WHAT IS THE OPTIMAL MODEL OF SERVICE DELVERY IN TRANSIENT
ISCHAEMIC ATTACK?

by

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ABSTRACT

Transient ischaemic attack (TIA) is associated with a high early risk of stroke which can be considerably reduced by early initiation of secondary preventive drugs including antiplatelets, statins and blood pressure lowering therapy. These treatments are usually initiated by a specialist after urgent out-patient review. However, variable access to timely specialist services means that initiation of these treatments is delayed for some patients.

The purpose of this thesis was to evaluate the cost-effectiveness of GP initiation of treatment following a suspected TIA compared with UK clinical practice. A Markov model was constructed to model the cost and effectiveness of urgent initiation of treatment following suspected diagnosis of TIA by GPs. In the base-case, GP initiation of treatment (followed by specialist review of treatments within a week) was compared with best practice, as stated in the National Stroke Strategy (2007).

Strategies involving same-day GP initiation of treatment was found to be highly cost-effective at willingness to pay thresholds typically applied in the UK.

This study illustrates the usefulness of modelling techniques to use secondary data sources to examine a policy relevant question around treatment urgency in a susceptible and identifiable group of patients where primary research is impracticable.

ACKNOWLEDGEMENTS

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ABBREVIATIONS

CEA Cost-effectiveness analysis

CEAC Cost-effectiveness acceptability curve

CI Confidence interval

CT Computed tomography

CVA Cerebrovascular accident (Stroke)

DWI Diffusion weighted imaging

ECG Electrocardiogram

EVPI Expected value of perfect information

GPiT the strategy involving **GP i**nitiation of **T**reatment

ICER Incremental cost-effectiveness ratio

Inc. Incremental

IQR Inter-quartile range

MI Myocardial infarction

MRI Magnetic resonance imaging

NAO National Audit Office

NB Net benefit

NICE National Institute for Health and Care Excellence

NIHR National Institute for Health Research

QALY Quality-adjusted life year

RR Relative risk

RCT Randomised controlled trial

SD Standard deviation

SE Standard error

SDO Service Delivery Organisation

TIA Transient ischaemic attack

TNA Transient neurological attack

WHO World Health Organisation

WTP Willingness to pay

PREFACE

The theme of this research (that also gives this thesis its title) reflects an identified research priority area within the UK NHS, preceding my involvement with the project. In 2006 the University of Birmingham's TIA steering group[1] made a successful funding application to the NIHR Service Delivery Organisation (SDO) to undertake research into the area. This culminated in the publication of an economic modelling project, looking at the role and capacity for rapid access clinics within the area. Part of the initial grant included funding for a PhD, to develop the research further. I was present in the latter stages of the TIA steering group meetings, but not involved in the development or dissemination of the results of that economic model. While this piece of work stands alone, it was also prepared in response to how that report was received, what recommendations to future research it made, and what research gaps it identified.

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[1] The TIA steering group was led by Professor Jonathan Mant, now at the University of Cambridge. The group was composed of a clinically trained Professor in Public Health, an academic GP and several Health Economists (including Dr Pelham Barton, Reader in mathematical modelling).

CHAPTER 1: INTRODUCTION

> **service innovation**: some combination of alternative sites of care or caregivers and new care processes, often enabled by new information or clinical technologies (The King's Fund, 2013)

1.1. Outline

The focus of this thesis is on a service innovation in stroke prevention. This chapter provides a précis of what Transient Ischaemic Attack is, how it is managed, and the relevance of Economics. Preliminary research questions are identified and the structure of the thesis is then described.

1.2. Background

Stroke is a major cause of both mortality (about one-third of patients do not survive) and morbidity in the UK, accounting for about 11% of all deaths in England and Wales, and costing the NHS in England about £2.8 billion per year in direct care costs (Mant et al., 2004).

It is known that many strokes are preceded by temporary interruptions of the blood supply to the brain known as transient ischaemic attack (TIA), which therefore provide an early warning signal for stroke (Mant et al., 2004). In particular, the risk of having a stroke is especially elevated in the few days (estimated to be up to 10% at 7 days) following TIA (Giles and Rothwell, 2007a). However, stroke is increasingly a preventable disease and treatments exist to prevent recurrent stroke in populations who have had TIA.

General Practitioners play a key role in the management of TIA. Often, they will be the first point of contact for patients seeking health care following an event, so being able to identify TIA correctly ensures that patients are managed appropriately. Guidance suggests that GPs can prescribe low-dose aspirin but the main recommendation is for urgent referral to a specialist TIA clinic for assessment and recommendations for treatment (Lasserson, 2013). This thesis explores the role of GPs in the management of TIA, and considers whether the current model by which patients are identified and treated is optimal. The economic perspective is instructive in deciding what is optimal.

Economic perspective

Population growth and pharmaceutical innovation has meant that more people are living longer and expect greater and higher quality care from their health care providers. Yet the budget for health care (funded in the UK by central taxation) is finite. In the face of resource scarcity and increased demand the economic perspective provides a possible solution for identifying the most efficient use of resource.

1.3. Thesis structure

Chapter 2 details the Current approach to stroke prevention in the UK, including the role of the GP in the management of TIA.

Chapter 3 considers the economic impact of stroke and its management. This chapter presents an analytical framework for determining the most efficient model of service delivery.

Chapter 4 provides a critical review of economic modelling studies in the disease area. An overview of the modelling methods used in each of the papers is provided in order to inform the structure and development of the decision model to be developed.

Chapter 5 begins by presenting the aims and objectives of the thesis. It then presents the methods for structuring and populating the decision model.

Chapter 6 is a narrative review of the diagnostic accuracy of GP diagnosis in TIA.

Chapter 7 reports the results from the decision model.

Chapter 8 provides discussion of this thesis' contributions, limitations and recommendations to future research.

Concluding thoughts are presented in **Chapter 9**.

CHAPTER 2: CURRENT APPROACHES TO STROKE PREVENTION IN THE UK

2.1. Introduction

Stroke is a major cause of both mortality (about one-third of patients do not survive) and morbidity in the UK, accounting for about 11% of all deaths in England and Wales, and costing the NHS in England about £2.8 billion per year in direct care costs (Mant et al., 2004). However, stroke is increasingly a preventable disease and treatments exist to prevent recurrent stroke in populations who have had Transient Ischaemic Attack (TIA) (sometimes referred to as a 'mini' stroke) and minor stroke. A number of European studies recently have reported substantial reductions in stroke recurrence following the introduction of rapid access clinics for assessing and treating patients with TIA and minor stroke.

It is known that many strokes are preceded by TIA, and as such TIA is often cited as an 'early warning signal' for stroke (Rothwell et al., 2007). In particular the risk of having a stroke is especially elevated in the few days (estimated to be up to 10% at 7 days) following TIA. As such, optimal prevention requires early initiation of treatment. In the UK, guidelines published by the Department of Health in The National Stroke Strategy and NICE suggest that patients with suspected TIA assessed as 'high risk' should be seen by a specialist within 24 hours of presenting symptoms in primary care (Department of Health, December 2007, NICE, 2008). However, in terms of current practice, there is little to suggest such targets are close to being attained. For instance recent audit of acute TIA

and minor stroke services found that the best stroke centres still take longer than 24 hours to assess patients (Royal College of Physicians London).

