Alteplase for the treatment of acute ischaemic stroke: A Single Technology Appraisal

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List of Abbreviations

aPTT	activated partial thromboplastin time
BI	Barthel Index
CI	Confidence interval
ICER	Incremental cost effectiveness ratio
ITT	intention to treat
LSR	Lothian Stroke Register
mRS	modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
RCT	randomised controlled trial
SICH	symptomatic intracranial haemorrhage
SSS	Scandinavian stroke scale

List of Definitions

Barthel Index	100-point scale assessing the activities of daily living (ADL), where 100 represents independence and 0 total dependence. However, patients who achieve the maximum score because they are independent in ADL may still have a significant handicap.
Glasgow Outcome Scale	5-point scale assessing outcome after severe brain damage, where a score of 1 indicates a good recovery and 5 represents death.
Modified Rankin Scale	7-point scale assessing overall function where a score of 0 indicates complete recovery and 6 is death. A score of 0-2 indicates functional independence while 3-5 indicates dependence.
National Institutes of Health Stroke Scale	42-point scale assessing neurological deficit where 0 represents normal function without neurological deficit.
Scandinavian stroke scale	48-point scale assessing neurological deficit, higher scores being indicative of better outcomes.
Symptomatic intracranial haemorrhage	Intracranial haemorrhage associated with either death or a clinical deterioration in the patient's neurological state, and confirmed by CT scan or post mortem examination. It may take the form of secondary bleeding into the infarct or new bleeding elsewhere in the brain or its surrounding spaces.

1 SUMMARY

1.1 Scope of the submission

The scope of the submission defines the population as adults with ischaemic stroke, after prior exclusion of intracranial haemorrhage. The intervention is defined as intravenous alteplase given within three hours of symptom onset in a secondary care setting under the guidance of experienced stroke and neuro-imaging specialists.

The comparator is restricted to placebo or standard medical and supportive management without thrombolysis. This is appropriate: it has recently been noted that the most important therapy in acute ischaemic stroke is restoration of the blood supply to the affected area of the brain.[1] No thrombolytic treatment other than alteplase is licensed in the UK for this purpose, and other stroke treatment or prevention therapies, which function in different ways, would not be relevant comparators.

The outcome measures identified in the scope are:

- Disability
- Proportion of patients making a good functional recovery by 3-6 months after treatment
- Neurological deficit
- Mental health, including anxiety and depression
- Survival
- Length of hospital stay
- Adverse effects of treatment, including bleeding events
- Health-related quality of life.

All of these outcomes are relevant. However, alteplase is associated with an increase both in the proportion of patients making a good functional recovery by 3-6 months after treatment and in the proportion suffering a symptomatic intracranial haemorrhage (SICH), an outcome which is associated with death or increased disability. Therefore, to capture both the risks and benefits of alteplase therapy, the single most clinically relevant and important outcome measure is the proportion of patients suffering death or dependency (ie scoring 3-6 inclusive on the mRS).[2]

The scope requires cost effectiveness to be expressed in terms of incremental cost per quality-adjusted life year. The time horizon for the economic evaluation is both short-term (12 months) and long-term (40 years). The long-term model is considered to be the base case analysis as it captures the long-term disability of stroke patients. Costs are considered from an NHS and Personal Social Services perspective.

1.2 Summary of submitted clinical effectiveness evidence

The submitted clinical effectiveness evidence indicates that, in highly selected patients, alteplase therapy administered within three hours of the onset of acute ischaemic stroke is associated with a statistically significant reduction in the risk of death or dependency at three months compared with placebo (relative risk 0.82, 95% confidence intervals 0.72-0.93, absolute risk reduction 11%) despite a significantly increased risk of symptomatic intracranial haemorrhage (SICH) within the first 7-10 days (RR 4.24, 95% CI 1.52-11.83, absolute risk increase 6%). Only one study, the NINDS study, presented data relating to a time-point later than three months from stroke onset: these data indicate that the benefit of treatment is sustained at six and 12 months.

However, as noted in a recent Cochrane review, the evidence for the use of alteplase within the 3-hour licensed window should be treated with extreme caution. It is based on a total of only 416 patients who received the current licensed dose of alteplase within that time window, and 312 of these were included in one trial, the NINDS trial, in which a substantial imbalance in baseline stroke severity, a key prognostic factor, favoured alteplase.

As the randomised trials were not stratified by any potential prognostic factor other than time to treatment, any post-hoc analyses designed to explore the extent to which different groups might benefit from therapy can only be regarded as hypothesis-generating. Nonetheless, it is potentially alarming that one such analysis[3] appeared to indicate that alteplase therapy was of significant benefit in women but not in men.

Observational studies suggest that few patients with ischaemic stroke will be eligible for alteplase therapy under the terms of the current licensing agreement. In particular, many patients will be excluded by virtue of their age, as alteplase is not licensed for patients aged over 80. Many more will be excluded by the restriction of therapy to patients in whom treatment can be initiated within three hours of symptom onset. In principle, it would be possible to increase the proportion of patients who reach the point of treatment within three hours, but to do so may require substantial investment in public education and service reconfiguration.

1.3 Summary of submitted cost effectiveness evidence

Boehringer Ingelheim have developed a state transition cohort model to compare the lifetime impact of treatment with alteplase within three hours of onset of stroke symptoms to standard treatment for stroke onset. The main data source for the model is a Cochrane review meta-analysis of the NINDS,[4] ECASS I,[5] ECASS II,[6] ATLANTIS A,[7] ATLANTIS B[8] and Haley et al[9] studies. Outcomes from this meta-analysis are extrapolated over a lifetime horizon in order to assess the long-term benefits and costs of alteplase. The model takes into account the increased rate of haemorrhage seen in alteplase-treated patients. The health states used within the model are considered to be appropriate for the required analysis.

The costs and utilities associated with each health state are considered to be appropriate for the economic analysis.

The Boehringer Ingelheim model estimated that, in the base-case analysis, alteplase was both less costly and more effective than standard treatment. This increased to a maximum of £50,000 upon one-way sensitivity analysis of the parameters.

The probabilistic sensitivity analysis presented within the submission suggests that the probability that alteplase has a cost-effectiveness ratio better than £20,000 per QALY gained is close to 1.

1.4 Commentary on the robustness of submitted evidence

1.4.1 Strengths

The model structure is appropriate and allows sensitivity analysis to be carried out easily.

- One-way sensitivity analysis suggests that variations in the majority of the parameters do not have a large effect upon the ICER.

- Alteplase dominates standard treatment; potential parameter variations are unlikely to increase the ICER beyond the currently accepted threshold values.

1.4.2 Weaknesses

- The evidence of clinical effectiveness on which the model rests is far from robust. The economic evaluation relies heavily on the results of the NINDS trial. The extreme caution that should be applied to the clinical effectiveness of alteplase should also be applied to the results of the cost-effectiveness analysis.

- However, no weaknesses in the model structure were identified that would alter the results significantly.

1.4.3 Areas of uncertainty

- The evidence for the clinical effectiveness of alteplase administered with three hours of symptom onset is not robust.

- A post-hoc analysis has raised the possibility that alteplase may confer no significant benefit in men.

- The risks and benefits of alteplase are unknown beyond 12 months, but the manufacturer's health economic model has used a lifetime horizon of 40 years.

1.5 Key issues

There is a major concern with the efficacy parameters in the model due to problems with the NINDS study. The cost-effectiveness results rely heavily on this study and must be viewed with extreme caution.

One important issue which is not explicitly taken into account in the economic modelling is the possible impact of trying to increase the number of patients who could be treated within the 3-hour window. This may have a significant cost impact to the NHS if there is a need to educate the public on the importance of early treatment, and if substantial service reconfiguration were necessary.

2 BACKGROUND

2.1 Critique of manufacturer's description of underlying health problem

The manufacturer's description of the underlying health problem is very brief. It states only that approximately 80% of acute strokes are ischaemic in origin. It does not indicate how many individuals a year in England and Wales suffer such a stroke, nor does it describe the implications of acute ischaemic stroke in terms of either short- or long-term health outcomes.

2.2 Critique of manufacturer's overview of current service provision

In section 4.1, the manufacturer's submission claims that, whilst the care of stroke patients originally took the form of general medical and nursing care, patients are increasingly being channelled to care in specialist stroke units, which have been shown to improve patient outcomes. However, this change in practice is not quantified. The submission also claims that CT scanning of the head has become the norm to distinguish haemorrhagic from ischaemic stroke both for management of the acute illness and to guide future interventions for secondary stroke prevention, but no evidence is given to support this.

The submission also claims that patients suffering acute ischaemic stroke will normally have called the emergency services to ensure rapid transit to hospital, but again no evidence is given to support this.

The submission rightly notes that treatment within a 3-hour window will require remarkable collaboration between the patient/family, the emergency services, and hospital services.

3 CRITIQUE OF MANUFACTURER'S DEFINITION OF DECISION PROBLEM

3.1 Population

The relevant patient population is defined as adults with acute ischaemic stroke, without CT evidence of intracranial haemorrhage, who can commence therapy within three hours of symptom onset. The submission identifies the following contraindications to alteplase therapy in adults with acute ischaemic stroke:

- Symptom onset more than three hours prior to initiation of treatment, or time of symptom onset unknown
- Minor neurological deficit or rapidly improving symptoms
- Severe stroke assessed either clinically (eg NIHSS >25) and/or by imaging
- Seizure at stroke onset
- CT evidence of intracranial haemorrhage or symptoms suggestive of subarachnoid haemorrhage
- History of prior stroke and concomitant diabetes
- Prior stroke within the previous 6 months
- Systolic blood pressure >185 or diastolic blood pressure >110 mm Hg
- Heparin within previous 48 hours and elevated aPTT
- Platelet count <100,000/mm^3
- Blood glucose <50 or >400 mg/dl (<2.8 or >22.2 mmol/L)
- Age under 18 or over 80.

No indication is given in this section of the proportion of ischaemic stroke patients who would be excluded by these criteria. However, two independent North American studies summarised in Tables 29 and 30 of the manufacturer's submission found that 93% of patients with acute ischaemic stroke were ineligible for alteplase treatment.

3.2 Intervention

Alteplase is a recombinant human tissue-type plasminogen activator (in other words, an enzyme which causes blood clots to dissolve). It is therefore potentially of value in ischaemic stroke, in which the flow of blood to the brain has been interrupted, commonly by a clot blocking a blood vessel. However, its use in a stroke caused by intracerebral or subarachnoid haemorrhage is potentially disastrous.

Alteplase was originally licensed for use in acute myocardial infarction. Since 30th September 2002, it has also been licensed in the UK for the treatment of acute ischaemic stroke. However, this EU approval was granted on two conditions:

- Entry into the SITS Monitoring Study (SITS-MOST) of data relating to all patients within specified European countries who were treated with alteplase according to the terms of the conditional licensing approval over the subsequent three years at sites which both chose and qualified (by having facilities which were considered appropriate) to participate in the study.[10,11] SITS-MOST formed a cohort within SITS-ISTR, a register which also included data on patients within the specified European countries who were either treated at sites which did not choose or qualify to participate in SITS-MOST or who did not meet the SITS-MOST inclusion or exclusion criteria, as well as on patients treated in other countries.[11] The main aims of the SITS-MOST study were to evaluate the safety and efficacy of alteplase in routine clinical practice as measured by the primary outcome measures of SICH within 36 hours and death within 3 months, and the secondary outcome measure of functional independence (mRS 0-2) at 3 months.[10]

- Performance of a placebo-controlled RCT (ECASS-III) of alteplase given to patients with acute ischaemic stroke 3-4.5 hours after symptom onset.

The SITS-MOST observational cohort study has recently reported,[11] and therefore a decision regarding the definitive EU approval of alteplase for acute ischaemic stroke within a 3-hour window should shortly be issued. However, although ECASS-III was originally scheduled to complete in October 2005,[12] the submission states that it will not complete before 2008. The extension of approval to the time-window of 3 to 4.5 hours will not be considered until the results of the ECASS-III study are available.

3.3 Comparators

The manufacturer's submission does not identify any active comparator for alteplase. This is appropriate because no thrombolytic agent other than alteplase is currently licensed within the

EU for use in acute ischaemic stroke. As it has recently been noted that the most important therapy in acute ischaemic stroke is restoration of the blood supply to the affected area of the brain,[1] other stroke treatment or prevention therapies, which function in different ways, would therefore not be relevant comparators.

3.4 Outcomes

The clinical outcomes identified in the manufacturer's submission are:

- Disability
- Proportion of patients making a good functional recovery by 3-6 months after treatment
- Neurological deficit
- Mental health, including anxiety and depression
- Survival
- Length of hospital stay
- Adverse effects of treatment, including bleeding events
- Health-related quality of life.

The submission does not specify how the first three of these outcomes (disability, good functional recovery, and neurological deficit) are to be measured, or what their implications would be for the affected individuals. The manufacturer's submission notes only that "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."

Both mental health and health-related quality of life are clearly important outcomes. However, they are not subsequently mentioned in the clinical effectiveness section of the manufacturer's submission other than to note that one study (ECASS II) measured quality of life at 90 days using the SF-36; the results of this are not reported.

The major adverse effect of alteplase therapy is the risk of bleeding, and in particular, in the case of stroke patients, the risk of intracranial bleeding. Such bleeding may be either symptomatic or asymptomatic. Symptomatic intracranial bleeding may be defined as bleeding which is either fatal or associated with a deterioration in the patient's neurological function.

The manufacturer's submission only presents data relating to symptomatic intracranial haemorrhage (SICH). There is evidence that alteplase therapy is also associated with an increased risk of asymptomatic ICH. The effect of such asymptomatic haemorrhages on overall outcomes is not clear[13] but, if they do cause any lasting ill effects, these will presumably be captured by the outcome measures related to disability, functional recovery and neurological deficit.

The outcomes in the economic model are independent stroke, dependent stroke and death. The dependent health state is defined as a modified Rankin score (mRS) of 3-5, while the independent health state is defined as a score of 0-2. The ERG's clinical advisors consider these definitions to be appropriate for the required analysis. The odds ratios used in the model for death, dependent stroke and independent stroke are derived from a meta-analysis of alteplase RCTs reported in a Cochrane review by Wardlaw et al.[2] Subjects may also experience a haemorrhage. The probabilities of haemorrhage for standard treatment and alteplase treatment are taken from a meta-analysis of the NINDS, ECASS and ATLANTIS trials.[14]

The health-related quality of life values and costs that have been applied to the above health states are taken from appropriate sources.

3.5 Time frame

Most studies of alteplase have a follow-up period of 3 months. Only one study, the NINDS study,[15] has provided data at later dates (6 and 12 months). This study found that the proportion of patients with a favourable outcome was similar at 3, 6 and 12 months, while the mortality rates increased in parallel in the alteplase and placebo groups (see Table 1). There seems no reason to believe that the other studies would have yielded substantially different results had they also extended follow-up to 12 months.

Table 1: NINDS study: results at different time periods

Time period	Favourable outcome (mRS 0-1)		Mortality	
	Alteplase (n=312)	Placebo (n=312)	Alteplase (n=312)	Placebo (n=312)
3 months[16,4]	43%	27%	17%	21%
6 months[15]	41%	29%	21%	23%
12 months[15]	41%	28%	24%	28%

The manufacturer's health economic model has used a lifetime horizon of 40 years to assess the long-term benefits of alteplase, which is justified.

