initial stroke event	Doubled to 5.0
Annual stroke mortality among patients with recurrent stroke	Halved to 0.125
Annual stroke mortality among patients with recurrent stroke	Doubled to 0.5
Annual Risk of stroke recurrence at 1 year stroke	Halved to 0.025
Annual Risk of stroke recurrence at 1 year stroke	Doubled to 0.1

Sensitivity analysis: where the outcomes associated with standard treatment are improved

It is assumed in the model that the LSR outcomes are representative of current specialised stroke units in patients who would be eligible for alteplase. If the results of the placebo arms in the main alteplase clinical trials are used as a proxy for outcomes in a specialised stroke unit, it would be fair to say the LSR is representative.

Table 17 summaries the distribution of independent, dependent at dead patients the LSR (at 6 months) and the alteplase clinical trials (for patients receiving placebo) at 90 days. As can be seen the results are broadly comparable.

However, if it is assumed that not all stroke patients recorded in the LSR were managed within a specialised stroke unit or that outcomes in specialised stroke units have improved since the publication Sandercock et al., (2002) study⁸ it could be said that outcomes in patients treated within a specialised stroke unit would better than that reported in the LSR.

An extreme scenario sensitivity analysis was therefore carried out assuming the following improvement in 6 month outcomes compared to that reported in the LSR for patients receiving standard treatment:

- 50% increase in the number independent patients
- 50% decrease in the number of deaths
- 18% decrease in the number of dependent patients

Table 17: The distribution across the three health states as reported in the LSR, alteplase clinical trials for patients receiving placebo, and those used in the sensitivity analysis.

	Independent	Dependent	Dead
LSR reported outcomes	40%	33%	28%
Distribution amongst patients receiving placebo in the alteplase trials*	40%	43%	17%
Distribution amongst standard treatment patients assumed in the sensitivity analysis	59%	27%	14%
*ATLANTIS A ³⁰ ; ATLANTIS B ³¹ ; NINDS ³² ; ECASS 1 ²³ and ECASS 2 ³³			

Assessing the impact of ECASS 1 on the cost-effectiveness of alteplase.

All the randomised clinical trials used to estimate outcome in alteplase treated patients except ECASS 1, included patients who received the licensed dose of alteplase. Patients in the ECASS I study received over the licensed dose of alteplase (1.1mg/kg, maximum dose 100mg). Table 13 presents the OR used in the base-case and the ORs when ECASS 1 is excluded. As can be seen excluding ECASS I does not significantly effect the ORs of death, or death and dependency, therefore the impact of excluding ECASS 1 was not assessed in the sensitivity analysis.

		OR reported in Sandercock et al., (2002) study ⁸ (including ECASS 1)	OR excluding ECASS 1
Death or Dependency	OR	0.64	0.64
	95% CI low	0.5	0.49
	95% CI high	0.83	0.84
Death	OR	0.97	0.93
	95% CI low	0.69	0.65
	95% CI high	1.36	1.33

6.2.10.2 Was probabilistic sensitivity analysis (PSA) undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated; including the derivation and value of 'priors'.

A probabilistic sensitivity analysis was carried out looking at the following scenarios

- Life time –All costs (NHS and social service costs) and acute care cost only
- Life time model– where the outcomes associated with standard treatment are improved by 50%. All costs (NHS and social service costs) and acute care cost only
- 12 month time horizon- all costs (NHS and social service costs)

The uncertainty in the cost of each health state is reflected by assigning beta-pert distributions to the 3 month costs used to calculate the annual cost.

Utilities and odds ratios are assumed to be normally distributed, in case of odds ratios the probabilistic sensitivity analysis assumes a normal distribution around the logOR.

Table 18: Table summarising distributions used in the PSA and their sources

Model Parameter	Base-case value	Probabilistic Distribution	Source/comments
Cost of alteplase	£480	N/A	Mean list price of agent delivered
Alteplase administration	£628.33	N/A	Based on Sandercock et al., (2002) ⁸
Cost of independent stroke year 1	£6,531 (NHS and Personal Social Services) £5,404 (Acute care costs only)	Beta-pert distribution	Youman <i>et al.</i> , (2003) ¹⁴
Cost of independent stroke post-year 1	£1,504	Beta-pert distribution	Youman <i>et al.</i> , (2003) ¹⁴
Cost of dependent stroke year 1	£14,851 (NHS and Personal Social Services) £11,562 (Acute care cost only)	Beta-pert distribution	Youman <i>et al.</i> , (2003) ¹⁴
Cost of dependent stroke post-year 1	£4,385	Beta-pert distribution	Youman <i>et al.</i> , (2003) ¹⁴
Cost of acute event fatal stroke	£7,428	Beta-pert distribution	Youman <i>et al.</i> , (2003) ¹⁴
CT scan	£69	Beta-pert distribution	2005 NHS reference costs
Utility: Independent	0.74	Normal distribution	Sandercock et al., (2002) ⁸
Utility: Dependent	0.38	Normal distribution	Sandercock et al., (2002) ⁸
OR for Death	0.97	normal distribution around the logOR.	Wardlaw <i>et al.</i> , (2006) ⁹
OR for Death and dependence	0.64	normal distribution around the logOR	Wardlaw <i>et al.</i> , (2006) ⁹

6.2.10.3 Has the uncertainty associated with structural uncertainty been investigated? To what extent could/does this type of uncertainty change the results?

The structural assumptions which contain uncertainty within this model are as follows:

1. The assumption that after the first year, deaths occurred at an equal rate in dependent and independent survivors.

2. The assumption that dependent patients who suffered a recurrent stroke either entered the death state or remained in the dependent state.
3. The assumption that independent patient suffering a recurrent stroke, who did not enter the death state, had a equal chance of transitioning to either the independent and dependent states.
4. The assumption that the utility associated with ICH is captured by the utility attributed to the three health states.

The one way sensitivity analysis in the lifetime and the 12 months cost-effectives results demonstrate that the cost-effectiveness of alteplase is not sensitive to the above assumptions

6.2.11 Statistical analysis

6.2.11.1 How were rates or probabilities based on intervals transformed into (transition) probabilities?

The approach taken in the Sandercock *et al.*, (2002) study⁸ makes use of the odds ratios reported in the 2003 Cochrane systematic review (meta-analysis)⁹ for 'death' and 'death or dependency', to calculate the distribution of outcomes in the alteplase treated population. This review published odds ratios for alteplase versus placebo in patients presenting less than 3 hours from treatment onset (see Figure 3 and Figure 4 for forest plots of the respective odd ratios). These odds ratios are applied to an existing patient outcome distribution ('standard treatment' group) which enables the calculation of the distribution of outcomes in the alteplase treated patient cohort.