The gulf between the aspirations of guidelines and the results from audit suggest that current service delivery as sub-optimal. There are two non mutually exclusive explanations. First, the apparently sub-optimal result may arise from underfunding of acute TIA services by the NHS. This is supported by a recent, empirically based study identifying the under-estimation of demand for TIA services in the UK NHS. Giles and Rothwell (2007b) identify a systematic shortfall in the Department of Health's forecasting of demand for TIA services arising from the use of incident-definite TIA rather than TIA. In the second case, the model[2] of service delivery may, in itself, be wrong. This would be true if changing the service delivery model could lead to more optimal management of TIA patients. This possibility provides the unique focus for the thesis (stated below).

The focus of this thesis is to evaluate alternative models of service delivery in TIA for patients presenting in primary care. The primary objective of this chapter is to describe Transient Ischaemic Attack (TIA) and its impact in terms of clinical sequelae. The chapter will also summarise the evidence of what is current best practice and associated care pathways used to manage and treat suspected TIA in the UK NHS. This information will be used to inform the structure of an economic model to evaluate the incremental costs and

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[2] N.B. Here the term 'model' refers to the medical management and care of the TIA patients from point of presentation through to follow-up.

benefits of GP initiation of treatment following suspected TIA compared with current best practice (see Chapter 5 for methods relating to the economic model).

2.2. Definitions of Transient Ischaemic Attack

During the writing of this thesis, the definition of TIA changed. The definition of a Transient Ischaemic Attack according to the AHA/ASA definition that is now accepted is:

> 'Transient ischemic attack (TIA): a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction' (Easton et al., 2009).

This tissue based definition of TIA replaced a time based definition:

> 'An acute loss of focal neurological symptoms lasting less than 24 hours' (Matthews et al., 2004).

Previously the time period was chosen to reflect the reversibility of damage, and was set arbitrarily. The technical advances in brain imaging meant that the reliability of the 24 hour rule was questioned, as many TIAs were revealed to have infarcts on scans. The new definition reflects the underlying pathophysiology of TIA as a milder event.

The key distinction between TIA (also sometimes called a 'mini stroke') and a minor stroke is now rests on whether there is damage to the tissue within the brain, which can only be known once the patient has a completed clinical work-up that is likely to include some form of neuro-imaging. Therefore, the time-based WHO definition might more accurately reflect the population presenting in Primary Care who have resolved symptoms. Strictly speaking the population for this thesis' intervention will therefore include some resolved minor stroke, which is akin to the time-based WHO definition. TIA and stroke

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can result in an array of different symptoms including: motor impairment on one or both sides (such as lack of coordination and/or limited ability to make learned purposeful movements despite having the physical ability to do so); speech impairment; visual disturbances; other sensory and cognitive problems (for instance, confusion); dizziness; difficulty swallowing; impaired consciousness and seizures (Mant et al., 2004). The management of TIA and stroke is the same in terms of secondary prevention.

2.3. Types of Stroke

There are a number of different types of stroke that are defined, using the ICD10 coding system in terms of the underlying pathology. Understanding the pathological sub-type of stroke is important because it influences the choice of secondary prevention and management of stroke in the acute phase.

Ischaemic stroke is the most common type of stroke, occurring in 85% of stroke cases. A correctly diagnosed TIA is generally a potential precursor of an ischaemic stroke. This type of stroke is caused when the blood flow to the brain is disrupted due to a thrombus (clot) formed either at the site (thrombotic stroke) or which has travelled from another part of the circulation (embolic stroke). The thrombus occludes (blocks) the artery, which causes the brain cells to be starved of oxygen, causing cerebral ischaemia. This may cause the cells in the surrounding area to die and result in 'an infarct' (a macroscopic area of damaged tissue). This infarct is sometimes visible if/when brain imaging is done at a later stage.

Another type of stroke is a haemorrhagic stroke, which occurs when there is bleeding from one of the arteries in the brain into the tissue in the brain. The artery bursts usually because of arterial disease. This can result in a haematoma (pooling of blood). It would be unusual, but not impossible, for a haemorrhagic stroke to present in primary care as a TIA (TIA steering group, 2008).

Sub-arachnoid haemorrhage (SAH) is a sub-type of haemorrhagic stroke, which can arise either spontaneously because of underlying arterial disease or physical abnormality in the artery, or, as a result of a traumatic brain injury. In a SAH there is arterial bleeding into the subarachnoid space between the two meninges (membrane) known as pia mater and arachnoidea. Essentially this means that there is bleeding into the skull rather than within the brain, which means that SAH is usually considered as a distinct entity from stroke, but a SAH may lead on to clinical stroke. SAH typically has a sudden presentation, which often includes a severe headache and impaired consciousness. This type of presentation means that in practice such a person, if they were to present in primary care, would not be considered as presenting with a possible TIA.

There is a further category of patients referred to as stroke or TIA 'mimics' because immediate symptoms suggest they have experienced a stroke or TIA but subsequent evaluation indicates they actually have non-stroke pathology.

2.4. Diagnosis of TIA and minor Stroke

The focus of this section is on the diagnosis of TIA or resolved minor stroke.

There is no 'gold standard' clinical test that can be used to diagnose a TIA or stroke. The diagnosis is based on the assessment of symptoms and 'adequate' investigation by a clinician. To be diagnosed as having experienced a TIA stroke a patient must have experienced at least one of the symptoms listed in Table 1. Other symptoms sometimes accompanying those listed in Table 1 include: dizziness, vertigo, localized headache, blurred vision of both eyes, diplopia (double vision), dysarthria (slurred speech), Impaired cognitive function (including confusion), Impaired consciousness, Seizures, Dysphagia (difficulty swallowing) (World Health Organization, 2006).

In Primary Care, the lack of a gold standard test means that the diagnosis of TIA and minor stroke in primary care largely depends on the clinician's judgement as to whether the patient's symptoms are consistent with TIA or minor stroke. Projections[3] from annual stroke incidence figures suggest that a GP may only see 1 or 2 TIAs a year so they have limited experience by which to make their judgment (Rothwell et al., 2004a).

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[3] Based on a standardised community incidence of first-ever stroke of 0.58 per 1,000 patients and assuming a GP has an average patient list size of 2,000.