3.6 Other relevant factors

No other relevant factors were identified.

4 CLINICAL EFFECTIVENESS

4.1 Critique of manufacturer's approach

4.1.1 Description of manufacturer's search strategy and comment on whether the search strategy was appropriate.

The searches undertaken by the manufacturer to identify relevant clinical trials were conducted in September 2006, using search strategies which were noticeably simpler than those used in the Cochrane review.[2] They obviously differed from the latter inasmuch as they were intended only to identify studies of alteplase, not all thrombolytic drugs. However, they also differed in that they were designed to be considerably less sensitive in identifying either randomised controlled trials or studies relating to stroke. Consequently, whilst the manufacturer's Medline search strategy identified the key publication relating to each of the included trials, it did not identify the important reanalysis of the NINDS study,[17] two supplementary analyses which the submission identified as relevant,[18,14] or the Cochrane review[2] on which the submission draws heavily.

The submission also draws on evidence from a number of observational studies. It is not clear how these studies were identified. Supplementary data provided by the manufacturer stated that a systematic search was undertaken for these, but did not provide a relevant search strategy. Section 5.1 of the main submission implies that the same search strategies were used to identify both clinical trials and studies investigating or evaluating service delivery or provision of technology. However, both the Embase and Medline searches contained a term limiting the search to clinical trials, and therefore neither would identify observational studies. It has not been possible, within the time available, for the ERG to conduct supplementary searches to ensure that relevant studies were not missed as a consequence.

The publicly available databases searched by the manufacturer were Medline, Embase, EBM reviews, and the Cochrane database of systematic reviews; the Cochrane Central Register of Controlled Trials does not seem to have been searched. Language restrictions do not appear to have been applied.

4.1.2 Statement of the inclusion/exclusion criteria used in the study selection and comment on whether they were appropriate.

The inclusion/exclusion criteria used in selecting studies of clinical effectiveness are not set out clearly in any one place. In section 9.2.6, the manufacturer's submission states that the inclusion criteria were as follows:

- RCTs of alteplase in acute ischaemic stroke
- Large observational cohort studies of thrombolysis in acute ischaemic stroke
- Evaluation studies of service delivery of thrombolysis in acute ischaemic stroke
- Any UK-based thrombolysis study (by which is presumably meant any UK-based study of thrombolysis for acute ischaemic stroke).

Section 5.1 further specifies that the searches sought to identify:

- RCTs which randomised more than 50 patients
- Reviews, editorials, and "studies investigating/evaluating service delivery/provision of the technology"
- Any study undertaken in the UK in relation to the technology.

The exclusion of RCTs simply because they randomised fewer than 50 patients is an arbitrary criterion, which requires further explanation.

Section 5.2.2 clarifies that studies of alteplase given intra-arterially were excluded, since this is not a licensed form of administration. However, no exclusion criteria were applied to exclude studies which used intravenous alteplase at an unlicensed dose, or outside the licensed time-window.

The inclusion and exclusion criteria for the observational studies are specified in sections 5.2.4 and 5.8. They are summarised in Table 2 below.

Table 2: Observational studies: inclusion and exclusion criteria used in the manufacturer's submission

Inclusion criteria	Exclusion criteria
• Mandated by regulatory authorities following the granting of marketing licences in the relevant countries/regions • Monitored by marketing authorisation holders • Included substantial numbers of patients in the treatment cohorts • Had evidence of competent data collection • Had relatively complete safety observations • Had outcomes which could be compared statistically with the RCT evidence	• Small size (<100 patients) • Add nothing to the conclusions which may be drawn from the larger studies • Are abstracts from conference presentations and, as such, incomplete reports

In section 5.8, the submission also states that the included studies were selected because they provide different messages, and summarises those messages as follows:

- mortality is higher in centres inexperienced in managing acute stroke patients with alteplase (SITS-MOST)
- it is important to avoid protocol violation (STARS, Cleveland)
- favourable results may be achieved with strict adherence to labelling (CASES)
- door to needle times can be reduced (Cologne study)
- telemedicine is feasible in rural areas (TEMPIS)
- the use of alteplase is feasible in the UK (UK study).

No indication is given as to the number of observational studies which otherwise met the inclusion criteria but were excluded solely because they did not provide a new message. The inclusion of such studies would have enabled estimation of the strength of evidence for the messages identified from the included studies.

As is clear from the summary above, the inclusion and exclusion criteria used to identify both clinical trials and observational studies could have been more clearly presented. Moreover, while most appear to be broadly appropriate, some of the exclusion criteria appear inappropriately arbitrary.

4.1.3 Table of identified studies. What studies were included in the submission and what were excluded

The manufacturer's submission identified six relevant RCTs[7,8,5,6,4] (for details, see Table 3). The manufacturer's submission also identified five other relevant analyses of the data which claimed to refine and improve the interpretation and understanding of the data from the original trials. Three of these relate to the NINDS studies,[15,19,18] and one to ATLANTIS A and B;[20] the fifth was a pooled analysis of data from the NINDS, ATLANTIS and ECASS studies.[14]

In addition to the RCT evidence, the manufacturer's submission also includes evidence from observational studies. As noted earlier, there is some lack of clarity as to how the included observational studies were identified.

Details of the observational studies included in the manufacturer's submission are set out in Table 4. The submission does not refer to two further relevant independent community-based studies, details of which are included in Table 5. We have included these additional studies, which were cited by Ingall et al in their reanalysis of the NINDS data,[17] because they were comprehensive studies of the use of alteplase for acute ischaemic stroke within their areas, rather than selective studies which only included individual centres or physicians who volunteered to participate. We recognise that there may be other relevant studies which we have not included because we were unable to undertake systematic searches within the time available.

Table 3: Randomised controlled studies identified in the manufacturer's submission: general information

Trial	Number of patients randomised	Number considered major protocol violation	Median time to treatment	Mean age in years (SD)	Median baseline NIHSS score (SD)	Comment
ATLANTIS A[7]	Alteplase 71 Control 71	No data	Alteplase 4h 36m Control 4h 30 m	Alteplase 67±13 Control 65±12	Not reported. Mean: Alteplase 13±7 Control 13±6	No protocol violations were reported
ATLANTIS B[8]	Alteplase 307 Control 306	Alteplase 16 (5.2%) Control 16 (5.2%)	Alteplase 4h 36m Control 4h 30 m	Alteplase 66±11 Control 65±11	Alteplase 10 Control 10	All reported protocol violations took the form of treatment before 3 hours or after 5 hours.
ECASS I[5]	Alteplase 313 Control 307	Alteplase 66 (21.1%) Control 43 (14.0%)	Mean: Alteplase 4.3h Control 4.4h	Alteplase 65±12 Control 65±11	Alteplase 12 Control 13	66 protocol violations were violations of the CT criteria (mainly extended early infarct signs on the CT scan (n = 52[16])); others included use of iv heparin in the first 24 hours, use of other prohibited concomitant therapy, unavailable for follow-up, and major deviations from the 90±14 day window for primary endpoint assessment. 61% of ineligible patients were randomised to alteplase, an imbalance for which the investigators have no explanation.

Trial	Number of patients randomised	Number considered major protocol violation	Median time to treatment	Mean age in years (SD)	Median baseline NIHSS score (SD)	Comment
ECASS II[6]	Alteplase 409 Control 391	Alteplase 34 (8.3%) Control 38 (9.7%)	No data	Not reported. Median age 68 in both groups	Alteplase 11 Control 11	Most protocol violations were violations of the CT criteria.
NINDS 1[4]	Alteplase 144 Control 147	Alteplase 29 (9.1%) Control 25 (8.0%)[16]	0-90 min stratum: Alteplase 89 min Control 88 min	Alteplase 67±10 Control 67±11	Alteplase 14 Control 14	The most common protocol violation involved the BP criteria.[16]
NINDS 2[4]	Alteplase 168 Control 165		91-180 min stratum: Alteplase 156 min Control 151 min	Alteplase 69±12 Control 66±13	Alteplase 14 Control 15	

Table 4: Observational studies identified in the manufacturer's submission, by date

Study	Country/ region	Study type, date	Number of patients receiving alteplase	Proportion of potentially eligible patients treated	Median baseline NIHSS score	Comments
Cologne[21]	Cologne, Germany (1 stroke centre)	Prospective case series March 1996-Aug 1997	100	41% (100/245) of patients taken to the stroke centre with a final diagnosis of acute ischaemic stroke, but only 5% (100/1950) of the estimated number of patients in all Cologne with that diagnosis over the same period.	12	The study appears to have been comprehensive, including all patients receiving alteplase in Cologne in the study period. Patients given alteplase also received immediate anticoagulation with heparin, and osmodiuretic drugs to prevent brain oedema.
UK[22]	UK (3 centres)	Prospective consecutive case series 1996-2001	120	Approximately 1% of total admissions with presumed stroke.	17	The study appears to have been comprehensive, including all patients receiving alteplase in the 3 centres in the study period.
STARS[23]	USA (57 centres)	Prospective phase IV study Feb 1997-Dec 1998	389	Not known.	13	There is a possibility of selection bias as the study was limited to centres participating in the ATLANTIS B study and further, although all of these were invited to participate, only 57/83 centres agreed. Investigators at each participating centre were asked to try to enrol every patient they treated with iv alteplase for acute stroke.

Study	Country/ region	Study type, date	Number of patients receiving alteplase	Proportion of potentially eligible patients treated	Median baseline NIHSS score	Comments
Cleveland[24]	USA (29 hospitals in and around Cleveland, Ohio)	Retrospective cohort study July 1997-June 1998	70	1.8% (70/3948) of patients with a primary diagnosis of ischaemic stroke (ICD-9-CM codes 434 or 436)	12	The study was comprehensive: participation was not voluntary and included all hospitals in the area except one Veterans Affairs Hospital. However, the investigators note that ICD-9-CM codes 434 and 436 have been shown to be only 85-90% accurate in identifying patients with ischaemic stroke. Moreover, baseline NIHSS scores were only available for 40% of patients treated with alteplase.
CASES[25]	Canada (60 centres)	Prospective consecutive case series 17.2.1999-30.6.2001	1135	Estimated by the investigators to be <2%.	14	There is a possibility of selection bias as centres chose whether to participate in the study. However, case reporting for participating centres was complete and sequential.
SITS-MOST[11]	Europe (259 sites)	Prospective cohort study 25.12.2002-30.4.2006	6483 (of whom 327 (5.0%) from UK)	Not known	12 (IQR 8-17)	There is a strong probability of selection bias: centres chose whether to participate in the study, and participation was further limited to centres whose facilities were considered to be appropriate (eg, having a staff of physicians specialised in neurological care and experienced in the diagnosis and management of acute

Study	Country/ region	Study type, date	Number of patients receiving alteplase	Proportion of potentially eligible patients treated	Median baseline NIHSS score	Comments
						stroke).[10] Moreover, although data were collected on all patients treated with alteplase at participating centres, patients who did not meet prespecified eligibility criteria determined by the conditions of the licensing approval (eg age ≤80, treatment >3 hours after symptom onset) were systematically excluded, but the number of patients excluded in this way was not recorded.[26]
TEMPIS[27]	Eastern Bavaria, Germany (12 regional hospitals, 2 stroke centres)	Prospective cohort study 1.1.2004-31.12.2004	225	225/6610 (3.4%) overall: 115/4727 (2.4%) of patients admitted to regional hospitals and 110/1889 (5.8%) of those admitted to stroke centres.	12 in regional centres, 11 in stroke centres	The study appears to have been comprehensive, including all patients receiving alteplase in Eastern Bavaria in the study period. The study compares the outcomes of patients treated at experienced stroke centres, and those treated at regional hospitals with telemedicine links to the stroke centres.

Table 5: Additional observational studies considered to be relevant

Study	Country/ region	Study type, date	Number of patients receiving alteplase	Proportion of potentially eligible patients treated	Median baseline NIHSS score	Comments
Connecticut [28]	USA (10 acute care hospitals in Connecticut)	Retrospective cohort study 1.5.1996-31.12.1998	63	No data	15	The study was comprehensive: participation was not voluntary, and included all hospitals in the state of Connecticut if they had prescribed alteplase for acute stroke within the study period.
Illinois[29]	USA (20 hospitals in central Illinois)	Retrospective case series June 1996 – Dec 1998	57	No data	15	The study was comprehensive: it included all 20 hospitals in 23 Illinois counties which were linked in the regional Stroke Network centred on the Saint Francis Medical Center.

Of the observational studies, only the TEMPIS study overlapped both temporally and geographically with the SITS-MOST study. However, the same hospitals do not seem to be involved, and there therefore seems to be no evidence of double-counting.

It should be noted that the Cleveland study[24] has been claimed to be the most compelling study of the effectiveness of alteplase for acute stroke because, as well as providing comprehensive results on every stroke patient treated in non-Veterans Association hospitals in the metropolitan Cleveland area over the period of a year, it involved neither sponsorship by the manufacturer nor the involvement of experts who had previously participated in the RCTs.[30] In this study, only 1.8% of 3948 patients hospitalised with acute ischaemic stroke received alteplase; half of these violated the protocols for the alteplase use (see Table 10). This highlights the fact that protocol violations are likely to be more common in ordinary practice than in RCTs, even though a very small proportion of patients receive alteplase therapy.

The manufacturer's initial submission did not contain QUOROM flow diagrams relating to any of the literature searches. Those provided subsequently are clearly incomplete: for example, the QUOROM flow diagram for RCTs deals only with the six potentially relevant RCTs which were identified and screened for retrieval, not with the number of hits produced by running the manufacturer's RCT search strategy (when this was run in Medline alone in November 2006, it produced 190 hits).

The manufacturer's submission notes that no relevant RCTs are due to report in the next 12 months. The ECASS-III trial, noted above as a condition of the licensing of alteplase for acute ischaemic stroke within the EU, is not now expected to report until 2008. The considerably larger, independent, IST-3 study (which is not mentioned in the manufacturer's submission) is not expected to report until 2010 at the earliest. Both of these studies include patients given alteplase after the current licensed window of 0-3 hours from symptom onset (see Table 6).

The manufacturer's submission notes that the SITS-MOST observational cohort study is clinically complete. It has subsequently reported.[11]

Table 6: Ongoing randomised controlled studies of alteplase

Trial	Study type	Dose of alteplase	Setting	Planned number of subjects	Patient age	Time from symptom onset	Primary outcome	Length of follow-up	Sponsor	Expected to report
ECASS-III[12]	Randomised double-blind placebo-controlled trial	0.9 mg/kg (max 90mg)	110 hospitals in 15 European countries	800	18-80	Originally 3-4 hours, later extended to 3-4.5	Modified Rankin scale 0-1 at 90 days	90 days	Boehringer-Ingelheim	2008 (according to manufacturer's submission)
IST-3[31,32]	Randomised open-label, blinded endpoint, controlled trial	0.9 mg/kg (max 90mg)	Up to 300 centres worldwide	6000	≥16	0-6 hours	Indepen-dence (mRS 0-2) and mortality at 6 months	6 months overall, 18 months in some countries	UK MRC, Health Foundation, Stroke Association (UK), Norwegian Research Council, Government of Poland, AFA Insurances (Sweden), Heart Lung Foundation (Sweden), Australian Heart Foundation	2010 or later

4.1.4 Details of any relevant studies that were not included in the submission

We have not been able, within the time available, to undertake full searches to identify all potentially relevant studies not identified by the manufacturer's search strategy. However, we have re-run both the sponsor's search strategy and the Cochrane review's search strategy in Medline on 29th November 2006. We sought to identify any relevant studies published too late for inclusion in the Cochrane review, whose latest searches were undertaken in January 2003, by screening all studies identified by the Cochrane search strategy and published in the years 2002 to 2006. We identified only one additional possibly relevant study, a Chinese study evaluating the efficacy and safety of alteplase, at doses of 0.9 mg/kg and 0.7 mg/kg, compared with no treatment, in Chinese patients with acute cerebral infarction.[33] As it was published in Chinese, we could only read the abstract, and from this it was not clear either whether the study actually was randomised (although it was indexed as a randomised trial in Medline) or whether it was limited to patients treated within 3 hours of symptom onset. The study appeared to find that alteplase was associated with improved outcomes at 90 days, and was not associated with a significant increase in mortality at 30 days.