Figure 3: Forest plot of thrombolysis versus control – death or dependency⁹

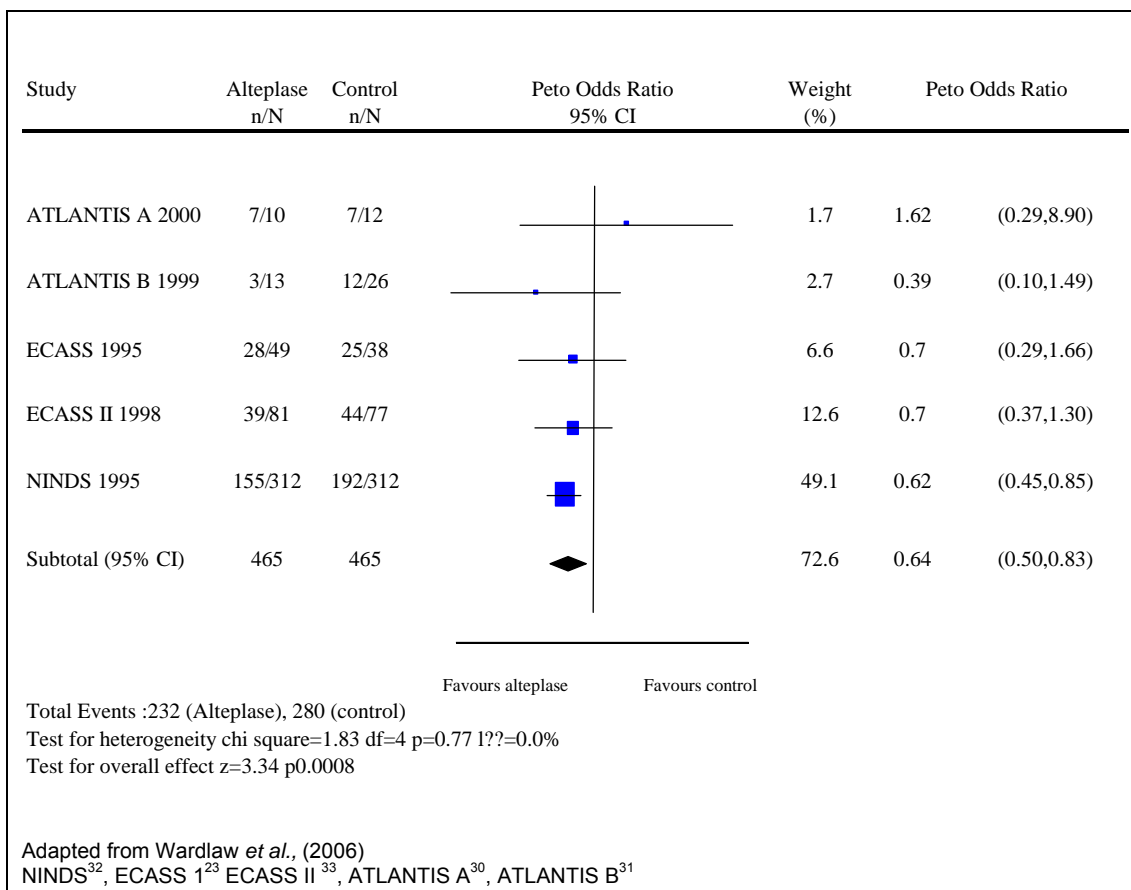
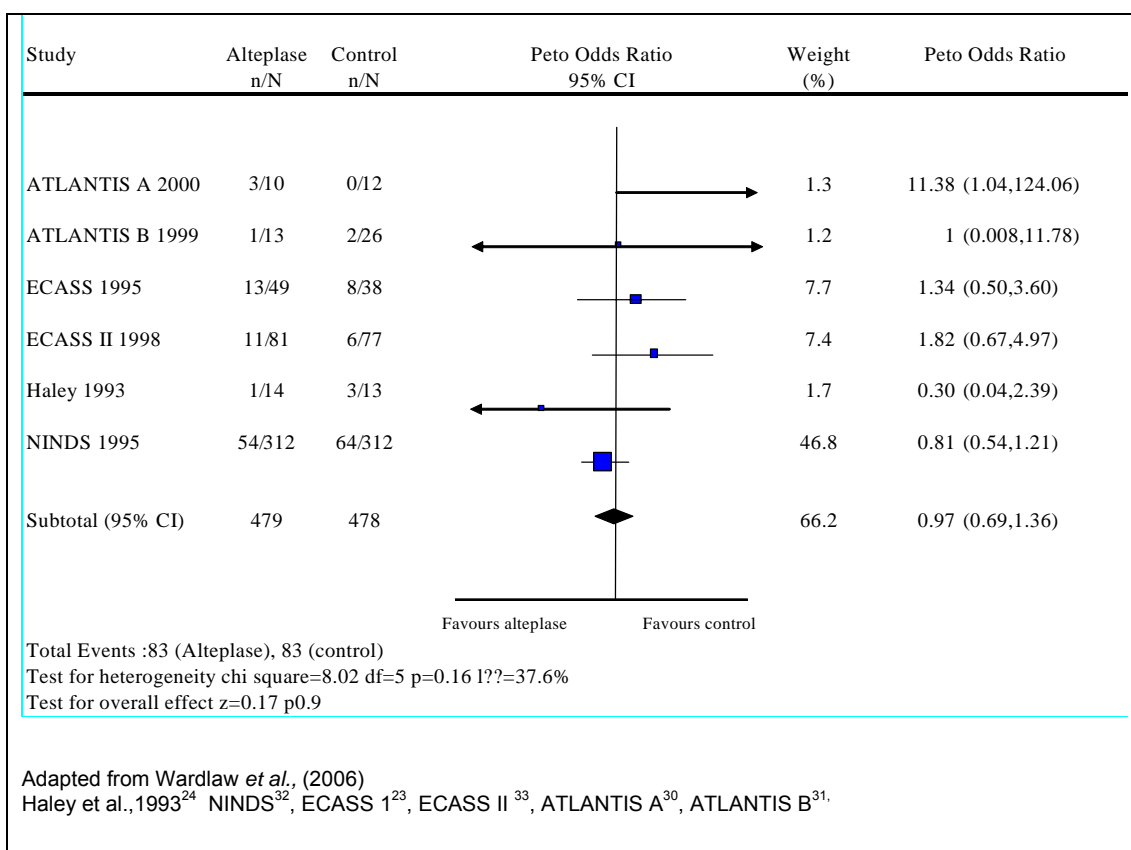


Figure 4: Forest plot of thrombolysis versus control – all cause death⁹



6.2.11.2 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

A 12 month follow up study³⁴ of patients within the NINDS trial and a 12 month observation study in Cologne³⁵ indicate a sustained benefit of alteplase over a 12 month period.

Most functional recovery in stroke patients occurs within the first 2 months. There is less functional recovery at 4 to 5 months post-stroke and after 6 months little further functional recovery can be expected¹⁷. It is therefore reasonable to assume that the capacity for functional improvement 12 months after the initial stroke event is limited. It is also a fair modelling assumption that long-term deterioration in independent patients may be linked to further stroke events.

6.2.12 Validity

Describe the measures that have been undertaken in order to validate and check the model.

The model structure and parameters were taken from an established NHS health technology body⁸. Costs were updated where appropriate. Clinical outcomes were based on a meta-analysis by the Cochrane group⁹.

The model was audited and checked by two health economists

6.3 Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following:

- **costs, QALYs and incremental cost per QALY**
- **disaggregated results such as life years gained, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment**
- **a statement as to whether the results are based on a probabilistic sensitivity analysis**
- **cost-effectiveness acceptability curves**
- **scatterplots on cost-effectiveness quadrants.**

Key Results

The lifetime health benefits accruing to the patient cohort are estimated to be 28 QALYs per 100 patients. This equates to 16 life years gained or 144 independent life years gained per 100 patients.

One-way, sensitivity analysis and the probabilistic sensitivity analysis results demonstrate the robustness of the lifetime cost-effectiveness of alteplase. At a threshold of £8,000 per QALY gained, the probability that alteplase is cost-effective is 0.99

With improved standard care for the treatment and management of stroke alteplase would still be cost-saving when considering both NHS and social service costs over a patient's life time.

Shortening the modelled time horizon to 12 months, where the full lifetime costs associated with disability due to stroke are not captured, does not alter the conclusion of the analysis is a cost-effective treatment in acute ischemic stroke.

6.3.1 Base-case analysis

What were the results of the base-case analysis?

The results of the lifetime (base-case) analysis, are summarised in Table 19,, in terms of incremental costs, QALY and life years gained.

The full consideration of life long rehabilitation costs, show that the increased number of individuals with independent status in the treated cohort results in overall cost savings and more QALY and life years gained.

Table 19: Base case (lifetime model) results

	Cost	Life Years Gained	Independent Life years Gained	QALYs	Incremental cost per QALY gained
Alteplase	£22,173	6.528	4.220	3.215	Alteplase dominant
Standard Treatment	£22,700	6.364	2.777	2.938	
Difference	-526.875	0.164	1.443	0.277	

Subgroup analysis

6.3.1.1 What were the results of the subgroup analysis/analyses if conducted?

Not applicable

6.3.2 Sensitivity analyses

6.3.2.1 What were the main findings of the sensitivity analyses?

In considering the full lifetime of the model cohorts, the conclusion that alteplase both reduces cost and improves outcomes in the long-term is a strong one. The lifetime health benefits accruing to the patient cohort are estimated to be 28 QALYs per 100 patients. This equates to 16 life years gained or 144 independent life years gained per 100 patients. Both one-way, sensitivity analysis and the probabilistic sensitivity analysis results demonstrate the robustness of the lifetime cost-effectiveness of alteplase. At

a threshold of £8,000 per QALY gained, the probability that alteplase is cost – effective is 0.99.