Table 1: Symptoms to inform the diagnosis of TIA (Mant et al., 2004)

Unilateral or bilateral motor impairment (including lack of coordination),

Unilateral or bilateral sensory impairment,

Aphasia/dysphasia (non-fluent speech),

Hemianopia (half-sided impairment of visual fields),

Forced gaze (conjugate deviation),

Apraxia of acute onset (inability to carry out learned purposeful movements),

Ataxia of acute onset (lack of coordination of muscle movement),

Perception deficit of acute onset

In practice, doctors in primary care and A&E may be less well trained compared with specialists in how to correctly recognise TIA/stroke symptoms and make appropriate subsequent referral. Some evidence suggests that the ratio of genuine TIA (true positive) to TIA mimic (false positive) referrals from primary care may be in the region of 1:1 (Lasserson, 2013). This translates to a greater demand for rapid access clinics than that implied by forecasts based on incident-definite TIA. This is well illustrated by findings from the most comprehensive study of incidence of TIA or first-ever minor stroke was the Oxford Vascular Study (OXVASC). This was a population-based study of some 91 106 individuals (registered at 9 general medical practices in Oxfordshire, UK) of any age experiencing acute vascular events in all arterial territories (but excluding sub-arachnoid haemorrhage) with near complete case ascertainment. The resulting crude annual incidence rate (95% CI) standardised for the 2005 population of England for all probable and definite stroke was 2.13 per thousand population (1.94-2.31), while the corresponding value for all

probable and definite TIA was approximately half of this 1.08 (0.95-1.21). Interestingly, incident-definite TIA amounted to just 0.54 (0.44-0.63) (Giles and Rothwell, 2007b).

2.5. Clinical sequelae

The comparative brevity of symptoms in TIA means that the majority of patients make a quick recovery within hours (and possibly minutes) of the event. The WHO definition of a TIA means that all patients will experience resolution within 24 hours. In contrast, a stroke may but *does not necessarily* result in lasting disability. In reality, as opposed to theoretically, the severity of stroke spans a continuum and the 24-hour threshold is arbitrary. A stroke tends to be defined in terms of the clinical sequelae and impact on a person's ability to perform usual activities and function independently. A more minor stroke has less impact on disability. The Rankin scale is used as a disability index used to formally define stroke severity (see Table 2). The Rankin scale has a scale from 0 (perfect health) to 6 (representing death). A score of 0 or 1 is usually be defined as a minor stroke.

Table 2: The Rankin Scale

Score	Symptoms
0	No symptoms
1	No significant disability. Able to carry out all usual activities, despite some symptoms.
2	Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
3	Moderate disability. Requires some help, but able to walk unassisted.
4	Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
5	Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
6	Dead.

The following section considers the current management of patients presenting with TIA symptoms. This includes predisposing risk factors for TIA. Subsequently, risk modifying interventions are considered and the evidence base to support their use. Finally existing approaches to the management of stroke are considered with a description of current practice in the UK.

2.6. Predisposing risk factors

There are two key reasons why it is important to identify the predisposing risk factors for stroke: policy and patient-level. At policy level, the relative contribution of each risk factor

to the overall burden of stroke can inform stroke prevention initiatives (Mant et al., 2004). Secondly, at patient-level it enables a tailored plan of clinical care to be developed by the appropriate healthcare professionals which addresses the essentially multi-factorial nature of the disease. While some risk factors are modifiable by lifestyle changes alone, others may require treatment or a combination of the two. There may also be a genetic predisposition to certain risk factors.

Table 3: Predisposing Risk factors for Stroke and evidence

Category	Risk factors	Evidence
Modifiable	Lifestyle (Diet, Exercise, Smoking, Heavy alcohol consumption)	There is strong evidence that smoking is an important independent risk factor for stroke, and some evidence that physical inactivity and excessive alcohol consumption can raise the risk (Mant et al., 2004).
	Hypertension (Elevated blood pressure)	There is strong evidence that hypertension is an important independent risk factor for stroke, and that lowering blood pressure confers a reduction in the risk of cardiovascular events. (Kjeldsen et al., 1998, Staessen and Wang, 2001) HOT, (UKPDS 1998). There is also a growing body of evidence that lowering blood pressure in populations who are not hypertensive but at risk of stroke is beneficial (Bilous, 1999, Law et al., 2009).
	Diabetes	There is established evidence that the diabetes is an independent risk factor for stroke (Johnston et al., 2000).
	Atrial Fibrillation (AF)	This is a clinical condition causing cardiac arrhythmia or "irregular heart beat", present in approximately 5% of the population over 65). The presence of Atrial

Category	Risk factors	Evidence
		Fibrillation has a strong association with elevated stroke risk, and in most cases can be treated effectively with anticoagulants.
	Carotid Artery Stenosis, Ischaemic Heart Disease)	Carotid artery stenosis occurs when the carotid arteries narrow due to the formation of artherosclerotic plaque. The need for surgery can be identified from carotid imaging (usually Doppler ultrasound), where the degree of narrowing can then be measured according to a standardised criteria such as used by the European Carotid Surgery Triallists' study group, (hereafter referred to as ECST criteria). Typically, the decision to operate can be taken if the degree of stenosis (narrowing) is above or equal to a certain percent value – for the more commonly used ECST measure, this is usually 70%. There is strong evidence to suggest that patients with severe carotid artery stenosis have a heightened risk of stroke. One study found that a sub-group of patients with severe stenosis (ECST 60-99%) experience a doubling of stroke risk (ECST 1998).
	High Cholesterol	At present there is little epidemiological evidence to suggest that high cholesterol is an important independent risk factor for stroke, but evidence from randomised controlled trials suggest that treatment with cholesterol lowering drugs (statins) does reduce the risk of major vascular events including all stroke (Mant et al.,

Category	Risk factors	Evidence
		2004).
Non-modifiable	Age	As can be seen from the age and gender specific incidence table below there is a clear trend towards higher event rates in older age groups. Males and females do not face equal risks either. Males generally have lower event rates of TIA mimic and genuine TIA, and higher rates of major stroke up to the age of 75.
	Sex	In addition there is some difference in the pathological causes of stroke experienced by the sexes. The Oxford Vascular study found that males have a higher relative event rate of ischaemic stroke and intracerebral haemorrhage but a lower rate of sub-arachnoid haemorrhage (Rothwell et al., 2004a).
	Ethnicity	Certain populations may be at higher risk of stroke, and evidence suggests that West African and Carribbean populations are most at risk, with South Asian, Irish and Scottish populations also at heightened risk.
	Deprivation	There is evidence that economic deprivation or socio-economic factors at childhood are correlated with higher stroke risk (Mant et al., 2004). This may explain regional variation in observed UK stroke rates.

Clinical features and duration of symptoms (when the patient has had an index TIA or stroke)

There is some evidence that patients whose symptoms include unilateral weakness or speech impairment are at higher risk of recurrence, as are patients whose symptoms last longer.

2.7. Assessing patient risk - ABCD2 score

Another way this risk can be assessed by a health service professional is via the use of a prognostic instrument such as the ABCD2 score (Johnston et al., 2007). Validated in several independent cohorts (Oxfordshire and California) the risk is a point score whose calculation depends on the sum of several of the risk factors which enter it additively. Together, presence of these features are strongly predictive of the risk of recurrence following TIA/minor stroke. Summing to give a total between 0 (lowest risk) and 7 (highest risk) the score is calculated as follows:

Age ≥ 60, 1 point

Blood pressure $\geq 140/90$ mmHg, 1 point

Clinical features: unilateral weakness, 2 points; speech impairment without weakness 1 point.