However, the manufacturer's searches identified a small pilot study for the NINDS trial[9] which met all their inclusion criteria in terms of population, intervention, comparator and study type, and was excluded purely because it did not meet the arbitrary size criterion mentioned in section 4.1.2 above.

The manufacturer's submission also draws on observational studies to assess the generalisability of the RCT evidence. The process by which these studies were identified is not transparent, and therefore could not be evaluated. As noted in section 4.1.3 above, two relevant observational studies were not included. It has not been possible within the time available to determine whether other relevant observational studies have also been excluded.

4.1.5 Description and critique of manufacturer's approach to validity assessment

The manufacturer's approach to validity assessment was somewhat opaque. It would have been easier to assimilate the data if they had been tabulated specifically by CONSORT[34] item, as required by the rubric to section 5.3. Thus, for example, although the submission's Table 1 contains elements of CONSORT items 8-11, it is not immediately apparent from this table that each trial did not provide information relating to each item.

Section 5.3.2 lists study inclusion and exclusion criteria, and provides baseline patient characteristics, or references to these. However, these are again provided separately for each study, again making it more difficult to compare studies than if the details had been tabulated.

The section does not highlight differences between patient groups as requested, although they exist in some studies (for example, in ATLANTIS A the prevalence of diabetes was significantly higher in the placebo arm than in the alteplase arm). The issue of comparability in the NINDS study, in terms of baseline stroke severity, will be discussed further below.

The tabulation of study outcomes (Table 8) in section 5.3.4 of the manufacturer's submission does not identify, as requested, which outcomes were specified in the trial protocols as primary or secondary outcomes. The primary outcomes for each study are therefore listed in Table 7 below. The submission's description of the measures used to investigate those outcomes (the NIHSS scale, Barthel Index, modified Rankin Scale, Glasgow Outcome Scale and Scandinavian Stroke Scale) is perfunctory.

Table 7: Included RCTs: primary outcome measures

Study	**Primary outcome measures**
ATLANTIS A	Clinical improvement defined as a decrease of $\geq$4 points on the NIHSS, or complete resolution of symptoms, from baseline to 24 hours and from baseline to 30 days Volume of cerebral infarct as measured by CT scan at 30 days
ATLANTIS B	Excellent neurological recovery at day 90 (defined as an NIHSS score of 0 or 1)
ECASS I	Differences in the activities of daily living as measured by Barthel Index 90 days after treatment Global clinical impression measured by modified Rankin scale score 90 days after treatment
ECASS II	Favourable outcome (0-1) on the modified Rankin scale 90$\pm$14 days after treatment
NINDS I	Early improvement, defined as complete resolution of the neurological deficit, or improvement of 4 or more points from baseline NIHSS score, 24 hours after stroke onset
NINDS II	Minimal or no neurological deficit at 3 months (a score of 0-1 on the NIHSS scale and mRS, 95 or 100 on the Barthel Index, and 1 on the Glasgow outcome scale)

In section 5.3.5, the manufacturer's submission does not state the primary hypothesis under consideration in the included RCTs as requested, nor does it indicate the power of the various trials together with details of the rationale and assumptions underlying the sample size calculation. However, it states that all the RCTs used intention-to-treat analyses, to which any

per-protocol analyses were secondary, and that few patients were lost to follow-up, although it notes elsewhere (section 5.4) that a substantial number of protocol violations were recorded in some studies. Moreover, while the submission states that sub-group analyses were generally pre-specified, it should be noted that, in the two ATLANTIS studies, randomisation was not stratified by time from symptom onset to treatment, and thus the subgroups of patients treated within 3 hours, and between 3 and 6 hours, do not form true randomised comparisons.

In section 5.3.6, the manufacturer's submission does not include a tabulation to support the critical appraisal of the included studies, making it less easy to compare their quality. Such a tabulation is therefore included as Table 8 below. However, the submission notes the criticism of bias in the NINDS trial caused by an unintentional imbalance in baseline stroke severity favouring alteplase: this came about because randomisation was not stratified by stroke severity.

The manufacturer's submission notes that in all studies, following randomisation, study allocation was concealed by the use of a matching placebo. It implies that this blinding was adequate, although none of the studies are reported as having assessed the success of the blinding process. However, the Cochrane review notes that blinding is not easy in trials of alteplase, for two reasons:

- the biological effect of thrombolytic therapy (prolonged bleeding at venepuncture sites, easy bruising, gingival or conjunctival haemorrhages etc) may be apparent

- alteplase froths when shaken in solution with water or normal saline, and thus normal saline does not form an identical placebo.

It is therefore possible that the physicians who cared for the patients in the acute phase could have guessed their treatment allocation accurately. The Cochrane reviewers therefore stress the importance of outcome assessment by individuals completely blinded to treatment allocation, who had not been involved in administration of the study drug or care of the patient in at least the first few days, and note that it is not clear how completely this was achieved.[2]

None of the studies used central telephone randomisation, and consequently they were unable to stratify randomisation for key baseline variables such as stroke severity.[2] This led to the imbalance in the NINDS study, and in particular in the 91-180 minute stratum, in which 19% of patients in the alteplase group had a mild stroke (defined as baseline NIHSS 0-5), compared with only 4% in the placebo group, while only 18% of patients in the alteplase

group had a severe stroke (defined as baseline NIHSS >20), compared with 28% in the placebo arm[19] (see further Table 8 below). The TOAST study[35] indicates that, by the natural course of the disease, patients with mild stroke have a 75% probability of an excellent outcome, compared with a 10% probability in patients with severe stroke. It has therefore been claimed that the skew in randomisation itself is sufficient to account for the final results of the NINDS trial.[36]

Table 8: Included RCTs: critical appraisal of study quality and generalisability

	ATLANTIS A[7]	ATLANTIS B[8]	ECASS I[5]	ECASS II[6]	NINDS I[4]	NINDS II[4]
What randomisation technique was used?	Blocked randomisation stratified by clinical centre	Blocked randomisation stratified by clinical centre	Not clear	Blocked randomisation stratified by centre for time since symptom onset (0-3 or 3-6 hours)	Permuted-block design with blocks of various sizes, with patients stratified according to clinical centre and time from stroke onset to start of treatment (0-90 or 91-180 minutes)	
How was the allocation sequence concealed until interventions were assigned?	Numbered treatment packs, the code for which was held by the co-ordinating centre.[2]	Numbered treatment packs, the code for which was held by the co-ordinating centre.[2]	Sealed drug prepacks	Sequentially numbered packs. The randomisation schedule was known only to the Clinical Trial Support Unit at Boehringer Ingelheim and to one member of the External Safety Committee. However, in emergencies, investigators had access to sealed opaque envelopes containing treatment allocation.	The Central Coordinating Centre received blind-labelled vials prepared by Genentech, plus a code list for the vial contents, and established a patient ID number which was then attached to the vial. These numbers were randomly ordered and randomly assigned to alteplase or placebo, with blocking by the 9 local clinical centres, not the 40 treatment centres. The 2 time strata were randomised separately. All treatment sites within each clinical centre's administration received an identically labelled supply of blinded vials, and a list indicating the order in which the patient numbers were to be utilised (ID numbers were random, not sequential). As each treatment site had the same list of numbers, when a patient was enrolled at one site, all sites were notified to mark off that number.[16]	

	ATLANTIS A[7]	ATLANTIS B[8]	ECASS I[5]	ECASS II[6]	NINDS I[4]	NINDS II[4]
Was a justification of the sample size provided?	Yes. However, enrolment was stopped prematurely because of concerns about safety in patients receiving alteplase 5-6 hours after symptom onset.	Yes. However, enrolment was stopped prematurely following an interim analysis which indicated that treatment was unlikely to prove beneficial.	Yes	Yes	Yes	Yes
Was follow-up adequate?	3 months	3 months	3 months	3 months	3 months (12-month data also available in the combined NINDS I and II analysis)	12 months
Were outcome assessors blinded to study allocation?	The clinical exams at 30 and 90 days were performed by an individual who was not present during study drug administration and did not see the patient in the first 24 hours. Also, all patients who died and had any type of ICH were reviewed by the blinded independent data	The clinical exams at 30 and 90 days were performed by an individual who was not present during study drug administration and did not see the patient in the first 24 hours. Also, the records all patients who died and had any type of ICH were reviewed by the blinded	Not clear for clinical examinations. All patients who died and had any type of haemorrhagic event on the CT scan were reviewed by the safety committee and the steering committee, who made the final decision about	Follow-up at 90 days was carried out at each local centre by one of the local investigators. Measures were taken to reduce the risk that the examiner would be able to identify the treatment received (eg they did not receive the results of coagulation	Each CT scan was reviewed for evidence of haemorrhage by a neuroradiologist blinded to clinical information. (When reviewing the submitted scans, this neuroradiologist was aware of symptomatic and asymptomatic ICHs reported by the treatment centres, and would confirm or reject the finding.[16]) Outcomes were determined by certified examiners who had neither performed the baseline examination nor been present during the initial treatment. To prevent premature extrapolation of the results of NINDS I to NINDS II,	

	ATLANTIS A[7]	ATLANTIS B[8]	ECASS I[5]	ECASS II[6]	NINDS I[4]	NINDS II[4]
	safety monitoring board.	independent data safety monitoring board.	haemorrhage-related death before unblinding the codes.	tests).	investigators remained unaware of the results of NINDS I until the completion of NINDS II.	
Was the design parallel-group or crossover?	Parallel-group	Parallel-group	Parallel-group	Parallel-group	Parallel-group	
Where was the RCT conducted in the UK?	North America	North America	Europe including the UK	14 European countries (including the UK), Australia, and New Zealand	USA	
Is clinical practice where study was conducted likely to differ from UK practice?	Yes	Yes	Yes in areas other than the UK (ie by far the greater part of the study area).	Yes in areas other than the UK (ie by far the greater part of the study area).	Yes. The manufacturer's submission notes that CT scans were conducted more frequently than expected UK practice.	
How do participants compare with patients likely to receive the intervention in the UK?	>85% were treated outside the 3-hour licensed window.	>90% were treated outside the 3-hour licensed window.	A very substantial number were treated outside the 3-hour licensed window.	80% were treated outside the 3-hour licensed window.	All were treated within the 3-hour licensed window	
What dosage regimen was used? Is it that detailed	Alteplase iv 0.9 mg/kg (max dose 90	Alteplase iv 0.9 mg/kg (max dose 90	Alteplase iv 1.1 mg/kg (max dose	Alteplase iv 0.9 mg/kg (max dose 90	Alteplase iv 0.9 mg/kg (max dose 90 mg)	

	ATLANTIS A[7]	ATLANTIS B[8]	ECASS I[5]	ECASS II[6]	NINDS I[4]	NINDS II[4]
in the Summary of Product Characteristics?	mg) Yes	mg) Yes	100 mg) No	mg) Yes	Yes	
Were the study groups comparable at baseline?	Broadly, but a significantly higher percentage of patients in the placebo group were diabetic.	Broadly, but a significantly higher percentage of patients in the alteplase group were diabetic.	Said by the investigators to be no major differences. However, the placebo group had a lower proportion of women, and a higher proportion of people on aspirin therapy, people with hypertension, previous stroke, previous TIA, atrial fibrillation and diabetes. A majority (66/109) of the patients considered major protocol violations were in the alteplase group, thus favouring the placebo group.	Said to be so by the investigators. However, the placebo group had a higher proportion of women, people on aspirin therapy, people receiving subcutaneous heparin, people with atrial fibrillation, but fewer people with previous MI.	Said by the investigators to be well matched in all respects except weight; there also seem to be discrepancies in terms of aspirin therapy and previous TIA. The FDA also draws attention to the fact that patients in the alteplase group have slightly less severe strokes than those in the placebo group[16]	Said by the investigators to be well matched in all respects except aspirin use; however, there also seems to be as much of a weight discrepancy as in NINDS I, where the investigators comment on it. The FDA also draws attention to a small but statistically significant difference in age, the alteplase group being older; they are also lighter and have slightly less severe strokes.[16]
					The FDA notes that, in both NINDS I and II, the excess of patients with the mildest strokes (baseline NIHSS 2-6) in the alteplase group has the potential to bias the	

	ATLANTIS A[7]	ATLANTIS B[8]	ECASS I[5]	ECASS II[6]	NINDS I[4]	NINDS II[4]
					study, especially for dichotomised endpoints where such patients need only improve slightly to meet the criteria for success.[16] The combined NINDS I and II reanalysis identified the following statistically significant imbalances: patients randomised to placebo were slightly younger, weighed slightly more, and were less likely to be on daily aspirin. The median baseline NIHSS values of the two groups were not significantly different (15 vs 14, p=0.10), but when patients were categorised as NIHSS 0-5, 6-10, 1-15, 16-20 and >20, a significant imbalance was detected both overall (p=0.005) and in the 91-180 minute stratum (p=0.001), though not in the 0-90 minute stratum. The greatest discrepancy lies in the proportion of patients with NIHSS score 0-5, of whom 72% were in the alteplase group, and only 28% in the placebo group (in the 91-180 min stratum, 81% were in the alteplase group and 19% in the placebo group).[17]	
Were the statistical analyses used appropriate?	Yes	Yes	Yes	Yes	Yes	Yes
Was an ITT analysis	Yes, using "last observation carried	Yes, using "last observation carried	Yes. The 10 patients from the alteplase	Yes. For missing values, the last	Yes. Patients who were not assessed	Yes. Patients who died before the 3-

	ATLANTIS A[7]	ATLANTIS B[8]	ECASS I[5]	ECASS II[6]	NINDS I[4]	NINDS II[4]
undertaken?	forward" method, with death as the worst outcome score on all measures.	forward" method, with death as the worst outcome score on all measures.	group who were not followed up were assigned the worst possible score for each outcome event, and the 4 from the placebo group were assigned the best possible score.	observation was carried forward. For the mRS and the BI, a worst-case imputation (mRS=5, BI=0) was made for missing values at day 90.	by NIHSS at 24 hours were considered to have had no improvement.	month assessment were given the worst possible score for all outcomes. For surviving patients with missing data, if no outcome data were available at 3 months, data from the measurement closest in time, but at least 7 days after randomisation, were used; otherwise, the worst possible score was assigned.
Were there any confounding factors which might attenuate interpretation of the results of the RCTs?	<15% of patients were treated within 3 hours. Thus, the overall results essentially apply to patients treated outside the licensed 3-hour window.	<10% of patients were treated within 3 hours. Thus, the overall results essentially apply to patients treated outside the licensed 3-hour window.	An unlicensed dose of alteplase was used. Also, as mean time to treatment was 4.4 hours, the overall results essentially apply to patients treated outside the licensed 3-hour window.	<20% of patients were treated within 3 hours. Thus, the overall results essentially apply to patients treated outside the licensed 3-hour window.	The imbalance in baseline stroke severity between the alteplase and placebo groups disadvantages the placebo group.	