These sensitivity analysis also showed that even with a significant improvement in standard care for the treatment and management of stroke and a reduced stroke recurrence rate, alteplase would still be cost-saving when considering both NHS and social service costs, and is cost-effective (ICER of £2,181 per QALY gained) when only acute costs are considered.

Shortening the modelled time horizon to 12 months, where the full lifetime costs associated with disability due to stroke are not captured, does not alter the conclusion of the analysis. The results demonstrate that alteplase, (whilst not cost-saving) is cost-effective over a 12 month period, with an ICER of £14,026 per QALY gained.

A simple one-way sensitivity analysis was also carried out on the 12 month timeframe. Results have been summarised in Table 27 below. These show that the 12 month analysis is sensitive to the efficacy of alteplase, where the OR for death and dependency is worsened (ICER per QALY gained of £50,209). However in the lifetime model where the full costs and disutility associated with dependency are captured alteplase is shown to be cost-effective (ICER per QALY gained £4,137 even when the OR for death and dependency are worsened. For all other variable tested in the 12month model, the incremental cost per QALY gained associated are within an acceptable range (that is, less than £30,000 per incremental cost per QALY gained).

The PSA analysis also demonstrates that alteplase is also cost-effective at 12 months even when the effectiveness of standard treatment is raised.

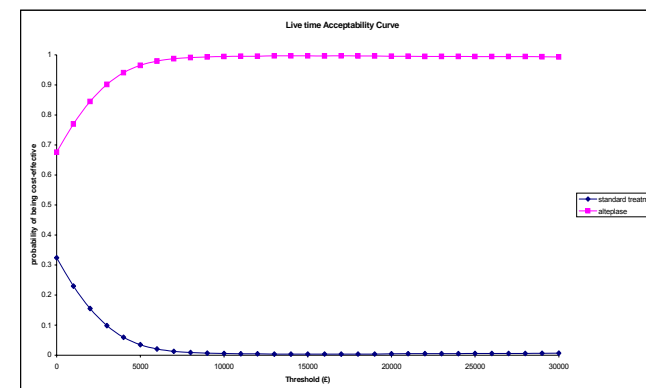
Probabilistic Sensitivity Analysis Results

Life time model: (NHS and Social Service costs)

Table 20: Results of the probabilistic sensitivity analysis in the life time model (NHS and Social Service costs)

	Standard Treatment			Alteplase			ICER per QALY
	Average	lower 95%CI	Upper 95% CI	Average	lower 95%CI	Upper 95% CI	
QALYS	2.850	2.612	3.104	3.109	2.768	3.452	Alteplase dominants
Costs	£23,456	£21,671	£25,150	£22,978	£20,801	£26,251	
Independent life years	2.719	2.711	2.730	4.092	3.683	4.431	
Life years	6.209	6.189	6.239	6.355	5.891	6.867	

Figure 5: Life-Time Acceptability Curve (NHS and Social Service costs)

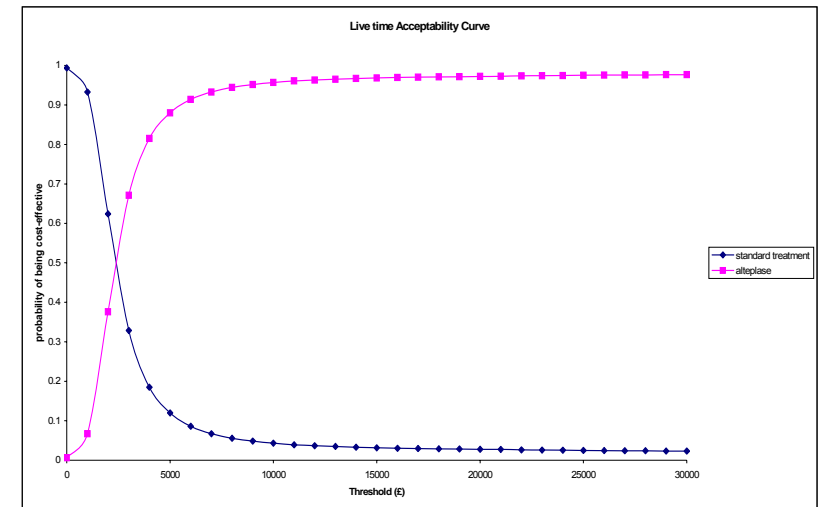


Life time model: (acute cost only)

Table 21: Results of the probabilistic sensitivity analysis in the life time model (acute cost only)

	Standard Treatment			Alteplase			ICER per QALY £2,181
	Average	lower 95%CI	Upper 95% CI	Average	lower 95%CI	Upper 95% CI	
QALYS	2.856	2.661	3.073	3.133	2.898	3.503	
Costs	£10,010	£9,395	£10,784	£10,614	£9,826	£11,462	
Independent life years	2.718	2.709	2.727	4.130	3.691	4.577	
Life years	6.207	6.183	6.230	6.337	5.811	6.768	

Figure 6: Life-Time Acceptability Curve (acute costs only)



Life time model– where the outcomes associated with standard treatment are improved

Table 22: Results of the PSA Life time model, where standard treatment outcomes are improved. NHS and Social Service costs

	Standard Treatment			Alteplase			ICER per QALY Alteplase dominants
	Average	lower 95%CI	Upper 95% CI	Average	lower 95%CI	Upper 95% CI	
QALYS	3.708	3.511	3.939	3.949	3.713	4.293	
Costs	£24,768	£23,348	£26,258	£24,060	£21,363	£26,259	
Independent life years	3.921	3.910	3.934	5.554	5.191	5.911	
Life years	7.530	7.506	7.558	7.631	7.282	7.990	

Table 23: Results of the PSA Life time model, where standard treatment outcomes are improved. Acute costs only

	Standard Treatment			Alteplase			ICER per QALY £2,670
	Average	lower 95%CI	Upper 95% CI	Average	lower 95%CI	Upper 95% CI	
QALYS	3.704	3.542	3.891	3.959	3.735	4.219	
Costs	£9,843	£9,488	£10,214	£10,525	£10,018	£11,026	
Independent life years	3.922	3.903	3.932	5.532	5.080	5.906	
Life years	7.533	7.494	7.553	7.686	7.323	7.947	

Figure 7: Life time Acceptability Curve NHS and Social Service costs.

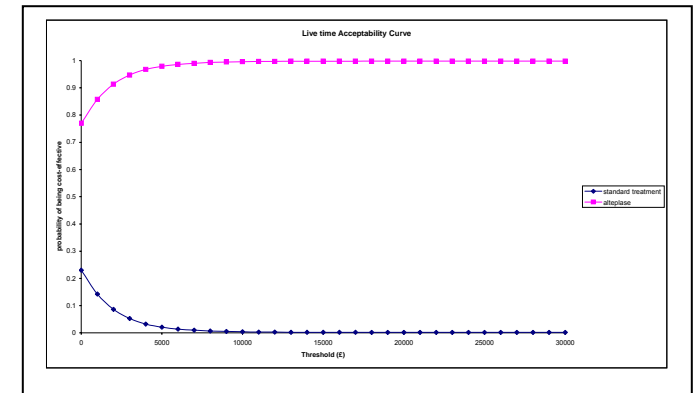
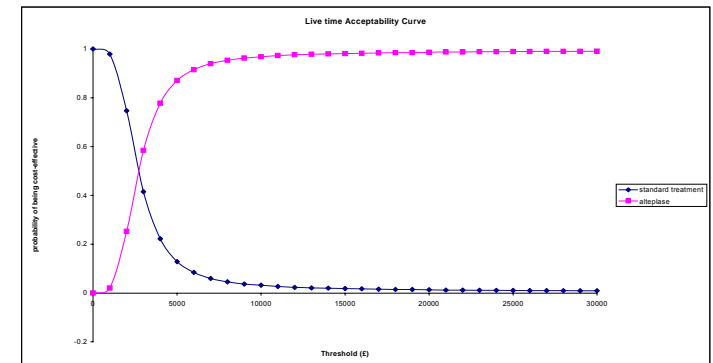


Figure 8: Life time Acceptability Curve Acute costs only



12 month model:

Table 24: Results of the probabilistic sensitivity analysis in the 12 month model (NHS and Social Service costs)