Duration of symptoms: ≥ 60 mins, 2 points; 10-59 mins, 1 point

Diabetes, 1 point

2.8. Secondary prevention of TIA

These measures relate particularly to strokes and TIA which are identified, or strongly suspected to be ischaemic in nature (which as previously identified is the majority of all strokes). The clinical management of haemorrhagic stroke is somewhat different and beyond the scope of the policy area of this thesis.

The summary table below (Table 4) shows the agents commonly used in the secondary prevention of stroke.

Table 4: Rationale for secondary preventive treatment agents

Drug	Used to:
Aspirin	Secondary prevention of <u>ischaemic</u> stroke/TIA, usually as a loading dose of 300mg daily.
Dipyridamole	Secondary prevention of <u>ischaemic</u> stroke/TIA.
Clopidogrel monotherapy	Secondary prevention of <u>ischaemic</u> stroke/TIA as alternative to aspirin particularly when the heart is thought to be the cause of embolism.
Anti-hypertensives (thiazide diuretic, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin-II receptor antagonists (AIIRAs), calcium channel blockers (CCBs), Beta blockers)	Control blood pressure levels in patients suffering from hypertension. Selection of anti-hypertensive class of drugs depends on individual patient factors (e.g. comorbidites such as Ischaemic heart disease, ethnic origin), tolerability and cost.
Statins	Reduce lipid levels, control hypercholesteremia.
Anti-coagulant	Prevent cardiac embolism in patients with Atrial Fibrillation.
Lifestyle advice	Identify what the patient can do to reduce risk of a subsequent event, for instance by measures aimed at smoking cessation, diet and alcohol approaches, exercise and relaxation.

2.9. Evidence for Secondary Prevention

The objective of this section is to identify and appraise the evidence relating to the individual treatment effect in terms of risk of a recurrent stroke outcome.

This involved a search for Medline original research and the following terms "secondary prevention" "recurrent stroke" "TIA". A more focussed search using the previous terms in conjunction with one of the following: "aspirin" "antiplatelet" "antihypertensive" "statin" "anticoagulation" "carotid endarterectomy". In addition, the population had to include either TIA and/ or minor stroke i.e. patients had to be candidates for secondary prevention. When more than one study existed, more weight was given to studies conducted in, or including UK populations. Studies had to be published within the last 10 years i.e. January 2000 onwards.

In spite of a rich evidence base in this area RCT evidence is lacking in the acute phase of TIA/stroke with many studies recruiting patients up to six months after the event. With the exception of the FASTER (Kennedy et al., 2007) study, no Randomised Control Trial to date has enrolled patients within 24 hours of symptoms suggestive of TIA which means that many patients may experience a subsequent event and/or die before they can be recruited into a trial (Kennedy et al., 2007). However, given the positive results from observational studies in secondary stroke prevention with a focus on early assessment and treatment, it may be that the evidence of effectiveness of these drugs from 'non acute' trials is of some relevance to this area (Giles and Rothwell, 2007a).

Evidence for Aspirin Monotherapy

Since it is both cheap, safe and has some early demonstrable efficacy aspirin is the most commonly prescribed agent following TIA/minor stroke. In one study conducted by the Antithrombotic Trialists' Collaboration (Antithrombotic Trialists' Collaboration, 2002) the percentage odds reduction in patients with previous stroke/transient ischeamic attack (SE) was 22% (4) in patients with a mean 29 months of treatment.

Evidence for Rapid Treatment with dual Antiplatelets

The European Stroke Prevention Study 2 (ESPS-2) used a 2x2 factorial design which investigated the possibility of an interaction between dipyridamole and aspirin, as well as in usage as single agents (Diener et al., 1996). While the entry criteria to the trial – TIA or ischaemic stroke 3 months prior to study entry – does not allow for easy comparison with the decision problem here, the study does demonstrate the significant efficacy of aspirin – dipyridamole in combination vs. aspirin alone in the primary outcome of stroke (RR 0.76; 95% CI: 0.63-0.93). However, there was no significant efficacy for the composite outcome of stroke and/or death (RR 0.87; 95% CI:0.75-1.00).

The European/Australasian Stroke Prevention in Reversible Ischeamia Trial (ESPRIT) found some evidence to favour dual therapy as compared to mono-therapy in patients who had a previous TIA or minor stroke up to six months previously (De Schryver et al., 1999). They report evidence of significant efficacy in the primary composite outcome of all vascular death, non fatal stroke, non fatal MI and bleeding complications (HR 0.80; 95% CI:0.66-0.98). However, while the point estimate appeared to favour the addition of

dipyridamole to aspirin for the outcome of first ischeamic stroke, the confidence intervals were too wide to establish significance (HR 0.84; 95% CI: 0.64-1.10).

The Fast assessment of stroke and transient ischaemic attack to prevent early recurrence (FASTER) study found evidence to support significant efficacy in clopidogrel vs aspirin in the outcome of stroke, and unlike the RCTs comparing aspirin-dipyridamole, the study population was recruited within 24h of symptom onset (RR 0.70; 95% CI: 0.3-1.2) (Kennedy et al., 2007). A more recent RCT in first recurrent stroke - PRoFESS demonstrated similar rates of recurrent stroke with aspirin–dipyridamole to clopidogrel and no evidence of superiority in either treatment arm (Diener et al., 2008). Date of randomisation was less than 90 days post ischemic stroke.

Evidence for Rapid Treatment with Statins

There is some evidence for the use of cholesterol lowering treatments (statins) in the prevention of major vascular events. However there is little data showing evidence of a clinically significant risk reduction in the acute phase following TIA/minor stroke. One such trial which does look at early initiation in the 90 day follow up period following ischaemic events was too small and so underpowered to detect a clinically significant risk reduction (Kennedy et al., 2007). In the absence, to date, of a clinical trial in the same population in the acute phase of illness which uses a protocol that enables the statin treatment effect to be distinguished from that of other drugs the best evidence comes from meta-analyses of randomised controlled trials not carried out in the acute phase. For instance, the Cholestrol Treatment Trialists' Collaboration identified an overall RR of 0.79 (95% CI 0.77-.81) per 0.001 per mmol/LDL cholesterol reduction in first major vascular

events. In addition, using the same cholesterol reduction, the RR for overall first stroke was 0.83 (95% CI: 0.78-.88) (Baigent et al., 2005).

A recent systematic review commissioned by the NHS HTA programme found that statins are associated with a significant reduction in the risk of non fatal stroke but not fatal strokes (Ward et al., 2007). In addition, in types of study which did distinguish between ischaemic and haemorrhagic stroke, it found that a significant reduction in the former. Evidence that statins may increase the risk of haemorrhagic stroke (fatal and non fatal) was not proven.