4.1.6 Description and critique of manufacturer's outcome selection

In section 5.4, the manufacturer's submission identified the most relevant clinical outcome as an NIHSS score of 0-1, indicating an excellent outcome, or an mRS score of 0-1, indicating minimal or no disability, or 0-2, indicating functional independence. Other researchers have suggested that an mRS score of 0-2 is the most relevant measure of efficacy.[10] Arguably, however, survival with functional independence is most accurately and completely assessed by measuring its opposite, namely the composite endpoint of death and dependency, defined as an mRS score of 3-6, the outcome measure used by the Cochrane review.[2]

4.1.7 Describe and critique the statistical approach used

The manufacturer did not undertake independent meta-analyses. Instead, the submission refers to those undertaken for the Cochrane review (calculated as odds ratios using the Peto fixed-effects method),[2] and the pooled analysis of the ATLANTIS A and B, ECASS II, and NINDS 1 and 2 trials[14] (which again uses the odds ratio). Consequently, it does not present relative and absolute risks, and tabulations or displays of the individual and combined results, as requested.

Moreover, the use of the odds ratio in this context is not wholly appropriate, for two reasons. First, the Cochrane Handbook (sections 8.2.1.1, 8.2.1.3) notes that patients and health professionals are more familiar with the concept of risk than with that of odds, and can interpret it more easily. Secondly, the Handbook also notes that, although the difference between odds and risk is small when the event is rare, it is large when events are common. It further notes (section 8.6.3.2) that Peto's method, which can only be used to pool odds ratios, "works well when treatment effects are small (odds ratios are close to one), events are not particularly common and the trials have similar numbers in experimental and control groups. In other situations it has been shown to give biased answers." It therefore does not recommend Peto's method as a default approach for meta-analysis.[37] As the Cochrane review[2] provides no justification of its choice of method, the ERG suggests that it would have been more appropriate to use relative risk in this instance, both because the events being measured are not uncommon, and because it is important that the results are communicated without ambiguity.

Furthermore, the submission does not present the results of the Cochrane meta-analyses in full, but only quotes their overall findings (which relate to all studies of intravenous alteplase regardless of whether they used the current licensed dose within the 3-hour time window) that:

- alteplase was associated with an overall net benefit, in terms of reduction of disability in the survivors despite a significant excess of SICH and of deaths within the first 7-10 days

- 55 of every 1000 patients given alteplase within 6 hours of stroke onset avoided death or dependency.[2]

It seems appropriate that the meta-analyses which support the manufacturer's submission should be limited to data relating to alteplase given within the conditions of its licence: ie at the current licensed dose of 0.9 mg/kg, within 3 hours of symptom onset. ECASS I should therefore be excluded because it used an unlicensed dose of alteplase, and arguably the ATLANTIS studies should also be excluded because they did not stratify randomisation by time to treatment, and therefore the subgroups of patients treated within 3 hours do not form true randomised comparisons. The meta-analyses would then include only the NINDS studies and the small study by Haley et al, both of which included only patients who could be treated within 3 hours, and the 0-3 hour subgroup of the ECASS II study, in which randomisation was stratified by time to treatment.

4.1.8 Summary statement

The manufacturer's submission appears to contain all the major Western randomised placebo-controlled studies of alteplase. It excludes the small study by Haley et al[9] on the basis of an arbitrary size criterion. However, because this study is so small, its exclusion is likely to have minimal effect on the results of any meta-analyses. As noted above, the submission also excludes a potentially relevant Chinese study.[33] It has not been possible within the time available to ascertain the effect of excluding this study.

The submission draws on meta-analyses which include the ECASS I study. This seems inappropriate in this context as this study uses an unlicensed dose of alteplase. Arguably, the inclusion of data from the ATLANTIS A and B studies relating to patients treated with alteplase within 3 hours of symptom onset is also inappropriate because randomisation in these trials was not stratified by time to treatment, and therefore any comparisons between the alteplase and placebo groups in this sub-group are not true randomised comparisons. However, the effect on any estimate of effectiveness of excluding these subgroups would be small as the vast majority of subjects in the two ATLANTIS studies (92% overall) were treated outside the licensed 3-hour window.

Whilst emphasising that alteplase is not licensed for use beyond 3 hours after symptom onset, the manufacturer's submission also discusses two studies which used MRI scanning to

identify suitable patients for treatment between 3-6 hours after symptom onset.[38,39] The ERG report does not discuss these studies because they do not deal with a licensed use of alteplase.

The submission also draws on observational studies to assess the generalisability of the RCT evidence. The process by which these studies were identified is not transparent. Some relevant studies are known to have been excluded, and it is possible that others may also have been.

4.2 Summary of submitted evidence

4.2.1 Summary of results

In the manufacturer's submission, it is difficult to compare the results of the included studies because these were not tabulated as requested. Table 9 below therefore presents such a tabulation. In some cases, data which were not available in the main study publication have been drawn from the Cochrane review. These data were obtained by the Cochrane reviewers from the principal investigators of the relevant trials.[2] For each study, we have calculated the relative risk and, for comparison with the Cochrane review on which the manufacturer's submission draws, the Peto odds ratio, using the Cochrane Collaboration's Review Manager software.[40] Because NINDS I and II were identical except for their choice of primary outcome measure,[4] and because many of the related publications treated the two parts as a single study stratified by phase, Table 9 presents the results as deriving from a single study.

Table 9: Randomised controlled trials of intravenous alteplase in acute ischaemic stroke: summary of key results

Study **Time from symptom onset to treatment (h)**	**Outcomes**	**Intervention group**	**Control group**	**Peto odds ratio** **(95% CI)**	**Relative risk (random effects model)** **(95% CI)**	**Absolute risk difference (intervention vs control group)**
ATLANTIS A 0-6	All-cause mortality at 3 months	16/71 (22.5%)	5/71 (7.0%)	3.39 (1.35-8.53)	3.20 (1.24-8.26)	+15.5%
	SICH within 7-10 days	8/71 (11.3%)	0	8.20 (1.98-33.99)	17.00 (1.00-289.05)	+11.3%
	Death or dependency (mRS 2-5) at 3 months[2]	64/71 (90.1%)	56/71 (78.9%)	2.35 (0.95-5.82)	1.14 (0.99-1.32)	+11.2%
ATLANTIS B 3-6 (later narrowed to 3-5)	All-cause mortality at 3 months	33/307 (10.7%)	21/306 (6.9%)	1.62 (0.93-2.83)	1.57 (0.93-2.64)	+3.8%
	SICH within 7-10 days[2]	21/307 (6.8%)	4/306 (1.3%)	4.10 (1.84-9.13)	5.23 (1.82-15.07)	+5.5%
	Death or dependency at 3 months[2]	141/307 (45.9%)	135/306 (44.1%)	1.08 (0.78-1.48)	1.04 (0.87-1.24)	+1.8%
ECASS I 0-6	All-cause mortality at 3 months	69/313 (22.0%)	48/307 (15.6%)	1.52 (1.02-2.27)	1.41 (1.01-1.97)	+6.4%
	SICH within 7-10 days[2]	62/313 (19.8%)	20/307 (6.5%)	3.18 (2.00-5.06)	3.04 (1.88-4.91)	+13.3%
	Death or dependency at 3 months	171/313 (54.6%)	185/307 (60.3%)	0.79 (0.58-1.09)	0.91 (0.79-1.04)	-5.7%

Study Time from symptom onset to treatment (h)	Outcomes	Intervention group	Control group	Peto odds ratio (95% CI)	Relative risk (random effects model) (95% CI)	Absolute risk difference (intervention vs control group)
ECASS II 0-6	All-cause mortality at 3 months	43/409 (10.5%)	42/391 (10.7%)	0.98 (0.62-1.53)	0.98 (0.65-1.64)	-0.2%
	SICH within 7-10 days[2]	36/409 (8.8%)	13/391 (3.4%)	2.59 (1.45-4.61)	2.65 (1.43-4.92)	+5.4%
	Death or dependency at 3 months	187/409 (45.7%)	211/391 (54.0%)	0.72 (0.55-0.95)	0.85 (0.74-0.97)	-8.3%
NINDS I and II 0-3	All-cause mortality at 3 months	54/312 (17.3%)	64/312 (20.5%)	0.81 (0.54-1.21)	0.84 (0.61-1.17)	-3.2%
	All-cause mortality at 12 months[15]	76/312 (24.4%)	87/312 (27.9%)	0.83 (0.58-1.19)	0.87 (0.67-1.14)	-3.5%
	SICH within 7-10 days[2]	20/312 (6.4%)	2/312 (0.6%)	5.44 (2.32-12.73)	10.00 (2.36-42.42)	+5.8%
	SICH at 3 months[15]	23/312 (7.4%)	4/312 (1.3%)	4.34 (2.01-9.39)	5.75 (2.01-16.43)	+6.1%
	SICH at 12 months[15]	25/312 (8.0%)	5/312 (1.6%)	4.05 (1.95-8.43)	5.00 (1.94-12.89)	+6.4%
	Death or dependency at 3 months	155/312 (49.7%)	192/312 (61.5%)	0.62 (0.45-0.85)	0.81 (0.70-0.93)	-11.8%

We have also produced Forest plots to display the relative risks for the major outcomes (all-cause mortality at 3 months, SICH within 7-10 days, and death or dependency at 3 months) for all studies using the licensed dose of alteplase within 6 hours of symptom onset (Figures 1-3).

Figure 1: Alteplase within 6 hours of symptom onset: all-cause mortality at 3 months

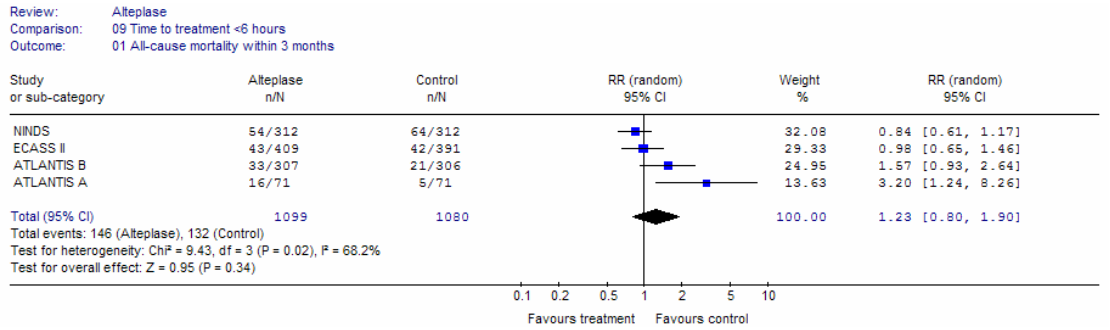


Figure 2: Alteplase within 6 hours of symptom onset: SICH within 7-10 days

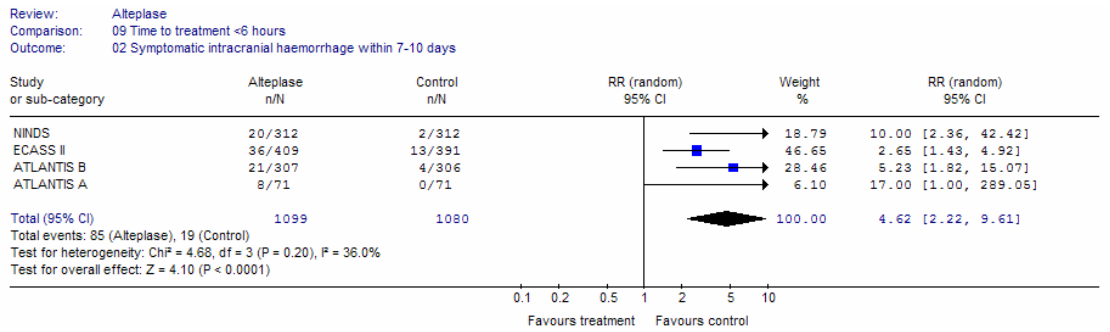
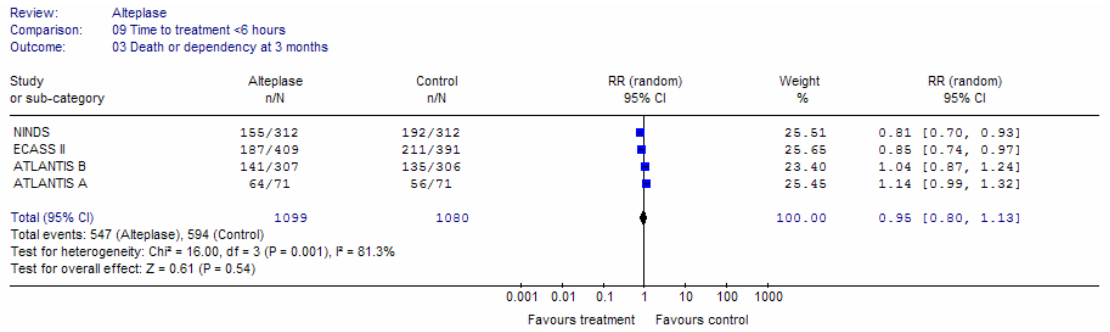


Figure 3: Alteplase within 6 hours of symptom onset: death or dependency at 3 months



It should be noted that full data were not available for ATLANTIS A, and therefore for this study the figures for death or dependency at 3 months include patients with an mRS score of 2.[2] This result is therefore not fully comparable with the results of the other studies, where the figures for death or dependency include only patients with an mRS score $\geq$3.

The NINDS study is the only study to present outcome data at 6 and 12 months.[15] As it presents the mRS data aggregated by scores of 0-1, 2-3, and 4-5, the rates of death or dependency at these time points cannot be calculated. However, as noted in section 3.5 above, the benefit of alteplase therapy in terms of both mortality and a favourable outcome (mRS 0-1) which was seen at 3 months appears to be sustained at 6 and 12 months.