	Standard Treatment			Alteplase			ICER per QALY
	Average	lower 95% CI	Upper 95% CI	Average	lower 95% CI	Upper 95% CI	
QALYS	0.399	0.365	0.434	0.437	0.390	0.485	£14,026
Costs	£9,492	£9,032	£10,108	£10,030	£9,359	£10,720	
Independent life years	0.385	0.385	0.385	0.492	0.436	0.540	
Life years	0.706	0.706	0.706	0.713	0.659	0.774	

Figure 9: 12 month Acceptability Curve (NHS and Social Service costs)

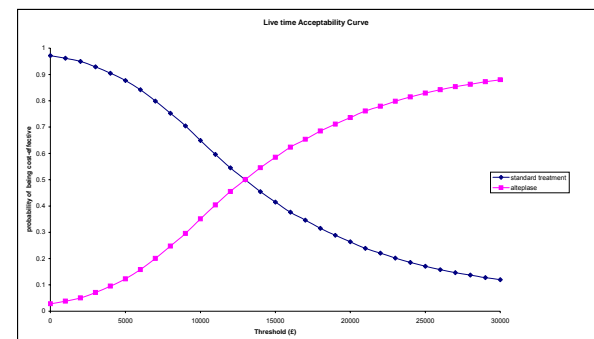
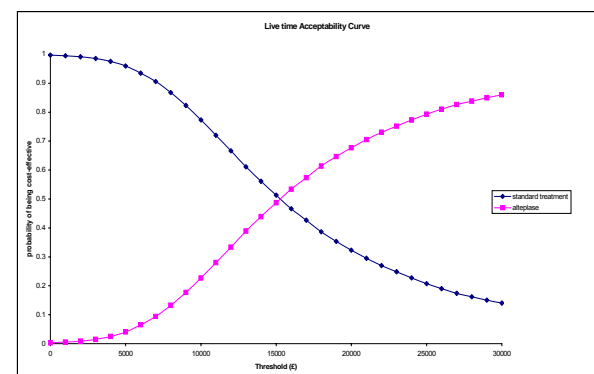


Table 25: Results of the PSA 12 month model, where standard treatment outcomes are improved. (NHS and Social Service costs)

	Standard Treatment			Alteplase			ICER per QALY
	Average	lower 95% CI	Upper 95% CI	Average	lower 95% CI	Upper 95% CI	
QALYS	0.522	0.495	0.551	0.557	0.520	0.602	£14,388
Costs	£9,122	£8,753	£9,475	£9,640	£8,990	£10,098	
Independent life years	0.572	0.572	0.572	0.680	0.631	0.731	
Life years	0.846	0.846	0.846	0.849	0.802	0.890	

Figure 10: 12 months Acceptability Curve (NHS and Social Service costs)



On-way sensitivity analysis

Life time model

The results showed that in all tested scenarios alteplase dominates standard treatment apart from those outlined in Table 26.

Table 26: Summary of one-way sensitivity analysis results in parameters where alteplase does not dominate standard treatment in terms of cost per incremental QALY gained (NHS and Social Service Costs.)

	Costs (£s)			QALYs			Incremental independent life years gained	Incremental life years gained	Incremental costs per QALY gained
	Alteplase	Standard Treatment	Incremental costs	Alteplase	Standard Treatment	Incremental QALYs			
OR for death and dependency increased to 0.83 (higher 95% CI)	£23,213	£22,700	£513	3.0622	2.9382	0.1239	0.9877	0.0970	£4,137
OR for death decreased to 0.69 (higher 95% CI)	£24,034	£22,700	£1,334	3.3879	2.9382	0.4497	1.4998	0.6777	£2,966
Staff costs doubled from £628 to £1256	£22,802	£22,700	£101	3.2150	2.9382	0.2768	1.4429	0.1638	£367
Cost of independent stroke year 1 doubled to £13,063	£25,578	£25,487	£91	3.2150	2.9382	0.2768	1.4429	0.1638	£328
Cost of dependent stroke year 1 halved to £7,425	£19,832	£19,822	£10	3.2150	2.9382	0.2768	1.4429	0.1638	£36

12 months model

Table 27: Results of the one-way sensitivity in the 12 month model. (NHS and Social Service costs)

	Costs (£s)			QALYs			Incremental independent life years gained	Incremental life years gained	Incremental costs per QALY gained
	Alteplase	Standard Treatment	Incremental costs	Alteplase	Standard Treatment	Incremental QALYs			
12 month time horizon NHS and Social Service costs.	£9,692	£9,151	£541	0.4426	0.4025	0.0401	0.1102	0.0091	£13,478
Alteplase efficacy									
OR for death and dependency increased to 0.83 (higher 95% CI)	£10,047	£9,151	£896	0.4203	0.4025	0.0178	0.0494	0.0072	£50,209
OR for death and dependency decreased to 0.5 (lower 95% CI)	£9,355	£9,151	£204	0.4637	0.4025	0.0612	0.1679	0.0109	£3,335
OR for death increased to 1.36 (higher 95% CI)	£9,304	£9,151	£152	0.4160	0.4025	0.0135	0.1083	-0.0602	£11,265
OR for death decreased to 0.69 (higher 95% CI)	£10,028	£9,151	£876	0.4656	0.4025	0.0631	0.1120	0.0690	£13,889
Utility Values									
Dependent state: decreased to 0.29 (95% CI)	£9,692	£9,151	£541	0.4232	0.3747	0.0485	0.1102	0.0091	£11,148
Dependent state: increased to 0.47 (95% CI)	£9,692	£9,151	£541	0.4620	0.4303	0.0317			£17,041

Independent state: decreased to 0.69 (95% CI)	£9,692	£9,151	£541	0.4182	0.3832	0.0350			£15,443
Independent state: increased to 0.79 (95% CI)	£9,692	£9,151	£541	0.4670	0.4218	0.0452			£11,957
Cost of alteplase treatment and administration									
Cost of alteplase £480 to £600 (max dose of alteplase)	£9,812	£9,151	£661	0.4426	0.4025	0.0401	0.1102	0.0091	£16,470
Staff costs doubled from £628 to £1256	£10,320	£9,151	£1,169	0.4426	0.4025	0.0401			£29,146
Cost of stroke treatment and management									
Cost of independent stroke year 1 halved to £3,266	£8,167	£7,904	£264	0.4426	0.4025	0.0401	0.1102	0.0091	£6,580
Cost of independent stroke year 1 doubled to £13,063	£12,740	£11,647	£1,094	0.4426	0.4025	0.0401			£27,274
Cost of dependent stroke year 1 halved to £7,425	£8,121	£7,085	£1,035	0.4426	0.4025	0.0401			£25,819
Cost of dependent stroke year 1 doubled to £29,701	£12,834	£13,283	-£449	0.4426	0.4025	0.0401			alteplase dominant £14,138
Cost of acute event fatal stroke reduced to £5,963 (95% CI)	£9,221	£8,654	£567	0.4426	0.4025	0.0401			£11,954
Cost of acute event fatal stroke increased to £10,813 (95% CI)	£10,780	£10,301	£479	0.4426	0.4025	0.0401			
Cost ICH: ICH rate lower 95% CI for placebo, higher 95% CI of alteplase, cost of CT scan increased from £69 to £102	£9,694	£9,151	£543	0.4426	0.4025	0.0401	0.1102	0.0091	£13,544

6.3.3 Interpretation of economic evidence

6.3.3.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

As discussed in section 6.1 a number of studies have evaluated the cost-effectiveness of alteplase in the treatment of acute ischemic stroke. Only Chambers *et al.*, (2002)²⁰ and Sandercock *et al.*, (2002)⁸ reported the cost-effectiveness of alteplase within a UK setting.

Chambers *et al.*, (2002)²⁰ reported that alteplase (administered within 3 hours of stroke onset) dominated standard treatment.

Sandercock *et al.*, (2002)⁸ reported that at 12 months alteplase was associated with an incremental cost of £13,581 per QALY gained compared to current practice. When life-time assumptions were applied alteplase dominated standard treatment.

While the above studies outline the cost-effectiveness of alteplase, it is believed that the model described in this submission is a more robust cost-effectiveness analysis of alteplase which more precisely addresses the decision problem under investigation within the NICE reference case. Unlike Chambers *et al.*, (2002)²⁰ and Sandercock *et al.*, (2002)⁸ the cost of a stroke event has been estimated from a UK burden of disease study rather than from clinical experts and unlike Sandercock *et al.*, (2002)⁸ this analysis evaluated the cost-effectiveness of alteplase in the treatment of acute ischemic stroke within three hours of symptom onset.