Evidence for Rapid Treatment with Antihypertensives

Results from the PROGRESS study identify the benefits of blood pressure lowering (Chalmers, 2003). The interesting result was that following stroke, blood pressure lowering reduces subsequent stroke risk irrespective of whether blood pressure was controlled or uncontrolled; the implication of this being that further lowering of blood pressure may be advisable in all patients with a history of stroke. The circa 28% reduction in stroke risk in both these studies applies to a stroke, not TIA population. However, it seems conceivable that blood pressure lowering is desirable. Recent guidance on the management of hypertension has identified the effectiveness of using a combination of antihypertensive drugs over single agents (Williams et al., 2004, NICE, 2011).

Evidence for carotid endarterectomy

The benefit of carotid endarterectomy largely depends on identifying degree of stenosis the surgical risks are outweighed by the risk of untreated carotid territory occlusion. In actual fact, this basic relationship is complicated by the fact that carotid imaging is not perfectly accurate. This is particularly of relevance if the level of stenosis is less severe than that suspected on inspection of the US scan or angiogram because the decision to operate will result in excess risk to the patient. Unlike the existence of dual antiplatelet therapy in acute stroke populations, carotid endarterectomy has been an area of active research, and the wealth of data which includes large multicentre international trials, HTA report and RCT evidence. Correspondingly, the results of these are reflected in the National Stroke Strategy and NICE guidelines which make recommendation for carotid endarterectomy to be carried out within 2 weeks of onset. However, in practice, the delay to receiving both assessment and surgery confer a less than favourable risk profile on the patient if surgery is indicated by the test alone (Rothwell et al., 2004b, Mehta et al., 2005).

2.10. Investigations commonly used to assess TIA symptoms

This section considers the standard investigations usually performed to confirm the diagnosis of stroke.

Predicting early stroke risk after TIA

Indeed, the ABCD2 score, now readily accepted as a recognised predictor of early recurrent stroke is to be used by practitioner's to identify high risk patients (ABCD2≥4)

presenting in primary care so that they can be treated urgently (Department of Health, December 2007).

There is also some evidence that certain risk factors are individually predictive of early recurrent stroke. In the acute phase of up to 30 days these may include: motor weakness and/or speech impairment lasting greater than 60 minutes as well as carotid artery stenosis ≥50%. For instance, Rothwell, Giles, Flossman et al. (2005) found that while motor weakness and speech disturbance attributed to just 30% of all suspected TIAs, they were responsible for 90% of the strokes occurring within 7 days.

Investigations commonly performed following suspected TIA/minor stroke (at the point of specialist referral)

Imaging is carried out to establish the type of stroke, and determine if carotid endarterectomy is likely to be effective in cases where surgical intervention is considered possible. The first-line test will usually be MRI to establish the type of stroke, plus Doppler ultrasound to assess the blood flow of the carotid arteries. Virtually all acute stroke units and rapid access clinics have such facilities, although access to them may be restricted by a shortage of slots or lack of staffing to provide a 24hr service. In cases where symptoms have resolved, brain imaging will only usually take place if there is uncertainty about the symptoms being of vascular origin – if a patient's clinical history is consistent with TIA there may be little benefit in scanning, and this may not be effective use of the resource. Carotid imaging meanwhile should always be carried out in the case when a vascular origin is definite, probable or possible – so long as the patient is a candidate for surgery. As is evidenced by the recommendations made by strategy (p.27) and evidence

(p.23) it is important that such imaging is timely. Finally, it should be noted that the accuracy of brain imaging techniques is not perfect; it depends on the skill of the radiographer or specialist stroke physician who interprets the test and the quality of the image produced.

Table 5: Imaging techniques commonly performed following TIA

Imaging technique/ Investigation	Used to:
Magnetic resonance imaging (MRI)	More accurate than a CT due to higher spatial resolution, used if there is uncertainty in diagnosis. Non-invasive procedure which produces a picture of the brain without the need for ionising radiation or iodine.
Carotid imaging of arteries around the throat	Used in the evaluation of TIA and stroke symptoms to identify if there is stenosis (narrowing) due to the formation/ulceration of artherosclerotic plaque in the carotid artery (usually more than 70% ECST criteria). Doppler ultrasound refers to a non invasive test which uses high frequency sound waves to determine the extent of blood flow through the carotid arteries in the neck. (National Audit Office, February 2010). Computed tomography and a from of MRI may be used to confirm the diagnosis and then to establish the degree of stenosis.
Computed tomography angiography (CT)	A technique that uses multiple x-ray beams and detectors moving around the brain which results in a two-dimensional cross sectional image. Typically this requires a contrast material being injected into a vein or artery using a needle or cannula. To determine if a stroke is ischaemic or haemorrhagic, minimally invasive.
Echocardiogram (ECG)	An echocardiogram (also known as an echo) uses sound waves that echo against structures in the heart to build up a detailed picture of the heart. This test is done to look at the structure of the heart and how well the heart functions. Used to detect AF , acute coronary syndrome or congestive heart failure (British Heart Foundation, 2013). Non-invasive.

2.11. Optimum management of TIA

This section outlines the guidance and recommendations made by NICE and the National Stroke strategy with regards to the delivery of services for TIA. In terms of the proposed management of TIA both sources share a number of common aspirations. Considered together, what emerges is NICE's/ the Department of Health's notion of a 'gold standard' for TIA service delivery. By way of contrast, this section also considers the management of TIA in practice. This is done by reference to the National Sentinel Stroke Audit (2012) and a recent key study evaluating UK TIA services.

Sentinel Stroke National Audit Programme (2012)

The National Sentinel Stroke Audit is prepared on behalf of the Intercollegiate Stroke Working Party (ICWP) by the Royal College of Physicians, London with a remit to evaluate the level of practice and service provision across the whole of the patient pathway (including rehabilitation services in the case of completed major stroke) in England, Wales and Northern Ireland. It is published every two years. A key aim of the audit is always to identify areas of progress since the previous (2010) audit 'against the National Clinical Guideline for Stroke'. . The key results with regards to organisational care in TIA reveal variation in practice across hospitals, so that overall progress compared to the recommendations of the National Clinical Guideline appear modest. For instance, just 36% of high risk patients (14% of low risk patients) are seen, assessed and treated on the same day, indicating sub-optimal use of resource.

National Stroke Strategy (2007)

In 2007, the Department of Health's development of a new National Strategy for Stroke has a 3-fold purpose: to be a quality framework for the management of stroke; to offer guidance to strategic health authorities about the planning of TIA and stroke services and to inform expectations of the general public.

Grounded in the evidence basis from which it emerges, the strategy's core message regarding the management of TIA is 'Time is brain'. Rapid referral, rapid imaging, rapid carotid endarterectomy where indicated (defined as an ECST grading of 70% or more) and immediate initiation of antiplatelet therapy are key features, as is the triaging of risk by ABCD2 score of 4 and above. The specific recommendations are described more fully in Table 6 below.