As noted earlier, in addition to the RCT evidence, the manufacturer's submission also includes evidence from observational studies. The results of these studies are summarised in Table 10. It is notable that two comprehensive independent community-based studies, the Cleveland[24] and Connecticut[28] studies, found major protocol violations to be very common in the administration of alteplase, affecting 67% of patients receiving alteplase in Connecticut and 50% in the Cleveland area. While some of these protocol violations were intentional, most seem to have been accidental.[28] The Connecticut study, the study with both the highest rate of major protocol violations and the highest mortality rate, found that patients with major protocol violations were substantially less likely to be discharged home without visiting nurse assistance than those without major protocol violations (2% vs 24%),[28] suggesting an association between protocol violations and worse outcomes. However, the Cleveland study reported a high rate of both (undefined) SICH and protocol violations, but did not find any statistically significant association between these factors.[24]

Table 10: Observational studies (by date): results

Study	Median baseline NIHSS score	Mean age	Median time to treatment from symptom onset (range)	Mortality	Death or disability (mRS 3-6)	Good functional outcome (mRS 0-1)	Symptomatic intracranial haemorrhage	Patients with at least 1 major protocol violation	Comments
Cologne[21]	12	63 (SD 11)	Mean time 2 hours 4 minutes	12/100 (12%) at 90 days	No data	40/100 (40%) at 90 days	5/100 (5%)	2/100 (2%)	Patients given alteplase also received immediate anticoagulation with heparin, and osmodiuretic drugs to prevent brain oedema.
Connecticut[28]	15	71 (SD 12)	No data	In-hospital mortality (days 0-36) 16/63 (25%)	No data	No data	4/63 (6%)	42/63 (67%)	The most common major protocol deviations were overdosing with alteplase (n=22), treatment >3 hours from symptom onset (n=14), known bleeding diathesis (n=6), evidence of active internal bleeding (n=5). Haemorrhagic complications and mortality were higher in patients treated despite protocol deviations.
Illinois[29]	15	71.6	Mean time 2 hours 28 minutes	5/57 (8.8%)	No data	47% at discharge from hospital	3/57 (5.3%)	5/57 (8.8%)	All protocol deviations were treatment >3 hours from symptom onset. Of the 35 patients treated at

Study	Median baseline NIHSS score	Mean age	Median time to treatment from symptom onset (range)	Mortality	Death or disability (mRS 3-6)	Good functional outcome (mRS 0-1)	Symptomatic intracranial haemorrhage	Patients with at least 1 major protocol violation	Comments
									community hospitals, 20 were treated at hospitals without on-site neurological expertise. This was generally done after telephone consultation with the Stroke Network neurologist, and after initiation of alteplase the patient was helicoptered to the specialist centre.
UK[22]	17	69 (range 22-93)	Mean time 2 hours 19 minutes	25/120 (21%) at 3 months	No data	37/119 (31%) at 3 months	6/116 (5%) at 3 months	11/120 (9%)	Protocol violations mainly involved treatment of patients with ischaemic change involving >1/3 of middle cerebral artery territory at baseline, or time to treatment >3 hours.
STARS[23]	13	69 (range 28-100)	2 hours 44 minutes	51/389 (13%) at 30 days	217/382 (57%) at 30 days	132/382 (35%) at 30 days	13/389 (3.3%) within 3 days of treatment	127/389 (32.6%)	90-day outcomes not collected. The most common protocol violations were time to treatment >180 minutes, and treatment with anticoagulants <24 hours.

Study	Median baseline NIHSS score	Mean age	Median time to treatment from symptom onset (range)	Mortality	Death or disability (mRS 3-6)	Good functional outcome (mRS 0-1)	Symptomatic intracranial haemorrhage	Patients with at least 1 major protocol violation	Comments
Cleveland[24]	12	68.8 (SD 12.5)	No data	In-hospital mortality 15.7%	No data	No data	11/70 (15.7%, 95% CI 8.1-26.4%)	35/70 (50%, 95% CI 37.8-62.2%)	Protocol violations were: use of anticoagulants or antiplatelet agents <24 hours (n=26); treatment >5 minutes outside the 3-hour window (n=9).
CASES[25]	14	Median 73 (IQR 63-80)	2 hours 35 minutes	22.3% at 90 days (95% CI 20.0-25.0%)	No data	31.8% at 90 days	52/1135 (4.6%, 95% CI 3.4-6.0%)	154/1135 (13.6%)	Protocol violations were mainly time to treatment >180 minutes (n=132).
SITS-MOST[11]	12 (IQR 8-17)	Median 68 (IQR 59-75)	2 hours 20 minutes (IQR 115-165 min)	701/6218 (11.3%, 95% CI 10.5-12.1%) at 3 months	45% at 3 months	39% at 3 months	468/6438 (7.3%, 95% CI 6.7-7.9%) using the definition used in the NINDS trial	None: any such patients were systematically excluded	Participation was limited to volunteer centres with appropriate facilities, and to patients treated within 3 hours.[10]
TEMPIS[27]	12 in regional centres, 11 in stroke	70 (SD 11)	2 hours 15 minutes in regional hospitals (65-210 minutes); 2	5/225 (2.2%) overall at 7 days; 4/115 (3.5%, 95% CI 1.0-8.7%) in regional	No data	No data	5.3% overall 9/115 (7.8%, 95% CI 3.4-14.3%) in regional	No data	Using the same definitions as other studies, the rates of SICH would be 6.1% for the regional hospitals and 1.8% for the stroke centres.

Study	Median baseline NIHSS score	Mean age	Median time to treatment from symptom onset (range)	Mortality	Death or disability (mRS 3-6)	Good functional outcome (mRS 0-1)	Symptomatic intracranial haemorrhage	Patients with at least 1 major protocol violation	Comments
	centres		hours 15 minutes in stroke centres (15-220 minutes)	hospitals, 1/110 (0.9%, 0.0-5.0%) in stroke centres In-hospital mortality: 9/225 (4%) overall; 4/115 (3.5%, 95% CI 1.0-8.7%) in regional hospitals, 5/110 (4.5%, 1.5-10.3%) in stroke centres			hospitals, 3/110 (2.7%, 0.6-7.8%) in stroke centres (p=0.14)		

To facilitate comparison, selected results of the RCTs and observational studies are presented in Table 11 below. As may be seen, the RCTs show no clear relationship between median baseline NIHSS score and clinical outcomes in patients receiving alteplase, whereas the observational studies hint at the possibility of such a relationship.

Table 11: Patients receiving alteplase: RCTs and observational studies, by study type and median baseline NIHSS score

	Date of study	Median baseline NIHSS score	Median time to treatment	Mean age	Mortality at 3 months	Death or dependency (mRS 3-6) at 3 months	Good functional outcome (mRS 0-1) at 3 months
RCTs							
ATLANTIS B	Dec 1993 – July 1998	10	4h 36m	66	10.7%	45.9%	41.7%
ATLANTIS A	Aug 1991 - Oct 1993	11	4h 36m	67	22.5%	90.1%	No data
ECASS II	Oct 1996 - Jan 1998	11	Not reported	Not reported Median 68	10.5%	45.7%	40.3%
ECASS I	Late 1992 - early 1994	12	Not reported Mean 4.3h	65	22.0%	54.6%	35%[16]
NINDS	Jan 1991 – Oct 1994	14	0-90 min stratum 89 min 91-180 min stratum 156 min	68	17.3%	49.7%	42.6%[16]
Selective observational studies							
SITS-MOST[11]	Jan 2003-Nov 2005	12	Not reported Mean 2h 16 min	Not reported Median 68	11.3%	45%	39%

	Date of study	Median baseline NIHSS score	Median time to treatment	Mean age	Mortality at 3 months	Death or dependency (mRS 3-6) at 3 months	Good functional outcome (mRS 0-1) at 3 months
STARS[23]	Feb 1997-Dec 1998	13	2 hours 44 minutes	69	No data 13% at 30 days	No data 57% at 30 days	35%
CASES[25]	17.2.1999-30.6.2001	14	2 hours 35 minutes	Not reported Median 73	22.3%	No data	31.8%
Comprehensive observational studies							
Cologne[21]	March 1996- Aug 1997	12	Mean time 2 hours 4 minutes	63	12%	No data	40%
Cleveland[24]	July 1997-June 1998	12	No data	69	No data In-hospital mortality 15.7%	No data	No data
TEMPIS[27]	1.1.2004-31.12.2004	12 in regional centres, 11 in stroke centres	2 hours 15 minutes	70	No data In-hospital mortality 4% overall (3.5% in regional hospitals, 4.5% in stroke centres)	No data	No data
Connecticut[28]	1.5.1996-31.12.1998	15	No data	71	No data In-hospital mortality (days 0-36) 25%	No data	No data
Illinois[29]	June 1996 – Dec 1998	15	Mean time 2 hours 28 minutes	72	8.8%	No data	47% at discharge from hospital
UK[22]	1996-2001	17		69	21%	No data	31%

It is well recognised that, for a number of reasons, RCTs whose main focus is the efficacy of the study intervention have limited ability to assess drug toxicity. They therefore need to be supplemented by other types of study, including post-marketing surveillance studies, which can follow up larger numbers of patients for longer periods of time, and which generally collect data relating to the target population treated in normal clinical practice rather than to highly selected populations treated under specialised circumstances.

As noted in the manufacturer's submission (section 5.7), the principal adverse effect associated with the use of alteplase for acute ischaemic stroke is intracranial haemorrhage. This may be severe, and even fatal. Haemorrhage in other organ systems is said to be rare in stroke patients. Anaphylactic reactions are rare and usually mild, but can occasionally be life-threatening. In relation to alteplase, the CASES observational study, which was almost twice the size of the NINDS study, was able to identify a significant risk of angioedema associated with alteplase therapy which had not been identified in any of the RCTs. Such angioedema occurred in 15 out of 1135 patients (1.3%, 95% CI 0.7-2.2%).[25]

It is difficult to compare rates of SICH across studies, as they do not all use the same definition. Moreover, the Cochrane reviewers note some concerns regarding the diagnosis of SICH within the RCTs, suggesting that:

- they may underestimate rates of fatal SICH because some patients who died did not receive a CT scan or post mortem examination

- they may overestimate non-fatal SICH because, when CT scans were carried out, the investigators may have been too ready to identify ICH as the cause of neurological deterioration, even when the volume of blood was small, because of the known association between alteplase and ICH.[2]

The submission does not present a clear synthesis of the RCT data for SICH (and indeed this is not straightforward, given that, as noted above, the studies do not all use the same definition of SICH). However, it quotes a rate of 8.6% (95% CI 6.1-11.1) from the Cochrane review for all patients treated with alteplase within 6 hours. We have failed to identify this rate within the Cochrane review, and our attempts to calculate a rate from the relevant studies included in its Analysis 01.03 have yielded a figure of 10.4%, or 7.7% excluding ECASS I which used an unlicensed dose of alteplase; the rate for all patients treated with the licensed dose within 3 hours (see Figure 5) is 6.7%. The submission adds that, using the definition used in the NINDS study (any haemorrhage plus an NIHSS score deterioration of $\geq$4 points), the SITS-MOST 6th report gives a rate of 5.2% (229/4381, 95% CI 4.6%-5.9%) for patients

treated in accordance with the licensed application. More recently, SITS-MOST has reported a higher SICH rate of 7.3% (468/6438, 95% CI 6.7-7.9%) using the NINDS definition,[11] compared with a rate of 6.2% in the NINDS study itself (see Table 9).

The SITS-MOST safety registry, the largest observational study, reports rates of SICH comparable with those seen in the RCTs. However, this comparison is inevitably biased: the patients included in the register received treatment at least 5, and generally 10, years later than those included in the trials, and may also have differed from the trial populations in other factors. Any comparisons must therefore be treated with caution, as there is no way of adjusting for case mix, or for changes in treatment over time (for example, an increase in the proportion of patients taking antiplatelet therapy, or refinement of the diagnostic tools used to select patients for alteplase therapy).[41] The possible importance of changes over even a relatively short period of time is indicated by the ECASS I and II studies: although both had similar inclusion criteria, the outcomes of patients given placebo were much better in ECASS II than in ECASS I (for example, in ECASS I 15.8% of patients in the placebo arm were dead by end of follow-up,[41] compared with 10.7% in ECASS II).[6]

4.2.2 Critique of submitted evidence syntheses

As noted in section 4.1.7 above, the manufacturer's submission relies on the meta-analyses published in a recent Cochrane review of thrombolysis for acute ischaemic stroke[2] and in a pooled analysis of data from the ATLANTIS, ECASS and NINDS studies.[14]

The outcomes measured in the Cochrane review were:

- All-cause mortality within 7-10 days
- All-cause mortality during follow-up
- Fatal ICH within 7-10 days
- Symptomatic (including fatal) ICH within 7-10 days
- Death or dependency at end of follow-up (3 months in the case of the alteplase studies).[2]

However, the review does not present data on all-cause mortality within 7-10 days or fatal ICH within 7-10 days specifically for patients treated with alteplase within 3 hours of symptom onset.

The manufacturer's submission presents some, but by no means all, of the results calculated in the Cochrane review. Specifically, the submission notes the Cochrane review's finding that alteplase, administered within 6 hours of stroke onset, was associated with a reduction in death or dependency at end of follow-up equivalent to 55 fewer patients per 1000 being dead or dependent, but also that there was significant heterogeneity among trials. It does not present the results for patients treated within 3 hours of symptom onset in terms of numbers needed to treat, which are not reported in the Cochrane review.[2]

The manufacturer's submission neither presents in full the results of the Cochrane meta-analyses, nor provides, as requested, the results of such meta-analyses in the form of relative and absolute risk reductions using both the fixed and random effects models. These meta-analyses have therefore been calculated as relative risks using a statistical package (Review Manager[40]) which incorporates a weighting method to account for the different trial sizes. They are presented in Table 12 below together with the absolute risk reductions and numbers needed to treat, which have been calculated using GraphPad.[42] Data are presented first for all patients in whom alteplase was used within its licensed applications (ie at the licensed dose and within the 3-hour window), and then for a sensitivity analysis excluding the ATLANTIS A and B trials in which randomisation was not stratified by time to treatment. Forest plots for all patients treated within 3 hours are presented in Figures 4-6, and those for all patients randomised to treatment within 3 hours in Figures 7-9.