6.3.3.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology?

The economic evaluation demonstrates that in stroke units, where patient receive alteplase within 3 hours of stroke symptoms, the use of alteplase could reduce the cost of stroke, and improve Quality of Life (QOL) and survival.

6.3.3.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

The main strength of the model is that it is based on a recognised structure from the published literature, with data inputs collected from robust and reliable sources⁸. The source of efficacy and safety data for alteplase is derived from an independent meta-analysis of alteplase RCTs⁹, further corroborated by large scale observational studies^{12,25,26}. The model does not rely on any expert opinion to inform input variables, as acute costs and long-term costs of stroke are taken from a published UK stroke burden of disease study¹⁴. Utilities were also derived from the published literature and were measured in UK stroke patients using the EQ5D⁸. The parameters of the deterministic sensitivity analysis are based on an independent health technology appraisal of alteplase versus standard treatment without thrombolytic⁸. The methodology of the analysis concurs with the NICE reference case.

The cost-effectiveness of alteplase has been tested extensively in the sensitivity analysis, including an analysis of both the 12 month and life-time cost-effectiveness. The analysis also looked at the cost-effectiveness of alteplase when only acute care costs were considered.

The main weaknesses of model are those regarding the following assumptions

- The assumption that the LSR outcomes are representative of current specialized stroke units.

- The assumption that the utility associated with ICH is captured by the utility attributed to the three health states
- The assumption that the rate of stroke recurrence is as reported from the LSR given the availability of products such as of clopidogrel and dipyridamole for the prevention of recurrent stroke, the improvement in the management of stroke risk factors , such as diabetes, high blood pressure and smoking.

The above assumptions were tested in the sensitivity analysis, which demonstrated that the cost-effectiveness of alteplase is not sensitive to reduced stroke recurrence rates, or reduced utility values. Similarly, neither the lifetime nor the 12-month ICERs are sensitive to improvements in standard treatment without thrombolytics.

Given the above it can be concluded that this evaluation, is both transparent and robust in its analysis that alteplase is a cost-effective treatment in acute ischemic stroke.

6.3.3.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

This analysis provides a robust argument for the cost-effectiveness of alteplase (in a stroke unit) in patients eligible for treatment with the product. It is not believed that further analysis is required to strengthen the cost-effectiveness evaluation of this product.

7 Assessment of factors relevant to the NHS and other parties

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will facilitate the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers. Further examples are given in section 3.4 of the NICE document 'Guide to the methods of technology appraisal'.

7.1 What is the estimated annual budget impact for the NHS in England and Wales?

Table 28 presents the estimated budget impact of alteplase treatment to the NHS in England and Wales for the years 2007 through 2011 inclusive. The budget impact is an indication of the incremental cost to the NHS during the acute treatment phase only and does not include potential longer-term cost offsets of treatment from reduced disability. The analysis shows that the impact of alteplase treatment is approximately £600,000 per percentage point of acute ischaemic stroke patients eligible for alteplase. Details of how these estimates were calculated are reported in the following sub-sections.

Table 28 Budget impact of alteplase treatment

Parameter	2007	2008	2009	2010	2011
Incremental cost of alteplase treatment ¹	£1,111				
<i>Proportion of AIS patients eligible for alteplase</i>					
2% eligible	£1,164,527	£1,177,227	£1,192,311	£1,208,229	£1,224,944
4% eligible	£2,329,054	£2,354,454	£2,384,622	£2,416,458	£2,449,889
6% eligible	£3,493,581	£3,531,680	£3,576,933	£3,624,686	£3,674,833
8% eligible	£4,658,108	£4,708,907	£4,769,243	£4,832,915	£4,899,778
10% eligible	£5,822,635	£5,886,134	£5,961,554	£6,041,144	£6,124,722

Notes:

1. The incremental cost of alteplase is calculated as follows: In the acute phase, additional costs consist of the drug acquisition (£480), administration (£628) and, for a proportion of patients (4.15%) an additional cost of an adverse event (£69). Details of this derivation are in Section 7.5 and 7.6.

Key: AIS, Acute Ischaemic Stroke

7.2 What number of patients were assumed to be eligible? How was this figure derived?

Relatively very few patients with acute ischemic stroke – irrespective of setting – currently receive alteplase treatment. The minority of patients who are able to be treated within the mandatory 3-hour window are then subject to an extensive further list of criteria which preclude the administration of alteplase. Evidence of mild or improving symptoms, extremely severe stroke, prior stroke, existing thrombolysis therapy and a variety of co-morbid conditions are all contraindicated for alteplase treatment.

Two studies from North America were identified from the published literature that attempted to quantify the proportion of stroke patients in clinical practice that were either actually receiving or were eligible for alteplase and the various reasons for exclusion. Barber *et al.*, (2001)³⁶ prospectively identified over 2,100 stroke patients over a 3-year period in a Canadian setting. For each patient they derived the exact clinical presentation of stroke and whether alteplase was actually administered and if not, the exclusion criteria that applied.

Kleindorfer *et al.*, (2004)³⁷ performed a similar analysis on a retrospective dataset of stroke events in a US setting. They identified more than 2,300 ischaemic stroke events and examined the case notes of each to determine whether those patients would hypothetically have met the eligibility criteria for alteplase. Table 29 and Table 30 present the results of these two studies respectively.

Table 29 Proportion of stroke patients receiving alteplase (Canadian setting)

Parameter	Number of patients	Proportion of acute ischaemic
Ischaemic stroke	1,168	100%
<i>Of ischaemic stroke</i>		
Not admitted within 3 hours of symptom onset	854	73%
Admitted within 3 hours of symptom onset	314	27%
<i>Of those admitted within 3 hours</i>		
Excluded due to mild stroke	41	4%
Excluded due to clinical improvement	57	5%
Excluded due to co-morbidity	25	2%
Excluded due to process/diagnosis delay	51	4%
Excluded due to age	4	<1%
Excluded due to protocol exclusion	44	4%
Excluded due to other reason	8	1%
Actually received alteplase	84	7%

Source: Results adapted from Barber *et al.*, (2001)³⁶

Table 30 Proportion of ischaemic stroke patients eligible for alteplase (US setting)

Parameter	Number of patients	Proportion of acute ischaemic
Ischaemic stroke	2,308	100%
<i>Of ischaemic stroke</i>		
Did not present to ER within 3 hours of symptom onset	1,902	82%
Presented to ER within 3 hours of symptom onset	406	18%
<i>Of those at ER within 3 hours</i>		
Excluded due to NIHSS<5	174	8%
Excluded due to hypertension	39	2%
Excluded due to seizure	28	1%
Excluded due to blood test contraindications	35	2%
Excluded due to other reasons	11	<1%
Actually eligible for alteplase	155	7%

Source: Results adapted from Kleindorfer *et al.*, (2004)³⁷

Whilst these studies took different approaches (one looking at actual administration of alteplase and the other at hypothetical eligibility) in different settings and time periods, they both reach remarkably similar conclusions. After considering both the logistical aspect of admitting patients within the 3-hour window and the contraindications for treatment, both studies conclude that approximately 7% of all ischaemic stroke events have been eligible in practice or would have been eligible in theory for alteplase treatment.

These studies provide useful benchmarks for estimating the proportion of patients in England and Wales that would be eligible for alteplase treatment. Although the above studies reach similar final estimates, the proportion admitted within 3 hours and the reasons for exclusion do differ somewhat. The Barber study estimated that 27% of ischaemic stroke patients were admitted within 3 hours compared to only 18% in the Kleindorfer study³⁷. Furthermore, the exclusion criteria applied for the patients admitted within 3 hours in each study show that there may be some differences between the reasons for exclusion actually used in practice and those as per protocol.

Nevertheless, it is evident that very few ischaemic stroke patients are eligible for alteplase treatment and this budget impact analysis reflects that. Taking the above studies into consideration, and alongside any anticipated differences in practice between North America and England and Wales, the analysis considers eligibility proportions in the feasible range of 2%-10%.