Table 6: National Stroke Strategy Guidelines

Guidelines following newly diagnosed TIA/minor stroke
Prevention Those at risk of stroke, or who have had a stroke/ TIA are assessed for are given advice about risk factors and lifestyle management. Clinical management to follow other guidelines such as those for hypertension, statins and diabetes
Rapid diagnosis and treatment rapid referral (within 24 hours) for patients at high risk of stroke ABCD2 ≥ 4 and urgent (≤ 7 days) for those with ABCD2<4 Loading dose of aspirin (300mg) (or other agents as evidence emerges which reinforce the findings of the EXPRESS study) (Rothwell et al., 2007).

Guidelines following newly diagnosed TIA/minor stroke

Specialist care - TIA and Stroke

Rapid MRI (incl. DWI) imaging (within 24 hours) in all patients seen acutely after TIA or minor stroke and in next scan slot (in working hours) or within an hour (out-of-hours).

Carotid imaging at initial assessment not more ≤24h for high risk ABCD ≥4.

Carotid endarterectomy within 48 hours where clinically indicated.

Follow up in primary or secondary care within a month of the event.

Specialist care - Suspected Stroke only

Patients with unresolved symptoms in the community to be directed to appropriate acute stroke unit or hospital providing hyper-acute stroke services by ambulance.

For patients with suspected stroke, immediate structured clinical assessment (e.g. using a tool such as ROSIER) followed by multidisciplinary assessment including a swallow screen, and identification of cognitive and perceptive problems if stroke is diagnosed.

While not intended as a clinical guideline and so there is little mention of risk modification via different agents (the strategy identifies this to be the remit of other organisations such as NICE), the strategy essentially identifies ideal and expedient management. The extent to which this is achievable may well vary on whether there is sufficient capacity to be able to respond to all suspected TIA and stroke in a timely way. Indeed, there is a clear gap between the desirability of carrying out carotid endarterectomy within 48 hours of symptoms and the observed typical delays in one Oxfordshire based study of 67 days (Mehta et al., 2007). Similarly, the mismatch between the desirability of policy on the one hand and limits on service capacity on the other are perhaps most likely to be evidenced by future audit of ambulance utilisation and stokes prevented due to thrombolysis.

In summary it is evident that the National Stroke Strategy, 2007 is strongly allied to the research question of the thesis as a whole in that it takes as its core the question of what needs to be done to optimally manage TIA/ minor stroke. However, it does not state how to deal with the broader service delivery problem. The 'evaluation of different models of access to TIA services in different settings, e.g. direct access to daily clinics in secondary care versus immediate assessment and management in primary care with onward referral to secondary care', it mandates, is one of the top ten priorities for stroke services research (National Stroke Strategy, 2007 p.65).

Clinical guidelines, NICE (2008, 2010), SIGN (2008)

The NICE guidelines (2008) for TIA and acute stroke (developed by the National Collaborating Centre for Chronic Conditions) supplements and reinforces the guidance from the National Stroke Strategy. In particular, the recommendations are as per the National Stroke Strategy with regards to initiation of aspirin at 300mg daily and rapid referral for those patients with an ABCD2 of four or above, and weekly for those with lower scores or presenting late. Where the guidance makes specific recommendation regarding clinical management that is slightly different from the National Stroke Strategy, they are outlined below:

i. Crescendo TIA

The guideline makes a special point about "crescendo TIA", which it defines as 2 or more TIAs in one week as being especially predictive of further stroke, and states that it should be treated within 24hours, even if ABCD2 is less than four.

ii. Timelines for CE surgery

The aim for carotid endarterectomy was for assessment within 1 week (if the patient is a candidate for surgery) and for surgery, if indicated within 2 weeks of the onset of symptoms.

iii. Ambulance transfer in cases of suspected stroke

There is no express recommendation that transfer to hospital needs to be by ambulance where stroke is suspected in the community, however, there is a recommendation for direct admission to an acute stroke unit.

In addition, the document reinforces the National Stroke Strategy on brain imaging (next slot and definitely within 1 hour, in this case *whichever is sooner*). However, it emphasises that this needs to be only done where there is uncertainty about the diagnoses of ischaemic stroke (e.g. indications for thrombolysis, on anticoagulants, a depressed level of consciousness, possible indications for haemorrhagic stroke, or other diagnoses such as tumour and migraine).

More recently, the publication of NICE quality standards in stroke "QS2" have heralded a potential way forward in terms of optimising the management of patients at key points in the care pathway (Stokes, 2013). The current list of statements (standards) is slightly more focused on the need for rapid assessment of unresolved neurological symptoms presenting in the community (which may be treated as potential strokes) as opposed to resolved transient neurological attacks which are the focus of this thesis (NICE, 2010). To date, quality standards have particularly emphasised key points on the stroke care pathway. Relevant to this thesis' population is statement 1 which covers the prompt identification of

suspected stroke in the community by the use of a validated screening tool (e.g. FAST, ROSIER).

Guidelines produced by SIGN for the management of acute stroke and TIA in Scotland are similar to the NICE guidance in most respects (SIGN Scottish Intercollegiate Guidelines Network, 2008). However the Scottish guidelines make a recommendation for the initiation of dual antiplatelet therapy (aspirin-dipyridamole) following suspected TIA. In this respect, the Scottish guidance appears to reflect the favourable evidence for dual antiplatelets above aspirin alone.

Guidelines into practice - Resource implications

Whilst there has recently been a growing consensus of evidence reflected in the above guidelines that best practice necessarily demands rapid assessment and treatment, less attention has been paid to how services should be organised to achieve this aim. However, the development of NICE quality standards may herald a means of measuring the extent to which guidelines has been successfully implemented in a measurable way.

While it is perhaps too early to assess the contribution of quality standards, the failure of current practice to meet the aspirations of guidance are demonstrated by findings documented by that of the National Sentinel Stroke Audit (2012) which identifies a median time from event to assessment of 2 days. (Stokes, 2013) Furthermore, the same audit identifies that close to 63% of the TIA clinics audited did not have a same-day rapid access clinics in operation.

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In addition, the demand for rapid access services is another unknown. Giles and Rothwell (2007) note that the use of incidence measures arising from the Oxford Community Stroke Project results in a serious underestimation of the actual numbers of referrals because the service will be the first point of call for TIA mimics, those suffering non disabling stroke and recurrent (in addition to incident) TIA. Such projections utilised by the Department of Health must therefore be interpreted cautiously – their usage of incident definite alone might only capture circa 18% of all referrals to outpatient services.

As a result, Giles and Rothwell (2007) conducted a population based retrospective study of all TIA, stroke and suspected stroke events occurring in the Oxford vascular study cohort between 2002 and 2005 stratified by in-patient and out–patient services. Based on their findings, they estimate a need for clinics in England to cater for some 150,000 referrals.