Table 12: Patients treated within 3 hours of stroke onset: key meta-analyses

Outcomes	**Intervention group**	**Control group**	**Relative risk (random effects model) (95% CI)**	**Relative risk (fixed effects model) (95% CI)**	Change in absolute risk (95% CI)	**Number needed to treat to benefit (95% CI)**	**Number needed to treat to harm (95% CI)**
All patients treated within 3 hours							
All-cause mortality at 3 months	69/416 (16.59%)	72/427 (16.86%)	1.15 (0.62-2.16)	0.97 (0.72-1.31)	-0.28% (-4.76 to +5.31%)	364*	Not applicable
SICH within 7-10 days	28/416 (6.73%)	5/427 (1.17%)	4.24 (1.52-11.83)	5.03 (2.12-11.95)	+5.56% (+2.94 to +8.17%)	Not applicable	18 (12-34)
Death or dependency at 3 months	204/416 (49.04%)	255/427 (59.72%)	0.82 (0.72-0.93)	0.81 (0.72-0.92)	-10.68% (-17.37% to -3.99)	10 (6-25)	Not applicable
All patients randomised to treatment within 3 hours (ie excluding ATLANTIS A and B)							
All-cause mortality at 3 months	65/393 (16.54%)	70/389 (17.99%)	1.05 (0.55-2.03)	0.92 (0.68-1.25)	-1.46% (-3.84 to +6.75%)	69*	Not applicable
SICH within 7-10 days	25/393 (6.36%)	5/389 (1.29%)	3.94 (0.61-25.47)	4.90 (1.90-12.61)	+5.08% (+2.42 to +7.74%)	Not applicable	20 (13-41)

Outcomes	**Intervention group**	**Control group**	**Relative risk (random effects model) (95% CI)**	**Relative risk (fixed effects model) (95% CI)**	Change in absolute risk (95% CI)	**Number needed to treat to benefit (95% CI)**	**Number needed to treat to harm (95% CI)**
Death or dependency at 3 months	194/393 (49.36%)	236/389 (60.67%)	0.81 (0.72-0.92)	0.81 (0.72-0.93)	-11.30% (-18.23 to -4.38%)	9 (6-23)	Not applicable

*CIs not calculated because the 95% CI for the absolute risk reduction extends from a negative number (indicating that treatment may be harmful) to a positive number (indicating that treatment may be beneficial)

Figure 4: All patients treated within 3 hours: all-cause mortality at 3 months

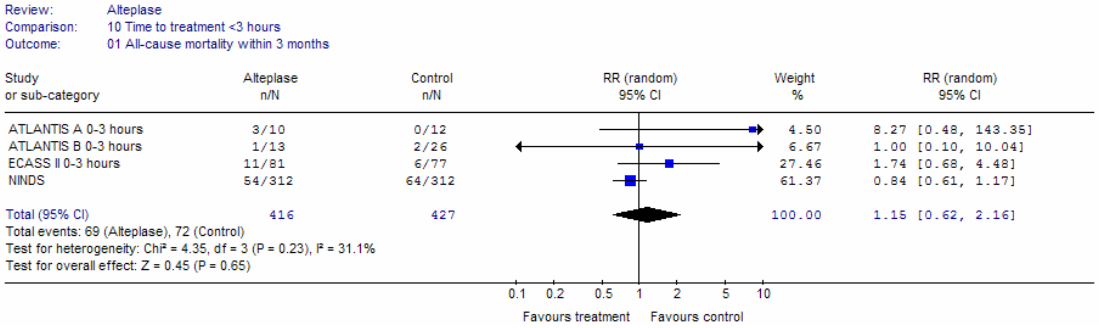


Figure 5: All patients treated within 3 hours: symptomatic intracranial haemorrhage within 7-10 days

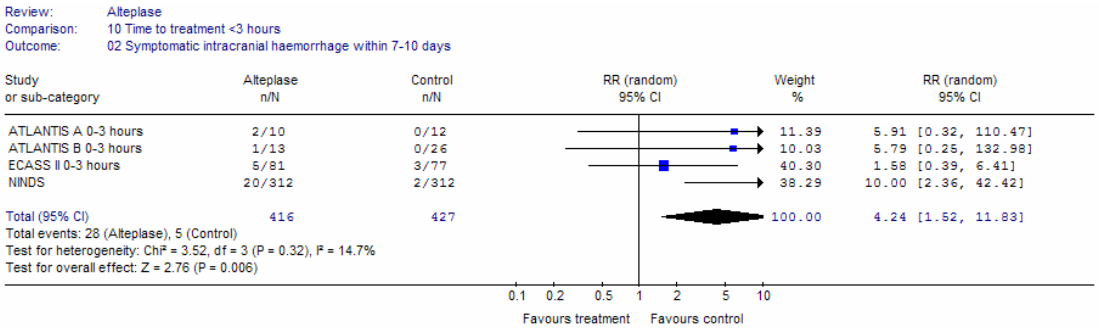


Figure 6: All patients treated within 3 hours: death or dependency at 3 months

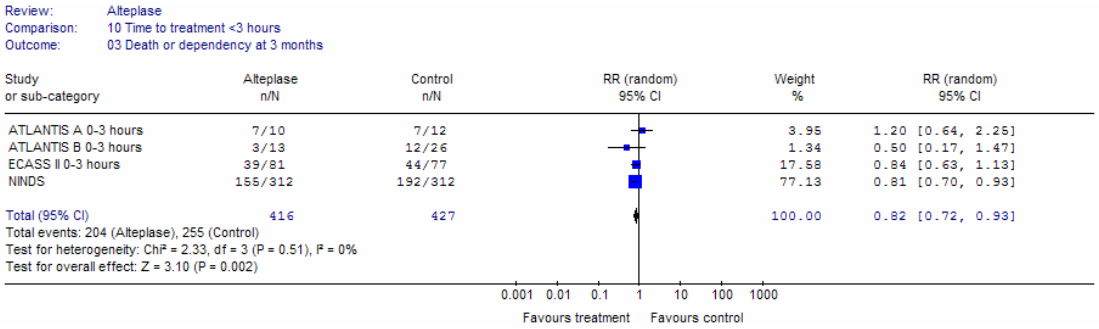


Figure 7: All patients randomised to treatment within 3 hours: all-cause mortality at 3 months

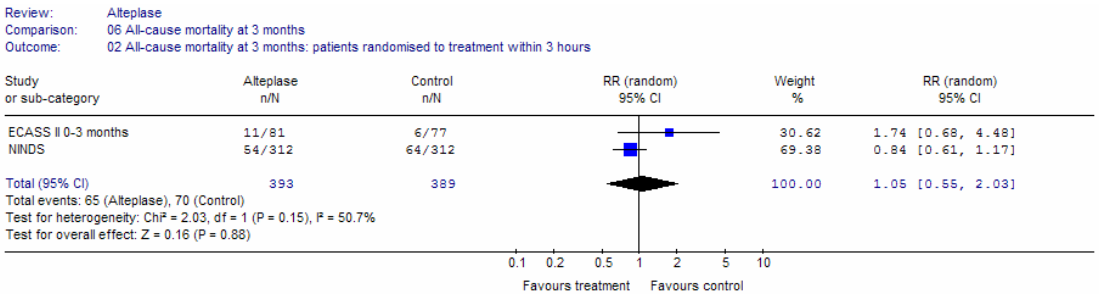


Figure 8: All patients randomised to treatment within 3 hours: symptomatic intracranial haemorrhage within 7-10 days

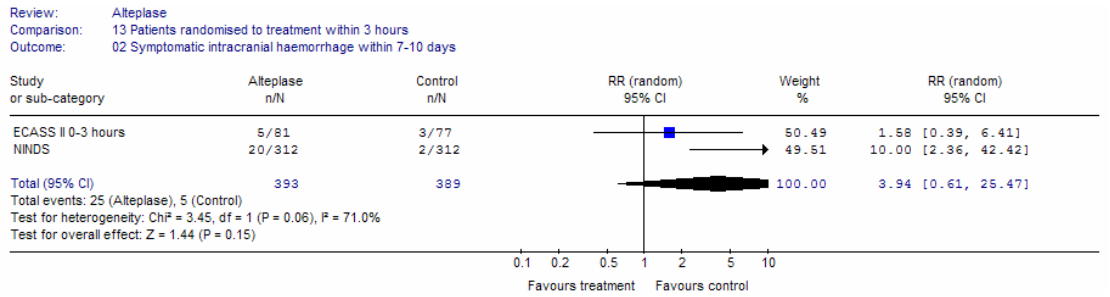
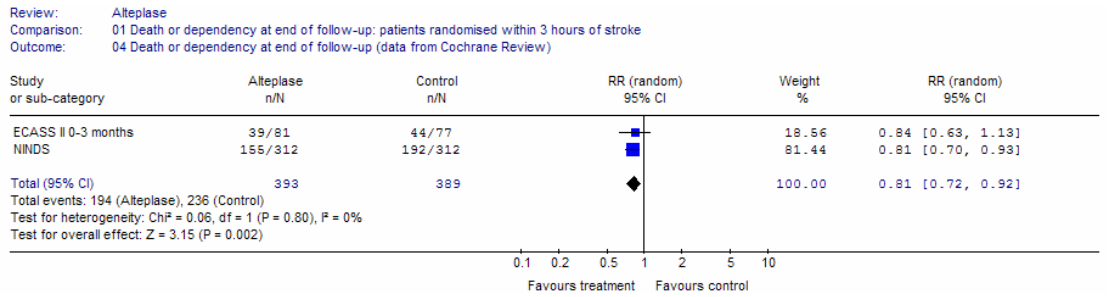


Figure 9: All patients randomised to treatment within 3 hours: death or dependency at 3 months



Thus it may be seen that alteplase, given within its licensed application, is associated with a statistically significant reduction in the risk of death or dependency at 3 months (RR 0.82, 95% CI 0.72-0.93, see Figure 6), despite an increase in the risk of early SICH (RR 4.24, 95% CI 1.52-11.83, see Figure 5). There is no significant difference in all-cause mortality at 3 months. The exclusion of data relating to the patients in the ATLANTIS studies who received treatment within 3 hours has little effect on the results, as they were few in number, but such effect as it does have is to improve the risk-benefit profile of alteplase (see Figures 7-9).

Only one study (the NINDS study) presented data relating to a time-point later than 3 months from stroke onset. As the manufacturer's submission notes, these data indicate that the benefit seen at 3 months is sustained at 12 months (see Table 9).

However, there is reason for caution in relation to the evidence for the efficacy of alteplase used within the 3-hour window. Although, in section 5.9.1, the manufacturer's submission identifies the clinical evidence supporting the use of alteplase in acute ischaemic stroke as coming "from double-blind, placebo-controlled RCT (sic) 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", this wording may make the evidence base appear wider than it actually is: the meta-analyses utilise on the RCT evidence, as does the pooled analysis. Moreover, as Warlow and Wardlaw point out, the body of RCT evidence for the efficacy of

alteplase given within 3 hours of symptom onset is not good, being based on RCTs which randomised only 957 patients;[43] only 791 of these were actually randomised to treatment within the 3-hour time window using the current licensed dose of alteplase. The submission cites the observational studies as suggesting that alteplase, used with strict adherence to the licensed indications, has a net benefit comparable to that seen in the RCTs, but it should not be forgotten that the observational studies are later in date than the RCTs, and that therefore the treatment other than alteplase received by those patients may have differed from that received by the trial populations.

As may be seen, the results of the meta-analyses of RCT evidence are heavily influenced by the NINDS trial, which contributed more patients than the other trials combined. An HTA report[44] has identified several problems in relation to the NINDS trial, as follows:

- There was a substantial imbalance in baseline stroke severity such that the control group contained a higher proportion of patients with severe strokes, who were likely to have worse outcomes; this was not adequately adjusted for in the study publications

- Adequate concealment of treatment allocation was not assured: each centre held envelopes with the unblinded treatment allocation

- Because of failure to use an effective system of stock control, delays in restocking centres led to centres using the wrong type of treatment (eg active instead of placebo) in at least 13 patients, and a box from the wrong time stratum in a further 18, a treatment error rate of at least 3.5%.

Moreover, the HTA report claimed that details of the trial analysis published on the FDA website showed that the 1995 analysis was not, as claimed, an unbiased ITT analysis but "a potentially more biased on-treatment analysis". It has not been possible to explore this claim, and its implications, within the time available to the ERG.

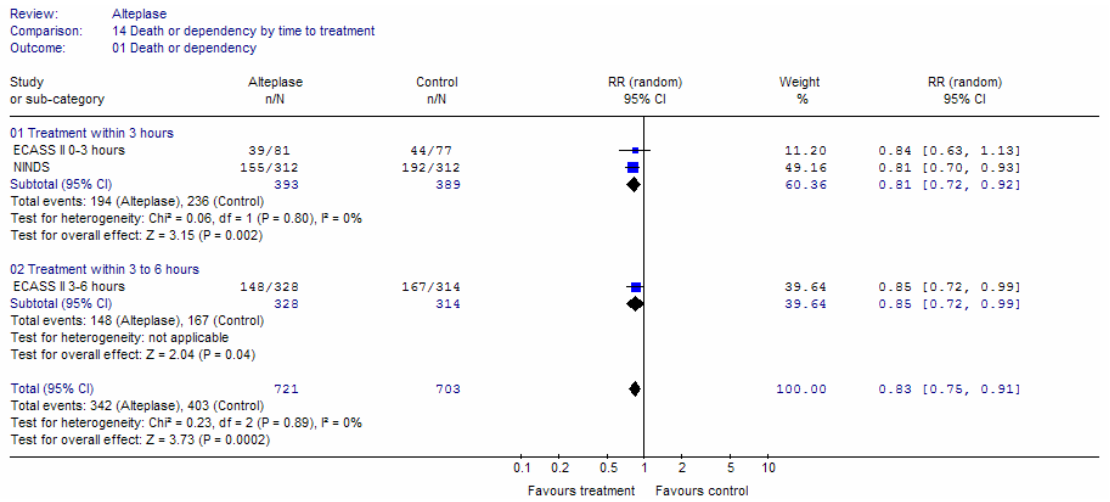
Opinions vary regarding the gravity of these problems. The HTA report claimed that they are such as to justify a sensitivity analysis which excludes the NINDS trial.[44] This would reduce the evidence base for patients randomised to treatment with the licensed dose of alteplase within 3 hours of symptom onset to a subgroup of the ECASS II study, and would not yield statistically significant results for the key outcome of death or dependency at 3 months (see results for ECASS II in Figure 9 above). However, the Cochrane reviewers noted that the imbalance in baseline stroke severity did not reach conventional statistical significance, and undertook an additional analysis which suggested that the imbalance probably caused the effect of alteplase on death and dependency to be overestimated by around 3%.[2] A subsequent

independent analysis of the NINDS data considered that there was no evidence that the imbalance in the distribution of baseline NIHSS scores had either a statistically or a clinically significant effect on the trial results.[17]

In addition to these issues, the use of urgent blood pressure reduction in the control as well as the intervention arm of the NINDS study has been questioned. The rationale for its use was to reduce the risk of cerebral haemorrhage in the intervention arm, because pilot studies had suggested that this risk was increased in patients with severe hypertension. However, such urgent blood pressure reduction was contrary to current standard recommendations for the management of stroke patients, and carried at least a hypothetical risk of harm. It has therefore been argued that patients in the control arm did not receive optimal standard treatment because they were exposed to a risk of hypotension with no likely benefit and that, without knowing how many patients received this treatment, and whether their outcomes differed from those of patients whose blood pressure did not need urgent treatment, it was not possible to assess whether patients in the control arm were disadvantaged so as to affect the study's conclusions.[45] As the risk/benefit of lowering blood pressure in acute stroke is currently the subject of on-going trials,[46] it is still not clear whether the control arm was disadvantaged by this treatment.

While it has generally been held that earlier treatment is associated with better outcomes, the evidence for this is not unassailable. The Cochrane review[2] found that the composite endpoint of death or disability associated with alteplase, expressed as a Peto odds ratio, was not significantly different in patients treated within 3 hours of, or between 3 and 6 hours after, stroke onset. They included in their calculations the results from the ECASS I study, which used a higher dose of alteplase than is now licensed, and from the ATLANTIS studies in which randomisation was not stratified by time to treatment, but excluded the NINDS study because it did not report results from both time windows. Nonetheless, when the results are recalculated as relative risks, excluding ECASS I and the ATLANTIS studies, but including the NINDS study, the effect of treatment appears very similar whether alteplase was given within 3 hours, or between 3 and 6 hours (see Figure 10). However, the Cochrane reviewers note that this does not necessarily mean that time to treatment is unimportant: other factors, such as stroke severity, may have affected the results.

Figure 10: Death or dependency at 3 months, by time to treatment



A pooled analysis undertaken using individual patient data from the ATLANTIS A and B, ECASS I and II, and NINDS trials explored the relationship between time to treatment (grouped as 0-90, 91-180, 181-270 and 271-360 minutes) and favourable outcome (mRS or NIHSS score of 0-1 or BI score of 95-100) at 3 months. This found a strong association between rapid treatment and favourable outcome as measured by the odds of a favourable outcome. This effect was stronger after adjusting for potential confounders such as baseline NIHSS.[14] Data were not presented in a form which allowed the calculation of the relative risks of death or dependency at 3 months for the four time bands. However, the proportions of patients in the alteplase and placebo arms suffering this outcome, summarised in Table 13, suggest that alteplase is beneficial when administered within, but not after, 270 minutes of symptom onset. However, it should be noted that the data are problematic because:

- they include data from the ECASS I study in which patients received a dose of alteplase which is no longer considered appropriate
- the ATLANTIS and ECASS I studies did not stratify randomisation by time to treatment, and ECASS II stratified only by 0-180 or 181-360 minutes
- simple pooling of data from different studies negates the benefit of randomisation.