In order to calculate the number of eligible patients in England and Wales, population projections were obtained from figures published by the Government Actuary^[38]. UK incidence rates of first-ever stroke were derived from the OXVASC study by Rothwell *et al.*, (2004)³⁹, with the proportion of ischaemic strokes estimated from the same study. Age and sex-specific incidence of ischaemic stroke was then estimated for all persons between the ages of 18 and 80 years as per the licensed indication. It was assumed that the incidence of disease is not time dependent. These estimations are presented in Table 31 for the years 2007 through 2011.

Table 31 Estimated incidence of acute ischaemic stroke

Parameter	2007	2008	2009	2010	2011
<i>18-34 years old</i>					
Males ¹	6,054,599	6,098,176	6,166,596	6,234,485	6,302,431
Incidence of first-ever stroke ²	-	-	-	-	-
Number of AIS ³	-	-	-	-	-
Females	5,933,580	5,961,948	6,015,647	6,074,036	6,132,619
Incidence of first-ever stroke	-	-	-	-	-
Number of AIS	-	-	-	-	-
<i>35-44 years old</i>					
Males	4,084,405	4,050,274	3,990,292	3,920,303	3,840,741
Incidence of first-ever stroke	0.00027	0.00027	0.00027	0.00027	0.00027
Number of AIS	939	931	917	901	883
Females	4,134,576	4,096,783	4,032,537	3,954,862	3,868,891
Incidence of first-ever stroke	0.00016	0.00016	0.00016	0.00016	0.00016
Number of AIS	563	558	549	539	527
<i>45-54 years old</i>					
Males	3,489,196	3,563,869	3,644,285	3,732,562	3,812,382
Incidence of first-ever stroke	0.00073	0.00073	0.00073	0.00073	0.00073
Number of AIS	2,168	2,214	2,264	2,319	2,369
Females	3,559,263	3,638,121	3,719,866	3,808,290	3,886,941
Incidence of first-ever stroke	0.00054	0.00054	0.00054	0.00054	0.00054
Number of AIS	1,636	1,672	1,710	1,750	1,787
<i>55-64 years old</i>					
Males	3,160,089	3,175,491	3,182,280	3,181,535	3,183,962
Incidence of first-ever stroke	0.00177	0.00177	0.00177	0.00177	0.00177
Number of AIS	4,761	4,784	4,794	4,793	4,797
Females	3,276,398	3,296,844	3,309,674	3,313,813	3,319,610
Incidence of first-ever stroke	0.00175	0.00175	0.00175	0.00175	0.00175
Number of AIS	4,880	4,911	4,930	4,936	4,945
<i>65-74 years old</i>					
Males	2,146,153	2,192,441	2,249,566	2,304,155	2,358,376
Incidence of first-ever stroke	0.00646	0.00646	0.00646	0.00646	0.00646
Number of AIS	11,800	12,055	12,369	12,669	12,967
Females	2,350,090	2,392,892	2,449,200	2,505,680	2,562,999
Incidence of first-ever stroke	0.00408	0.00408	0.00408	0.00408	0.00408
Number of AIS	8,161	8,310	8,505	8,701	8,900
<i>75-80 years old^a</i>					
Males	893,963	903,532	914,448	929,928	947,186
Incidence of first-ever stroke	0.00942	0.00942	0.00942	0.00942	0.00942
Number of AIS	7,168	7,244	7,332	7,456	7,594
Females	1,154,197	1,150,651	1,149,225	1,151,683	1,157,112
Incidence of first-ever stroke	0.01051	0.01051	0.01051	0.01051	0.01051
Number of AIS	10,325	10,293	10,280	10,302	10,351
Total number of AIS	52,401	52,972	53,651	54,367	55,119

Notes:

1. All population estimates are drawn from the Government Actuary.
2. Age and sex-specific incidence of first-ever stroke is reported in the OXVASC study.
3. The number of AIS is calculated by multiplying the population of the demographic by the annual incidence rate of first-ever stroke, then again by the proportion of first-ever stroke that are AIS. The OXVASC study reports that 85.1% of first-ever strokes were AIS, and this figure is used throughout.
4. The OXVASC study reported incidence for the 75-84 years age group. This incidence rate has been applied to population in the range of 75-80 years in line with the licensed indication.

Key: AIS, Acute Ischaemic Stroke

Finally, the eligibility proportions as outlined above were applied to the incidence estimates to arrive at the final number of eligible patients (Table 32).

Table 32 Estimated numbers of patients eligible for alteplase

Parameter	2007	2008	2009	2010	2011
Total number of AIS	52,401	52,972	53,651	54,367	55,119
<i>Total patients eligible for alteplase</i>					
2% eligible	1,048	1,059	1,073	1,087	1,102
4% eligible	2,096	2,119	2,146	2,175	2,205
6% eligible	3,144	3,178	3,219	3,262	3,307
8% eligible	4,192	4,238	4,292	4,349	4,410
10% eligible	5,240	5,297	5,365	5,437	5,512

Key: AIS, Acute Ischaemic Stroke

These patient numbers are then applied to the incremental cost of alteplase in the acute treatment phase to arrive at the estimates of budget impact outlined in the response to question 7.1.

7.3 What assumption(s) were made about current treatment options and uptake of technologies?

As outlined in Section 6, it is assumed that alteplase is given to eligible patients in addition to current treatment, rather than instead of it. Therefore it is assumed that the budget impact of alteplase in the acute treatment phase will be equal to the incremental cost of alteplase treatment over and above the costs of current treatment. It is assumed that 100% of the patients that meet the strict eligibility criteria outlined in the response to question 7.2 receive alteplase treatment.

7.4 What assumption(s) were made about market share (where relevant)?

No assumptions about differential or time-dependent market share are necessary given that there are no alternative treatments to consider. For the purposes of budget impact it is assumed that 100% of the patients that meet the strict eligibility criteria outlined in the response to question 7.2 receive alteplase treatment.

7.5 What unit costs were assumed? How were these calculated?

The unit costs of alteplase treatment and administration are outlined in Section 6.2.9. Assuming an average dose of 68.78mg (as reported in SITS-MOST 6th report) would result in the use of one 50 mg vial and one 20 mg vial. This equates (including wastage) to a total cost of £480 per administration. In addition, each administration requires specialist care and a cost of £628 for health professional time is included in the incremental cost of alteplase. The derivation of this cost is presented in Table 12.

7.6 In addition to drug costs, consider other significant costs associated with treatment. What is the recommended treatment regime – for example, what is the typical number of visits, and does treatment involve daycase or outpatient attendance? Is there a difference between recommended and observed doses? Are there likely to be any adverse events or a need for other treatments in combination with the technology?

As outlined in the economic evaluation, the only other additional cost of treatment considered in the acute phase is that associated with an ICH event. In this case, the economic evaluation assumes that an extra CT scan is performed, with all other management costs already accounted for by the costs of standard care. The budget impact model assumes that the incremental cost of alteplase treatment is equal to the base case costs of

alteplase acquisition (£480) and administration (£628) for all patients, and an extra CT scan (£69) for the base case incremental risk of ICH in the alteplase group (4.15%). The total incremental cost is equal to £1,111 per patient.

7.7 Were there any estimates of resource savings? If so, what were they?

As alteplase is assumed to be given in addition to, rather than instead of, current treatment it is assumed that there are no immediate cost offsets in the acute treatment phase.

7.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

As clearly demonstrated in the results of the modelled economic evaluation in Section 6, as well as in the bulk of published economic evaluations of alteplase in this indication, there are significant cost offsets in the long-term management of stroke patients that can be realised from the addition of alteplase to current practice. Indeed the probabilistic sensitivity analysis presented in Section 6.3 showed that on average alteplase treatment is likely to lead to sufficient cost savings over the lifetime of the patient to more than offset the initial incremental cost in the acute phase. Please refer to Section 6.3 for a full discussion.