2.12. Description of current practice

The objective of this section is to describe current practice in TIA service delivery including the associated care pathways in the UK NHS. The identification of current practice is important because it has implications for the selection and justification of a comparator for the economic model considered later. In addition it helps the formulation of the specific research aim and objectives of the thesis.

In describing current practice, the potential for variation (both in terms of process and clinical outcomes) across different parts of the NHS is considered. This may arise due to restrictions in service capacity (due to the finite budget for healthcare) and/or inefficiencies in service delivery, subjects considered in Chapter 3. Both factors result in a

divergence between the aspirations set out by the National Stroke Strategy and Department of Health documented previously and observed clinical practice. This is most notably the case in respect to process outcomes that are collected routinely from TIA clinics as part of the Quality and Outcomes Framework (QOF) and National Audit. A prominent example of the divergence between best and current practices is evidenced by the delay to timely investigation and treatment; in 2007, nationwide audit reported a median delay to treatment in TIA of 40 days from onset of symptoms compared with 1 day in the very best stroke centres (Rothwell et al., 2007).

In order to characterise current practice, a review of recent evidence on existing approaches to the management of suspected TIA was necessary. Table 7 summarises the evidence found. Evidence was identified through a variety of methods, including internet searches for clinical guidelines, audits and summary data.

Table 7: Summary table of evidence

Title	Author(s)	Study Type	Purpose
National Stroke Strategy, 2007: A new ambition for stroke	(Department of Health, December 2007)	Strategy document	To provide a quality framework for local services. To provide guidance to healthcare professionals. To inform the patient expectation of health and social care with regards to Stroke.
NICE guideline 2007	(NICE, 2008)	Clinical guideline (CG38)	To provide guidance to healthcare professionals.
What is the optimal model of service delivery in TIA and minor stroke? 2007	(Mant, 2008)	Mathematical modelling study	To determine the clinical and cost-effectiveness of different strategies prepared on behalf of the National Collaborating Centre for Service Delivery and Organisation (Birmingham TIA model).

Title	Author(s)	Study Type	Purpose
A transient ischaemic attack clinic with round-the-clock access (SOS-TIA): feasibility and effects	(Lavallee et al., 2007)	Observational (non UK-France): prospective cohort	To identify the stroke risk following the introduction of 24-h access hospital clinics for patients with suspected or identified causes of TIA.
Effect of urgent treatment of transient ischaemic attack and minor stroke on early recurrent stroke (EXPRESS study) 2007	(Rothwell et al., 2007).	Observational: prospective population-based sequential comparison conducted in two phases, (Apr 1, 2002 to Sept 30, 2004 and Oct 1, 2004 to March 31, 2007)	To determine the effect of more rapid treatment after TIA and minor stroke in patients not admitted to hospital.

Table 8: Relating process of care and clinical outcomes to policy

Study	Process of care components described	Primary outcome	Key policy implication(s)
EXPRESS (Rothwell et al., 2007)	• Delay to first call to medical attention from index event subsequent delay to assessment in study clinic. • Proportion of patients on different forms of secondary preventive medications and time to carotid surgery all assessed at 1 month follow-up.	Stroke rate at 90 days. Early initiation of treatment is associated with an 80% relative risk reduction in recurrent stroke compared to the 'before' phase of the study.	Long delays to assessment in TIA clinics are not acceptable; initiation of secondary preventive treatments needs to take place in secondary care if they have not been initiated in primary care; and preferably in as soon as patients seek medical attention (with the exception of dual antiplatelets) following recent TIA.

Study	Process of care components described	Primary outcome	Key policy implication(s)
SOS-TIA (Lavallee et al., 2007)	• Time to assessment following telephone call to TIA clinic. Number of admissions to an inpatient stroke unit and subsequent length of stay. • Proportion of patients undergoing different types of imaging. • Proportion of patients on different forms of secondary preventive medications prescribed.	Stroke rate at 90 days. Early initiation of treatment is associated with an 80% relative risk reduction in recurrent stroke compared to those rates predicted by ABCD2 scores.	The implementation of TIA clinics with 24 hour access to assessment, diagnosis and initiation of treatment might have implications in terms of reduced hospital stay and subsequent risk of stroke.

Table 9: Other studies

Title (Author/Year)	Main process of care attributes reported	Key policy implication
What is the optimal model of service delivery in TIA and minor stroke? (Mant, 2008)	• Clinic frequency • Clinic setting i.e.dedicated TIA clinics versus TIA clinics nested within other services with flexible resources. • Use of ambulance transfer .	Implications for service delivery, patient and GP education: The recommendations for policy identified by the report extend to the configuration of rapid access clinics, in-patient admission and the use of emergency services. The key result is that clinics should ideally allow for same day referral (Monday-Friday). If capacity is limited, an ABCD2 score of 4 may be applied, however, if capacity is more restricted than this it is cost-effective to refer at the higher thresholds.

2.13. Discussion

The purpose of this chapter was to review current approaches to stroke prevention following TIA in the UK. This documented the usual approach for the management of a suspected (and resolved) TIA patient presenting in Primary Care.

First of all the diagnosis, prognosis and options for risk modification (including treatment) of TIA was described. Where TIA is suspected by a GP, following consideration of the patient's ABCD2 risk score (ABCD2≥4), high risk patients may be fast tracked to a specialist for an assessment within 24 hours of the index consultation. Patients with lower risk scores should still be seen within one week. In terms of how the delivery of the service is arranged, the GP is responsible for making referral to a specialist stroke service and it is the specialist who initiates treatment. Providing there is no known contra-indication at this stage, this is normally dual antiplatelets (in addition to statins and antihypertensive as necessary).

A notable finding was that while the general approach to managing patients appears fairly standardized, there is nevertheless considerable variation across the UK in terms of some of the process of care measures collated by national audit. A striking example of this is the variation in terms of the timeliness of treatment within different service settings where median times varied from 1 to 28 days (Royal College of Physicians London, 2012). Although causality between expedient treatment and stroke outcomes is established, no primary research has suceeded in investigating the potential for same day initiation of optimal secondary prevention. A planned pilot trial, RAPID-TIA, recently failed to recruit suggesting that primary research in this area is impracticable (Mant, December 2012).

CHAPTER 3: THE ECONOMIC IMPACT OF STROKE AND ITS MANAGEMENT

3.1. Introduction

The objective of this chapter is to describe the economic impact of stroke and its management. The chapter begins by describing the budget impact of stroke from different perspectives. It goes on to explain the importance of opportunity cost in the context of a finite healthcare budget and the need to understand the relative costs and benefits of management strategies for stroke with a focus on primary care. The framework for the design and conduct of economic evaluations together with the key approaches to designing economic evaluations are then described.