Table 13: Pooled data from the ATLANTIS A and B, ECASS I and II, and NINDS studies: proportion of patients suffering death or dependency (mRS score 3-6) at 3 months, by time to treatment[14]

Time to treatment	Death or dependency (% of patients)	
	Alteplase	Placebo
0-90 minutes	51	59
91-180 minutes	50	62
181-270 minutes	51	58
271-360 minutes	51	51

Unsurprisingly, there is considerable interest in the possibility of identifying subgroups of patients with acute stroke for whom the balance of risks and benefits associated with alteplase treatment might be particularly favourable. However, the evidence is limited because none of the trials stratified randomisation by potentially relevant factors such as age, gender, or current aspirin use. Consequently, the Cochrane review limits its subgroup analyses to time to treatment (<3 hours and 3-6 hours), and its conclusions (quoted in full in the manufacturer's submission) note that:

- there is insufficient evidence to identify by any other parameters (such as age, or clinical or radiological features) the patients most likely to benefit from (or be harmed by) treatment
- further large-scale randomised trials are needed to identify the categories of patient most likely to benefit (or be harmed), especially in elderly patients (age >75).[2]

The manufacturer's submission notes the existence of a more recent body of evidence suggesting that alteplase may produce favourable results in the very elderly, albeit with a greater risk of ICH than in younger patients, but does not provide references to these studies on the grounds that alteplase is not licensed for use in patients aged over 80. Post-hoc subgroup analyses of data from the NINDS study, the main source of information for the efficacy of alteplase in patients treated within 3 hours of symptom onset, found that factors including age as well as stroke subtype, early CT findings, baseline NIHSS score, prior aspirin use, and history of diabetes significantly influenced outcome following acute ischaemic stroke, but did not alter the likelihood of responding favourably to alteplase therapy. However, the oldest age-band used in this analysis was the over-75s[47] rather than the over 80s. Several observational studies[48,49,50,51] found that patients aged 80 and over were not at increased risk of SICH following alteplase therapy, although mortality was higher in this

group than in the under 80s; two of these studies[48,49] found that favourable outcomes were less common in patients aged 80 and over than in those aged under 80, while the other two[50,51] found no significant difference between age groups in this respect.

A pooled analysis of data from the ATLANTIS A and B, ECASS II, and NINDS studies[3] compared the likelihood of a favourable outcome (mRS 0-1) at 90-days in men and women, using logistic regression to control for potential confounders. This analysis found that women were significantly (p=0.04) more likely than men to benefit from alteplase therapy. Although there was no significant difference between the proportions of women and men who had a favourable outcome following alteplase therapy (p=0.50), the outcome for untreated women was significantly worse than that for untreated men (p=0.03), and therefore alteplase was associated with a significant increase in the proportion of women (p<0.001), but not of men (p=0.52), with a favourable outcome (see Table 14). Because none of the studies stratified randomisation by gender, this is not a true randomised comparison. However, the investigators note the evidence of other studies that, in the absence of thrombolytic therapy, women with stroke generally have worse functional outcomes than men, and suggest that alteplase therapy may be used to redress this balance.[3] This study did not compare rates of SICH in men and women, leaving unexplored the possibility that, if the risk of SICH associated with alteplase is the same regardless of gender, the balance of risks and benefits of therapy may differ, being potentially considerably less advantageous in men than in women.

Table 14: Proportion of patients with a favourable outcome at 90 days (mRS 0-1): pooled analysis of data from the ATLANTIS A and B, ECASS II, and NINDS studies[3]

	Alteplase	**Placebo**	**P value**
Men	38.5%	36.7%	0.52
Women	40.5%	30.3%	p<0.001
P value	0.50	0.03	

In section 5.3.6, the manufacturer's submission claims that there is reason to believe that the RCT results are generalisable to those patients in the UK who are likely to receive alteplase, provided that prescribing recommendations are carefully followed. However, a number of points have been raised regarding the generalisability of the RCT evidence, as follows:

- All the studies were conducted in centres specialised in the management of acute stroke, and it has therefore been suggested that the use of thrombolytics in less experienced centres could result in much greater hazard, which might reduce or even negate any

potential benefit.[2] As the manufacturer's submission notes, the SITS-MOST study found that mortality was higher in centres which were not experienced in managing acute stroke patients with alteplase, although the rate of SICH was no higher than in experienced centres; this was attributed to "a form of learning curve that seemed to disappear after the centre had treated some 10-15 patients."

- The study populations were not typical of patients with acute ischaemic stroke. The Greater Cincinnati/North Kentucky stroke study found that, even ignoring the exclusion criterion affecting patients who could not be treated within 3 hours, only 29% of patients with acute ischaemic stroke who presented to an emergency department at any time after symptom onset would have met the NINDS inclusion criteria. In this study, the major reason for ineligibility, affecting over 50% of patients, was mild stroke severity (NIHSS score <5).[52] Moreover, the ATLANTIS and ECASS studies excluded patients aged over 80 and, although the NINDS study did not, such patients only formed a small proportion of its study population[16] (42/624 (6.7%) according to Warlow and Wardlaw[43]), whereas we are advised that, in real life, patients aged over 80 represent approximately 50% of stroke patients in the UK.[53]
- None of the alteplase trials tested its interaction with aspirin, although the MAST-I trial of streptokinase, with or without concomitant aspirin, for thrombolysis in acute ischaemic stroke indicated a highly statistically and clinically significant adverse interaction which increased case fatality at all stages. There is thus no evidence relating to the effect of thrombolysis on patients who are already taking aspirin at the time of their stroke,[44] although such patients formed approximately 35% of the NINDS study.
- It has been claimed that patients with stroke mimics (seizure, tumour, infection etc) constitute perhaps 15-25% of patients diagnosed with "stroke" in community practice.[54] Such patients cannot benefit from alteplase therapy, but can be harmed by it, and thus any benefit indicated by the clinical trials could easily be negated by the erroneous treatment of even a few such patients.
- Similarly, it has been claimed that the treatment of a few patients with subtle haemorrhage which was undetected because the CT scan was not read by a specialist neuroradiologist would negate the benefit indicated by the clinical trials.[54] Even within a trial setting, the ECASS trials mistakenly identified approximately 8% of patients as suitable for alteplase therapy in violation of the CT criteria (see Table 3).

In section 5.9.2, the manufacturer's submission identifies time to treatment as the major factor influencing the generalisability of study results to patients in routine clinical practice. The submission states that the evidence suggests that treatment earlier in the 0-3 hour window is

associated with better outcomes than treatment relatively late in that window, but the SITS-MOST study shows that most patients who receive treatment are not treated until relatively late within the 3-hour period. This is not surprising: the NINDS trial only recruited so many patients within 90 minutes because the study protocol required investigators to recruit equal numbers in each time stratum, and the difficulty of doing this is reflected in the fact that, in the 0-90 minutes stratum, the median time for starting treatment is 89 minutes in the alteplase group, and 88 in the placebo group.[19] Although the SITS-MOST study did not publish data on the number of patients who were ineligible for alteplase therapy because of the time factor, a Canadian and a US study summarised later in the manufacturer's submission (section 7.2, Tables 29 and 30) found that respectively 73% and 82% of patients with acute ischaemic stroke were ineligible because they were not admitted to hospital within 3 hours of symptom onset. Comparable data are not available from the UK, but the North American data indicates the optimism of the submission's statement that the achievement of treatment earlier rather than later in the 3-hour window requires better recognition of stroke symptoms by patients and their families, acceptance by the emergency services of stroke as a treatable emergency, and configuration of services within hospitals to minimise door-to-needle time: it seems more probable that all of these factors would be required to get patients to the point of treatment at any time within the 3-hour period, let alone early within it.

4.2.3 Summary

The manufacturer's submission states correctly that the proof of clinical benefit of alteplase used within a 0-3 hour time window rests primarily on the NINDS study, which has contributed more patients in this category than all the other trials of alteplase put together. Because of this, and in the light of the problems relating to the NINDS study, the Cochrane reviewers have emphasised strongly that the RCT evidence relating to alteplase used within three hours of stroke onset should be regarded with EXTREME CAUTION (their capitals) and confirmed by future trials. Moreover, they note that there is no evidence whether the risk-benefit ratio seen in the RCTs applies in patients who are already taking antithrombotic drugs for stroke prevention.

The data from the SITS-MOST study suggest that, with strict adherence to the prescribing information, equally good outcomes may be achieved in non-trial as in trial settings. However, such comparisons should be treated with caution because of the likelihood both of differences between the populations treated in the studies and in ordinary practice, and of changes over time in other aspects of stroke care which might have affected patient outcomes. As noted earlier, observational studies have shown both how few patients with acute ischaemic stroke receive alteplase in normal clinical practice, and what a high proportion of these receive it in violation of the protocols.

Thus, it is clear that the use of intravenous alteplase therapy for acute ischaemic stroke is challenging in practical terms, in ensuring that stroke patients both reach hospital and are assessed in time to receive therapy within the 3-hour window. Moreover, it would not necessarily result in the level of benefit indicated by the trial data.

5 ECONOMIC EVALUATION

5.1 Overview of manufacturer's economic evaluation

A state transition model was used to evaluate the lifetime impact of treatment with alteplase within three hours of onset of stroke symptoms compared to standard treatment. In addition, a short-term (12-month follow-up) model is included. The model is based on work published as part of the Health Technology Appraisal (HTA) of thrombolytic therapy by Sandercock *et al.*, (2002).[44] The economic model extends the Sandercock study by:

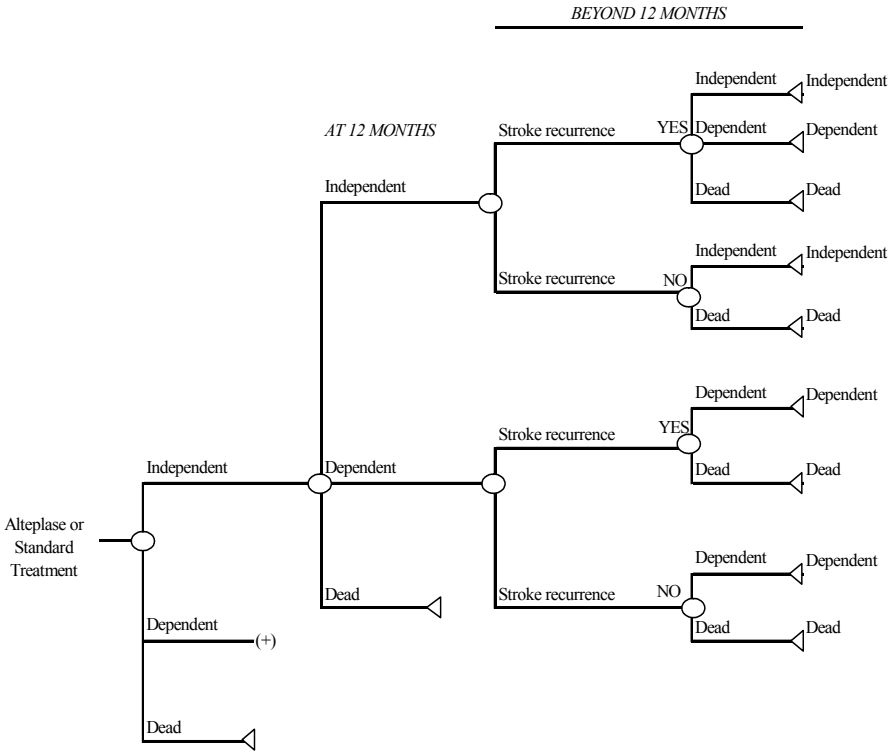
- Adding an initial 6 month transition state that incorporates an odds ratio for treatment with alteplase
- Incorporating the costs of long-term rehabilitation accruing to the Social Services budget and short-term acute care costs associated with death, independent stroke and dependent stroke as reported in the Health Technology Appraisal of clopidogrel and dipyridamole[55]
- 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).[44]

The model includes three health states: independent stroke, dependent stroke and death. The odds ratios for death, dependent stroke and independent stroke are based on a meta-analysis of alteplase RCTs reported in a Cochrane review by Wardlaw et al.[2] Subjects may also experience a haemorrhage. The probability of haemorrhage for standard treatment and alteplase treatment are taken from a meta-analysis of the NINDS, ECASS and ATLANTIS trials.[14] Transition variables between states were taken from the studies by Sandercock et al.[44] and Wardlaw et al.[2] Costs were taken from PSSRU costs and NHS reference costs and a UK stroke burden of disease study.[56]

The health states used within the model are considered to be appropriate for the required analysis.

The health states and model structure are shown in Figure 11, below.

Figure 11: Boehringer Ingelheim model structure



The key assumptions of the model are:

- Efficacy of standard treatment at 6 months is based on the Lothian Stroke Register (LSR). These patients were admitted to hospital within 6 hours of stroke onset. There is therefore an assumption that no additional benefit can be gained from standard treatment given within 3 hours. It is the opinion of the ERG's clinical advisor that there is no benefit gained from giving standard treatment within 3 hours.
- The distribution of outcomes at six months is based on the LSR and is assumed to be the same for both groups.
- 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.
- After the first year, deaths occurred at an equal rate in dependent and independent survivors.
- The risk of a recurrent stroke and death due to a recurrent stroke was equal in dependent and independent patients.
- Patients in the dependent health state 12 months after the index stroke event could only recycle into the dependent heath state or transition to the death health state.

- Patients in the independent health state suffering a recurrent stroke, who did not enter the death state, had an equal chance of transitioning to either the independent and dependent states.
- Alteplase is not prescribed in patients who have suffered multiple strokes.
- Costs for mild and moderate strokes describe the cost of independent stroke survivors and costs for severe stroke describe the cost of dependent stroke survivors.

5.2 Modelling of disease natural history and treatment effectiveness within the submission

5.2.1 Natural History

The disease natural history of stroke patients is taken from the Sandercock et al. study,[44] and is based on data from the Lothian Stroke Register. At the time of the analyses, the LSR contained data from 1779 prospectively-identified consecutive patients with a definite or probable stroke who had required inpatient care from September 1989 to June 2000. Follow-up data in the LSR was examined to ascertain Modified Rankin Scale (mRS) scores at 6 and 12 months after stroke onset. Surviving patients were categorised as dependent (mRS $\geq$ 3) or independent (mRS < 3).

Survival in the first year was estimated by calculating the median survival for those who survived up to 6 months, and for those who survived up to 12 months. For survival after 1 year, it was assumed that deaths occurred at an equal rate in dependent and independent survivors. Published estimates of all-cause mortality, adjusting for age and history of previous stroke, were used under the assumption that the overall death rate after the first year was 2.5 times the age-adjusted mortality of the UK. Amongst patients who had a recurrent stroke, case fatality was that from LSR, assuming the risks to be equal in dependent and independent patients. It was also assumed that, of those independent patients remaining alive after the recurrent stroke, 50% suffered independent strokes and 50% suffered dependent strokes.

The standard treatment 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. The distribution of these patients at 6 months can be seen in Table 15, below.

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, which are in Table 16.