8 References

Please use the Vancouver style (that is, consecutive numbering throughout the main text). In the reference list, the names of up to six authors should be given, followed by et al.; for example:

References: Section 1- 4

1. Monthly Index of Medical Specialities. November 2006
2. Sandercock P, Berge E, Dennis M, Forbes J, Hand P, Kwan J et al. (2002) A systematic review of the effectiveness, cost-effectiveness and barriers to implementation of thrombolytic and neuroprotective therapy for acute ischaemic stroke in the NHS. Health Technol Assess 6 (26).
3. Wardlaw JM, del Zoppo G, Yamaguchi T, Berge E. (2006) Thrombolysis for acute ischaemic stroke (Cochrane Review) In The Cochrane Library, Issue 3. Oxford: Update Software.
4. Adams H, Adams R, del Zoppo G and Goldstein LB. (2005) Guidelines for the early management of patients with ischemic stroke: 2005 Guidelines Update A Scientific statement from the Stroke Council of the American Heart Association/American Stroke Association. Stroke 36:916-921
5. Hacke W, Kaste M, Bogousslavsky, Brainin M, Chamorro A, et al. Prophylaxis and treatment – information for doctors in hospitals and practice – update 2003/2004 – EUSI (European Stroke Initiative).
6. The European Stroke Initiative Executive Committee and the EUSI Writing Committee. European Stroke Initiative Recommendations for stroke management – Update (2003). Cerebrovascular Disease 16:311-337

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7. Adams HP, Adams RJ, Brott T, del Zoppo GJ, Furlan A et al (2003). Guidelines for the early management of patients with ischemic stroke Stroke 34:1056-1083
 8. Use of intravenous tPA for the management of acute stroke in the emergency department (2002)
 9. Thrombolysis for acute ischemic stroke (2002).
<http://www.tigc.org/eguidelines/thrombolyticstroke03.htm>
 10. Kaste M, Thomassen L, Grond M, Hacke W, Holtas S et al. Thrombolysis for acute ischemic stroke: A consensus statement of the 3rd Karolinska Stroke Update, October 30-31, 2000. (2001). Stroke 32:2717-2718
 11. Albers GW, Amarenco P, Easton JD, Sacco RL, Teal P. Antithrombotic and thrombolytic therapy for ischemic stroke (2001). Chest 119;300-320
 12. Canadian guidelines for intravenous thrombolytic treatment in acute stroke (1998)

References: Section 5

1. Marler JR, rtPA Study Group. (1995) Tissue plasminogen activator for acute ischemic stroke. New England Journal of Medicine 333(24):1581-1587
2. Hacke W, Kaste M, Fieschi C, Toni D, Lesaffre E, Kummer R von, et al. (1995). Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke: the European Cooperative Acute Stroke Study (ECASS). Journal of the American Medical Association 274(13):1017-1025.

3. Hacke W, Kaste M, Fieschi C, Kummer R von, Davalos A, Meier D. (1998). Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). *Lancet* 352(9136):1245-1251.

4. Clark WM, Albers GW, Madden KP, Hamilton S. (2000) The rtPA (alteplase) 0- to 6-hour acute stroke trial, part A (A0276g): results of a double-blind, placebo-controlled, multicenter study. *Stroke* 31(4):811-816.

5. Clark WM, Wissman S, Albers GW, Jhamandas JH, Madden KP, Hamilton S. (1999) Recombinant tissue-type plasminogen activator (alteplase) for ischemic stroke 3 to 5 hours after symptom onset: the ATLANTIS study: a randomized controlled trial. *Journal of the American Medical Association* 282(21):2019-2026.

6. Kwiatkowski TG, Libman RB, Frankel M, Tilley BC, Morgenstern LB, Lu M. et al. (1999) Effects of tissue plasminogen activator for acute ischemic stroke at one year. *New England Journal of Medicine* 340(23):1781-1787

7. Marler JR, Tilley BC, Lu M, Brott TG, Lyden PC, Grotta JC et al. (2000) Early stroke treatment associated with better outcome: the NINDS rt-PA stroke study. *Neurology* 55(11):1649-1655.

8. Broderick JP, Lu M, Kothari R, Levine SR, Lyden PD, Haley EC et al. (2000) Finding the most powerful measures of the effectiveness of tissue plasminogen activator in the NINDS tPA stroke trial. *Stroke* 31 (10) : 2335-2341

9. Albers GW, Clark WM, Madden KP, Hamilton SA. (2002) ATLANTIS trial: results for patients treated within 3 hours of stroke onset. *Stroke* 33(2):493-495

10. Marler JR and Hacke W. (2004) Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. *Lancet* 363(9411):768-774

11. Haley EC, Brott TG, Sheppard GL, Barsan W, Broderick J, Marler JR et al. (1993) Pilot randomized trial of tissue plasminogen activator in acute ischemic stroke. *Stroke* 24(7):1000-1004.

12. Wardlaw JM, del Zoppo G, Yamaguchi T, Berge E. Thrombolysis for acute ischaemic stroke (Review). The Cochrane Collaboration. *The Cochrane Library* 2006, Issue 3.

13. Hill, MD, Buchan AM, for the Canadian Alteplase for Stroke Effectiveness Study (CASES) Investigators. (2005) Thrombolysis for acute ischemic stroke: results of the Canadian Alteplase for Stroke Effectiveness Study. *Canadian Medical Association Journal* 172 (10): 1307 – 1312

14. Albers GW, Bates VE, Clark WM, Bell R, Verro P, Hamilton SA (2000). Intravenous tissue-type plasminogen activator for treatment of acute stroke: the Standard Treatment with Alteplase to Reverse Stroke

(STARS) study. *Journal of the American Medical Association* 283(9):1145-1150.

15. Grond M, Stenzel C, Schmuelling S, Rudolf J, Neveling M, Lechleuthner A et al. (1998) Early intravenous thrombolysis for acute ischemic stroke in a community-based approach. *Stroke* 29(8):1544-1549.

16. Audebert HJ, Kukla C, Vatankehah B, Gotzler B, Schenkel J, Hofer S et al. (2006) Comparison of tissue plasminogen activator administration management between Telestroke Network hospitals and academic stroke centers: the Telemedical Pilot Project for Integrative Stroke Care in Bavaria/Germany. *Stroke* 37(7):1822-1827

17. Walters MR, Muir KW, Harbison J, Lees KR, Ford GA. (2005) Intravenous thrombolysis for acute ischaemic stroke: preliminary experience with recombinant tissue plasminogen activator in the UK. *Cerebrovascular Disease* 20(6):438-442.

18. SITS-MOST, Unpublished report no. 6: Data on file. Boehringer Ingelheim 2005

19. Katzan IL, Furlan AJ, Lloyd LE, Frank JI, Harper DL, Hinchey JA et al. (2000) Use of tissue-type plasminogen activator for acute ischemic stroke: the Cleveland area experience. *Journal of the American Medical Association* 283(9):1151-1158.

20. SITS-MOST, Unpublished report no. 5: Data on file, Boehringer Ingelheim 2005.

21. Wahlgren NG. Presentation: Leading Stroke Experts Workshop – Update on thrombolysis – SITS-MOST, SITS-ISTR. 24-25 October 2006, Cape Town.

22. Ingall TJ, O'Fallon WM, Asplund K, Goldfrank LW, Hertzberg VS, Louis TA, Christianson TH. (2004) Findings from the reanalysis of the NINDS tissue plasminogen activator for acute ischemic stroke treatment trial. *Stroke* 35(10):2418-2424.

23. Harraf F, Sharma AK, Brown MM, Lees KR, Vass RI, Kalra L (for the Acute Stroke Intervention Study Group. (2002) A multicentre observational study of presentation and early assessment of acute stroke. *British Medical Journal* 325:17

24. Hacke W. (2005) The desmoteplase in acute ischaemic stroke trial (DIAS): A phase II (MRI-based 9-hour window acute stroke thrombolysis trial with intravenous desmoteplase. *Stroke* 36:66-73

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

-
26. Ribo M, Molina CA, Rovira A, Quintana M, Delgado P, Montaner J. (2005) Safety and efficacy of intravenous tissue plasminogen activator stroke treatment in the 3- to 6-hour window using multimodal transcranial doppler/MRI selection protocol. *Stroke* 36(3):602-606.
27. Götz T, Schwark C, Sobesky J, Bluhmki E, Fiebach JB, Fiehler J et al. (2006) Outcome and symptomatic bleeding complications of intravenous thrombolysis within 6 hours in MRI-selected stroke patients. Comparison of a Germany multicenter study with the pooled data of ATLANTIS, ECASS, and NINDS tPA trials. *Stroke* 37:852 – 858
28. Wardlaw JM, Sandercock PAG, Berge E. (2003) Thrombolytic therapy with recombinant tissue plasminogen activator for acute ischemic stroke: where do we go from here? A cumulative meta-analysis. *Stroke* 34(6):1437-1442
29. Larrue V, Kummer R von, Mueller A, Bluhmki E. (2001) Risk factors for severe hemorrhagic transformation in ischemic stroke patients treated with recombinant tissue plasminogen activator: a secondary analysis of the European-Australasian Acute Stroke Study (ECASS II). *Stroke* 32(2):438-441.
30. Heuschmann PU, Kolominsky-Rabas PL, Roether J, Misselwitz B, Lowitzsch K, Heidrich J. (2004) Predictors of in-hospital mortality in patients with acute ischemic stroke treated with thrombolytic therapy. *Journal of the American Medical Association* 292(15):1831-1838.

References: Section 6 and 7

1. Demaerschalk B, Yip T. (2005) Economic Benefit of Increasing Utilization of Intravenous Tissue Plasminogen Activator for Acute Ischemic Stroke in the United States. *Stroke*; 36:2500-2503.
2. Mar J, Begiristain J, Arrazola A (2005). Cost-Effectiveness Analysis of Thrombolytic Treatment for Stroke *Cerebrovascular Diseases*;20:193-200.
3. Moodie M, Carter R, Mihalopoulos C, Thrift A, Chambers B, Donnan G et al., (2004). Trial Application of a Model of Resource Utilization, Costs, and Outcomes for Stroke (MORUCOS) to Assist Priority Setting in Stroke. *Stroke*; 35:1041-1046
4. Sandercock P, Berge E, Dennis M, Forbes J, Hand P, Kwan J (2004). Cost-effectiveness of thrombolysis with recombinant tissue plasminogen activator for acute ischemic stroke assessed by a model based on UK NHS costs. *Stroke* 35, 6: 1490-1497.
5. Solomon N, Glick H, Russo C, Lee J, Schulman K. Patient preferences for stroke outcomes. *Stroke*, 25: 1721-1725
6. Alteplase Summary of Product Characteristics
7. National Service Framework for Older People. Department of Health. March 2001
8. Sandercock P, Berge E, Dennis M, Forbes J, Hand P, Kwan J et al. (2002) A systematic review of the effectiveness, cost-effectiveness and barriers to implementation of thrombolytic and neuroprotective therapy for acute ischaemic stroke in the NHS. *Health Technol Assess* 6 (26).
9. Wardlaw JM, del Zoppo G, Yamaguchi T, Berge E. (2006) Thrombolysis for acute ischaemic stroke (Cochrane Review) In *The Cochrane Library*, Issue 3. Oxford: Update Software

-
10. Clopidogrel and modified-release dipyridamole in the prevention of occlusive vascular events. Nice Technology Appraisal 90. May 2005. Assessment Report. <http://www.nice.org.uk/page.aspx?o=110689> (last accessed on 10.11.2006)
 11. The ATLANTIS, ECASS, and NINDS rt-PA Study Group Investigators. (2004) Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. *Lancet*, 363: 768–74
 12. SITS-MOST, Unpublished report no. 6: Data on file. Boehringer Ingelheim 2005; Table 2.1 (page 36), and Table 4.1 page 43
 13. Curtis L, Netten A. (2005) Personal Social Services Research Unit. Unit Costs of Health and social Care. University of Kent,
 14. Youman P, Wilson K, Harraf F, Kalra L (2003) The Economic Burden of Stroke in the United Kingdom. *Pharmacoeconomics*; 21 (1): 43-50.
 15. National Institute of clinical Excellence. Guide to the Methods of Technology Appraisal. April 2004
 16. Fagan S, Morgenstern S, Petitta S, Ward S, Tilley S, Marler J. et al., (1998), Cost-effectiveness of tissue plasminogen activator for acute ischemic stroke. *Neurology*; 50 (4): 883-890.
 17. Kwakkel G, Wagenaar RC, Kollen BJ, Lankhorst GJ. (1996) Predicting disability in stroke--a critical review of the literature. *Age Aging*; 25(6):479-89.
 18. Stahl E, Furie K, Gleason S, Gazelle S. (2003) Stroke: Effect of Implementing an Evaluation and Treatment Protocol Compliant with NINDS Recommendations. *Radiology*; 228:659–668
 19. Sinclair S, Frighetto L, Loewen P, Sunderji R, Teal P, Fagan S, Marra C. (2001) Cost-Utility Analysis of Tissue Plasminogen Activator

-
- Therapy for Acute Ischaemic Stroke. A Canadian Healthcare Perspective. *Pharmacoeconomics*; 19 (9): 927-936
20. Chambers M, Koch P, Hutton J. (2002) Development of a Decision-Analytic Model of Stroke Care in the United States and Europe. *VALUE IN HEALTH*; 5: 82-97
21. NHS reference costs 2005. Department of Health
22. Kwiatkowski T, Libman R, Frankel M, Tilley B, Morgenstern L, Lu M. (1999) Effects of tissue plasminogen activator for acute ischemic stroke at one year. The New England journal of medicine *N Engl J Med*; 10;340(23):1781-7.
23. Hacke W, Kaste M, Fieschi C, Danilo T, Lesaffre E, von Kummer R, et al., (1995) Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. *JAMA*; 274(13):1017–1025
24. EC Haley, Jr, TG Brott, GL Sheppard, W Barsan, J Broderick, JR Marler, GL. (1993) Pilot randomized trial of tissue plasminogen activator in acute ischemic stroke. The TPA Bridging Study Group. *Stroke*;24:1000-1004
25. Michael D. Hill, Alastair M. Buchan (2005) Thrombolysis for acute ischemic stroke: results of the Canadian Alteplase for Stroke Effectiveness Study. *CMAJ* 2005; 172 (10):1307-1312.
26. Albers GW, Bates VE, Clark WM, Bell R, Verro P, Hamilton SA (2000) Intravenous tissue-type plasminogen activator for treatment of acute stroke: the Standard Treatment with Alteplase to Reverse Stroke (STARS) study. *JAMA*; 283(9):1145-1150
27. Monthly Index of Medical Specialities. November 2006

-
28. Kalra L, Evans A, Perez I, Knapp M, Donaldson N, Swift C. (2000) Alternative strategies for stroke care: a prospective randomised controlled trial. *The Lancet*; 356: (9233) 894-899
 29. Royal college of physicians guidelines on stroke. National clinical Guidelines for stroke. June 2004
 30. Albers GW, Clark WM, Madden KP, Hamilton SA. The ATLANTIS T-PA Acute Stroke Trial: results for patients treated within 3 hours of stroke onset. *Stroke* 2000; 31(1):307.
 31. Clark W, Wissoman S, Hamandas J, Albers G, Madden K, Hamilton S, et al. (1999) Recombinant tissue type plasminogen activator (Alteplase) for ischemic stroke 3 to 5 hours after symptom onset. The ATLANTIS Study: a randomized controlled trial. *JAMA*; 282:2019–26.
 32. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group (1995). Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med*;333(24):1581–7.
 33. Hacke W, Kaste M, Fieschi C, von Kummer R, Davalos A, Meier D, et al., (1998) Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). *Lancet*; 352:1245–51.
 34. Kwiatkowski T, Liberman R, Frankel M; Tilley B, Morgenstern B, LU M, et al., (1999). Effects of tissue plasminogen activator for acute ischemic stroke at one year. *New Engl J med*; 340 (23):1781-178.
 35. Schmülling S, Grond M, Rudolf J, Heiss W (2000). One-Year Follow-Up in Acute Stroke Patients Treated With rtPA in Clinical Routine. *Stroke*;31:1552-1554
 36. Barber P, Zhang J, Demchuk A, Hill M, Buchan A. (2001) Why are stroke patients excluded from TPA therapy?: An analysis of patient eligibility. *Neurology* 2001;56;1015-1020

-
37. Kleindorfer D, Kissela B, Schneider A, Woo D, Khoury J, Miller R. (2004) . Eligibility for Recombinant Tissue Plasminogen Activator in Acute Ischemic Stroke: A Population-Based Study. *Stroke*;35;27-29
38. The 2004-based principal projection of the population of England and Wales. Government Actuary Department, available online: <http://www.gad.gov.uk/Population/index.asp?v=Principal&y=2004&subYear=Continue> Last Accessed 9th November 2006.”
39. Rothwell P, Coull A, Giles M, Howard S, Silver L, Bull L et al., (2004). Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). *THE LANCET* ;363, 1925-1933