Table 15: Baseline distributions at 6 months

Independent	Dependent	Dead
0.3953	0.3256	0.2791

Table 16: Transition probabilities at 12 months for standard treatment and alteplase

		From	
		Independent	Dependent
To	Independent	0.8750	0.1111
	Dependent	0.0938	0.7407
	Dead	0.0312	0.1482

5.2.2 Treatment effectiveness

The model assumes that treatment effectiveness occurs within the first 6 months of treatment. Odds ratios for 'death' and 'death or dependency' are applied to the baseline distributions, enabling the calculation of the distribution of outcomes in the alteplase treatment cohort at 6 months. Odds ratios for alteplase treatment were taken from a 2003 Cochrane review meta-analysis.[2] The RCTs included in this meta-analysis were the NINDS,[4] ECASS 1,[5] ECASS II,[6] ATLANTIS A,[7] ATLANTIS B[8] and Haley et al[9] studies.

Table 17: Efficacy of alteplase

Efficacy of alteplase	OR	95% CI	
Odds ratio for death	0.97	0.69	1.36
Odds ratio for death or dependency	0.64	0.5	0.83

The use of odds ratios instead of relative risks is not considered appropriate by the ERG (see section 4.1.7). However, an additional analysis by Boehringer Ingelheim shows that replacing odds ratios with relative risks has little impact on the magnitude of the results.

Boehringer Ingelheim was requested to justify the selection of an initial 6-month cycle when the majority of trial outcomes data relates to 90 days results. The initial 6-month cycle was justified on the basis that the initial outcomes for patients receiving standard treatment were derived from the 6-month outcomes following a stroke event recorded in the Lothian Stroke Registry and 90-day outcomes were not available for standard treatment. A 12-month follow-up study[15] of patients within the NINDS trial, and a 12-month observation study in Cologne,[57] indicated a sustained benefit of alteplase over a 12-month period. The assumption that 90-day

outcomes are sustained at 6 months following a stroke event is based on clinical evidence and appears reasonable.

The clinical effectiveness section of this report notes that proof of the clinical benefit of alteplase rests primarily on the NINDS study, and that Cochrane reviewers have emphasised strongly that this evidence should be treated with extreme caution. The economic evaluation presented by Boehringer Ingelheim also relies heavily on the NINDS trial, and the results should therefore also be treated with extreme caution.

5.3 Health-related quality of life

Utility scores for the dependent and independent states are based on the responses to the EuroQoL quality of life questionnaire of a sample of 147 LSR patients as described in Sandercock et al.[44] and the Health Technology Appraisal of clopidogrel and dipyridamole.[55]

The classification of dependence used in the LSR study has been validated against the modified Rankin Scale where a mRS score of 3-5 defined dependency.[58] The ERG is satisfied that the source data for QALY measures followed a similar dependence classification to that used in the economic model.

Boehringer Ingelheim carried out a further literature search to identify studies published since the Sandercock et al. study. Only one additional study[59] was found which reported utility scores for independent (defined by a mRS score of 0-2) and dependent (defined by a mRS score of 3-5) states. This was a study with German patients with a smaller sample size than the LSR study. The utility scores from this study are lower than those from LSR used in the model (Table 18) but these have little effect on the magnitude of the results. It appears reasonable that Boehringer Ingelheim have used the LSR study utilities as these values were elicited from a UK population, and were measured and valued using the EuroQol as per the NICE reference case.

Table 18: Utility values used in the Boehringer Ingelheim model

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

5.4 Modelling of resources and costs

5.4.1 Cost of administering and acquiring alteplase

The additional staffing costs needed to administer alteplase were estimated at £628, and are based on the Sandercock study (see Table 19 below). The disaggregated staff cost on which this estimate is based was considered to be reasonable by the ERG's two clinical advisors.

Table 19: Extra staffing resource required to administer alteplase as outlined in Sandercock et al. (2002)[44]

Extra staffing requirements	Cost per hour	Unit cost	Source /comments
5min additional nurse time	£46	£3.83	PSSRU 2005 (staff nurse 24hr ward)
190 min Registrar time	£46	£145.67	PSSRU 2005 (specialist registrar costs)
50min consultant time	£107	£89.17	PSSRU 2005 (Medical consultant costs)
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)
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)
Senior nurse requires 1:1 care for 5 hours	£64	£320.00	PSSRU 2005 (ward manager 24hr ward)
10 min overnight junior staff review	£25	£4.17	PSSRU 2005 p181 Pre-registration house officer

The estimated acquisition cost of alteplase is based on the mean dose (68.8 mg) reported in the 6th report of the SITS-MOST registry.[60] In order to maintain consistency between treatment and efficacy, it is normal practice to use the mean dose of treatment from the trials on which efficacy is based. Boehringer Ingelheim provided no information on the mean dose within the trials. However, the mean dosage in the NINDS[4] trial (the largest trial in the meta-

analysis from which efficacy is taken) is in the region of 68.4 mg (based on the mean bodyweight and dose per kg). This is comparable to the mean dose found in the SITS-MOST registry.

5.4.2 Cost of intracranial haemorrhage

The use of alteplase in acute ischemic stroke increases the risk of intracranial haemorrhage (ICH). It is claimed by Boehringer Ingelheim that both the acute and long-term costs of IHC with alteplase have been captured by the proportion of patients entering the dependent, independent and death states. The cost of ICH in the alteplase arm of the model would be captured by these health states if the original data on which costs are based included a substantial number of alteplase patients. It is the opinion of the ERG's clinical advisor that the numbers of patients on alteplase in the Youman et al. study (from which stroke costs are taken) would have been very small. The cost of these health states is therefore based on patients on standard treatment and does not reflect the additional cost of treating patients with ICH due to the use of alteplase. However, it is the opinion of the ERG's clinical advisor that the additional cost of treating ICH due to the use of alteplase would be small. Alteplase patients cannot be operated on due to the risk of bleeding, and therefore alteplase patients with ICH would receive standard care which might involve a small increase in staff care. It is the opinion of the ERG that the cost of stroke for those on alteplase treatment should be marginally higher than for standard treatment, but this would have a small impact on the overall results.

The additional cost of CT scan to determine the cause of neurological deterioration is included in the model.

5.4.3 Cost of stroke management and rehabilitation

The annual cost of stroke has been taken from a study by Youman et al.[56] This study applied national unit costs to resource-use data from a large, randomised, prospective trial[61] of stroke care in the UK to calculate the 3-month cost of acute events and long-term care. Stroke was divided into mild, moderate and severe events, defined by the Barthel Index. For the purpose of the model, it is assumed that mild and moderate strokes described the costs of independent stroke survivors, and that severe stroke described the cost of dependent stroke survivors. It is the opinion of the ERG's clinical advisors that the Youman et al. study is the best available evidence for the cost of stroke in the UK.

5.5 Discounting

Boehringer Ingelheim have assumed a discount rate for both costs and health benefits of 3.5%. This is in line with the current NICE guidance.

5.6 Sensitivity analyses

Boehringer Ingelheim carried out a univariate and probabilistic sensitivity analysis (PSA). For the univariate analysis, lower and upper CIs were used for alteplase efficacy and utility values, and all other variables were both doubled and halved. The only exception was the cost of alteplase, which was increased to reflect the maximum licensed dose. The values used for all parameters appear to be reasonable.

5.7 Results

The results of the Boehringer Ingelheim model from the original submission are presented in Table 20, below. Confidence intervals for the base were not included; however they are available from the probabilistic analysis.

Table 20: Discounted base case disaggregated cost-effectiveness results (lifetime model)

	Cost	Life Years	Independent Life years	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	-£527	0.164	1.443	0.277	

Univariate sensitivity analysis was carried out on all parameters. Variability in the odds ratio for alteplase efficacy on death and dependency, staff costs, and the cost of independent and dependent stroke in year one, had the greatest impact upon the ICER. These analyses resulted in ICERs between £26,000 and £50,000.

The probabilistic sensitivity analysis on the lifetime model presented within the submission suggested that the probability that alteplase has a cost-effectiveness ratio better than £20,000 per QALY gained is close to 1. The PSA results from the lifetime model are shown in Figure 12 and Table 21, below.

Figure 12: Life-Time Acceptability Curve lifetime model (NHS and Social Service costs)

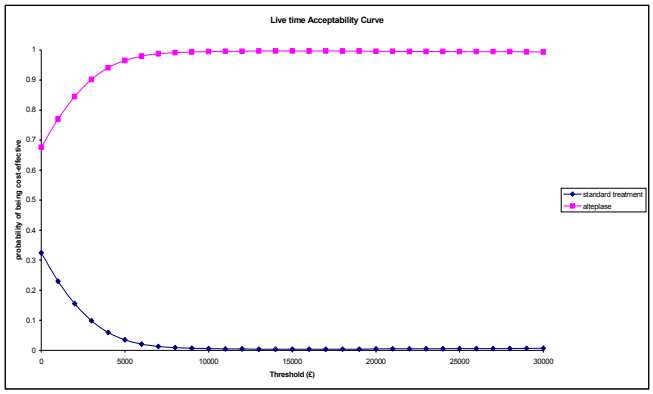


Table 22: Results of the probabilistic sensitivity analysis in the lifetime model (NHS and Social Service costs)

	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 dominant**
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	

The ICER for the 12-month model was approximately £14k, and the probability that alteplase has a cost-effectiveness ratio that is better than £20,000 per QALY gained is approximately 0.7. The PSA results from the 12 month model are shown in Figure 13 and Table 22, below.

Figure 13: 12 month Acceptability Curve month (NHS and Social Service costs)

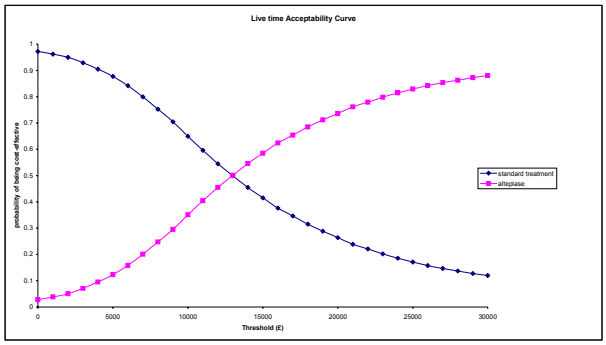


Table 22: Results of the probabilistic sensitivity analysis in the 12-month model (NHS and Social Service costs)

	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	

5.8 Model validation reported within the submission

Boehringer Ingelheim consider that, as the model structure and parameters were taken from published HTA appraisals and the clinical outcomes from a Cochrane review, no further validation is necessary. The ERG are not aware of any further trials or models against which the Boehringer Ingelheim model could be validated. An attempt could possibly have been made to compare the results of the 12-month follow-up in the NINDS study with the LSR for standard treatment.

5.9 Summary and discussion of manufacturer's economic evaluation

The state transition model which Boehringer Ingelheim used is considered to be appropriate for the economic analysis.

The sensitivity analysis shows that applying the higher 95% CI for the death and dependency odds ratio has the largest impact upon the model results, increasing the ICER to £50,000.

The cost of stroke is based on a cohort of patients receiving standard treatment. There is a possibility that the cost of stroke would be higher if it were based on a cohort of patients receiving alteplase, due to the extra care needed to treat ICH. However, the opinion of the ERG's clinical advisor is that the impact on overall results would be small.

The use of odds ratios instead of relative risks has little impact on the model results.

The critical appraisal of the Boehringer Ingelheim model undertaken by the ERG suggests that alteplase costs less, and is more effective, than standard treatment.

However, although the ERG consider the model structure to be appropriate, it must be noted that the clinical effectiveness section of this report casts doubt on the reliability of the proof of the clinical benefits of alteplase. The proof of clinical benefit of alteplase rests primarily on the NINDS study, and Cochrane reviewers have emphasised strongly that this evidence should be treated with extreme caution. The economic evaluation presented by Boehringer Ingelheim also relies heavily on the NINDS trial, and the results should therefore also be treated with extreme caution.

6 DISCUSSION AND CONCLUSIONS

6.1 Summary of clinical effectiveness results

The RCT evidence suggests that, in highly selected patients, alteplase administered within 3 hours of the onset of acute ischaemic stroke is associated with a statistically significant reduction in the risk of death or dependency at 3 months compared with placebo despite the statistically significant increase in the risk of early SICH. There is no significant difference in all-cause mortality at 3 months. Evidence from the NINDS study suggests that the benefit of treatment is sustained at 12 months.

However, as noted in a recent Cochrane review, the evidence for the use of alteplase within the 3-hour licensed window should be treated with extreme caution. It is based on a total of only 416 patients who received the current licensed dose of alteplase. 312 of these patients were included in one trial, the NINDS trial, in which a substantial imbalance in baseline stroke severity, a key prognostic factor, favoured alteplase.

The randomised trials were not stratified by any potential prognostic factor other than time to treatment, and therefore any post-hoc analyses designed to explore the extent to which different groups might benefit from therapy can only be regarded as hypothesis-generating. Nonetheless, it is potentially alarming that one such analysis appeared to indicate that alteplase therapy was of no significant benefit in men.

Observational studies suggest that few patients with ischaemic stroke will be eligible for alteplase therapy under the terms of the current licensing agreement. In particular, many patients will be excluded because they are aged over 80, and many more will be excluded because treatment cannot be initiated within 3 hours of symptom onset. Any increase in the number of patients in whom treatment can be initiated within 3 hours is likely to require substantial efforts in terms of public education and service reconfiguration.

6.2 Summary of cost effectiveness results

The critical appraisal of the Boehringer Ingelheim model undertaken by the ERG suggests that alteplase can result in long-term cost savings and is more effective than standard treatment.

In the univariate sensitivity analysis, the odds ratio for alteplase efficacy on death and dependency, staff costs, and the cost of independent and dependent stroke in year one had the greatest impact upon the ICER. These analyses resulted in ICERs between £26,000 and £50,000.

The probabilistic sensitivity analysis suggested that the probability that alteplase has a cost-effectiveness ratio better than £20,000 per QALY gained is close to 1.

The ICER for the 12-month model was approximately £14k, and the probability that alteplase has a cost-effectiveness ratio better than £20,000 per QALY gained is approximately 0.7.

6.3 Commentary on the robustness of results

The ERG considers that the model structure used by Boehringer Ingelheim is appropriate for the economic analysis and allows sensitivity analysis to be carried out easily.

Applying the higher 95% CI for the death and dependency odds ratio has the largest impact upon the model results, increasing the ICER to £50,000.

In the baseline results, alteplase is both less costly and more effective than standard treatment, and it is unlikely that parameter variations will increase the ICER beyond the currently accepted threshold values.

However, the economic evaluation relies heavily on the results of the NINDS trial. The extreme caution that should be applied to the clinical effectiveness of alteplase should also be applied to the results of the cost-effectiveness analysis.

6.4 Issues requiring further work

One important issue which is not explicitly taken into account in the economic modelling is the possible impact of trying to increase the number of patients who could be treated within the 3-hour window. This may have a significant cost impact to the NHS if there is a need to educate the public on the importance of early treatment and if substantial service reconfiguration were necessary.

6.5 Conclusion

The Boehringer Ingelheim model is considered to be appropriate for the economic analysis. The basecase analysis suggests that alteplase is a cost-effective alternative to standard treatment. It is unlikely that parameter variation will increase the ICER beyond currently accepted threshold values. However, the results must be viewed with extreme caution due to problems with the main evidence base identified by Cochrane reviewers.

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