3.2. Economic impact of stroke

Stroke is one of the leading causes of mortality and morbidity in the UK. The financial burden of stroke can impact on the economy, the healthcare service and an individual who has had a stroke and their family members and carers. It is useful to consider different perspectives when describing the economic impact of stroke. The societal viewpoint considers the effect on the entire economy. In 2008, the National Audit Office estimated that stroke cost the British Economy to be £7bn. This figure includes direct costs of informal care and the indirect costs as a result of lost productivity resulting from potentially economically active members of society being unable to work. A major impact of stroke is the hidden cost of providing informal care for people suffering from the sequelae of a previous stroke. There are around 900,000 people living in England who

have had a stroke and approximately half of these will be dependent on others for performing their daily activities, which results in estimates of informal care costs of around £2.4 billion (National Audit Office, 2005). Stroke is not only experienced by older people. Around one quarter of all strokes occur in people of working age, with productivity losses resulting in annual indirect costs of £1.8 billion (National Audit Office, 2005).

It is estimated that major stroke costs in the region of £2.8bn in direct hospital care and accounts for almost 5% of all health service costs in the UK (Hankey, 2008, National Audit Office, 2005). The societal burden of stroke is higher, with one source estimating this at £8.9bn (Saka et al., 2009). Stroke has a larger financial burden on the NHS than heart disease (Rothwell, 2001).

It is also important to consider the economic burden on the individual whom has experienced a stroke. There are a number of potential costs to the individual. First of all, there is the direct cost for care and support if the stroke results in a disability that means they can not look after themselves or perform day-to-day tasks. Secondly, there may also be loss of earnings coupled with a rise in medical care costs resulting from prescription charges for medicines and travel costs to attend hospital and GP appointments. Stroke also has an impact on the family and friends of the person who has had a stroke. The family and friends are often the ones who provide informal care. Luengo-Fernandez et al. (2009a) estimated an average cost of stroke/TIA per patient of $22,377 US, approximately £15,700 (using the purchasing power parity exchange rate of £0.70 to 1 US$ (OECD, 2013)).

3.3. The budget for health care

The UK has a publicly funded healthcare system, funded in the most by centralised (UK) taxation, which is characterised by a system that is 'free at the point of use'. The total level of funding is therefore determined every year and set by government and civil servants. In 2012 the budget was £108.8bn (Department of Health, 2012).

Up to April 2013,the annual healthcare budget for England was distributed between 152 primary care trusts (PCTs) according to population and needs, (Department of Health, 2012). PCTs had authority for purchasing healthcare from independent providers to meet local need. Since April 2013, the PCTs have been replaced by the introduction of clinical commissioning groups (CCG) which has granted more powers to GP partners to commission the goods and services they want. Healthcare decisions in the rest of the UK (Scotland, N. Ireland and Wales) remain devolved and made at country level. Across the UK. while funding is not ring-fenced, there are requirements to provide certain treatments and services, as well as quality standards (including those relating to the management of stroke patients) to try and ensure equality of access. Notwithstanding these attempts, there is still regional variation in the patient experiences regionally and nationally.

The potential management options for stroke were previously described in Chapter 2.
These interventions for the treatment and management of stroke, particularly the use of antiplatelet medicines and antihypertensive medicines to control blood pressure, have resulted in a steady decline in mortality rates. However, such interventions and management options must be funded from a finite healthcare budget. This means that the allocation of NHS resources to treat and manage stroke diverts resources from other

healthcare treatments (for instance in heart disease, diabetes and cancer as well as less prevalent but expensive to treat diseases). Decision makers allocating healthcare resources have to make decisions about which interventions represent the most effective use of scarce resources.

In the context of stroke these decisions are whether to increase expenditures on (primary and secondary prevention) or on acute stroke unit care and rehabilitation.

Treatment versus prevention

It is estimated that one third of non-fatal strokes result in lasting disability, which imposes a significant burden to the NHS and broader economy. However, as Chapter 2 has evidenced, the sequelae of stroke could be prevented if patients with TIA were placed on appropriate secondary medications or if primary prevention measures were developed to detect and treat people with atherosclerosis or if public health measures improved healthy lifestyles in cohorts at risk of future stroke. With appropriate planning services could be set up to prevent stroke reducing the treatment burden.

3.4. Methods of economic evaluation

Opportunity cost is a concept that considers choices must be made in the context of a finite budget.

When resources are invested in a good or service, the opportunity cost is the benefit foregone of the next best alternative use. Within the context of health care, when resources are invested in one intervention, the opportunity cost of that choice is the intervention that

can not now be funded. The theory of opportunity cost is central to the understanding of efficiency in Economics as an efficient outcome is one that secures the most optimal use of resources.[4]

Economic evaluation is a framework for comparing the costs and consequences of a health care intervention (Drummond, 2005). A healthcare intervention can be a new drug, a new device or a new way of managing patients. Typically comparison is made across alternatives; nearly always this includes comparison against the existing use of resource.

There are different techniques of economic evaluation. The most commonly used within health technology assessment is that of *cost-effective analysis* (CEA). In CEA benefits are measured in natural units (e.g. units of effect, or life years) .A special subset of CEA is cost-utility analysis (CUA), which measures benefits (utility) using a summary index measure of health status. The majority of cost-utility studies measure benefits using quality-adjusted life-year (QALY).

Cost-effective analysis provides a decision maker with an estimate of the value for money of one intervention compared with other uses of the healthcare budget. On the assumption of a given available healthcare budget CEA provides a basis for maximising health gain

More precisely the cost effectiveness of an intervention, x, is usually stated in terms of the expected mean cost of achieving an additional unit of health benefit (either an outcome

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[4] Within this thesis I use efficien are used interchangeably.

based measure such as lives saved, strokes averted or an additional unit of utility). In Health Economics utility is normally the health benefit (or detriment in the case of a utility loss) that accrues to the patient who receives the intervention.

There are several standardised measures of health status; the most generic across different disease areas being the QALY (Briggs et al., 2006). A QALY or quality-adjusted life-year considers that life has two dimensions: length and quality of life. One way of thinking about this is to consider the value an extra year of life when quality of life is considered: one QALY will be equal to one year of life in excellent health, whereas 0.5 QALYs can be equal to half a year of life at full health or a year of life with an impaired quality of life, quantitatively half of that of 'full health'. In practice, the way in which QALYs are elicited and utilised is one area of *uncertainty* in the analytical methods used to perform CEA. For instance, in Economic Evalation, it is generally held that the quality of life weights should capture the preference for being in that health state, versus others. This means that QALYs should reflect the individual's or public's value for the attributes of health being measured (Neumann et al., 2000).

The ICER is defined as the: difference in costs/ difference in consequences. It is incremental because it considers the relative difference in costs (per measure of consequence) of option 1 vs. option 2. In the case where there are more than two options, the calculations are rolled out so that the ICER is calculated for every permissible pair of options. Notice that the calculation of the ICER does not make sense in the scenario where one option is said to 'dominate' another i.e. because it has lower costs and better or comparable efficacy than the alternative option.

3.5. Types of cost-effectiveness analyses

There are two main options when performing cost-effectiveness analyses: trial based economic or decision models.

Economic evaluations alongside randomised controlled trials

One vehicle for performing cost-effective analysis is the RCT. In these instances, the trial will be the single source of data for the comparative analysis of costs and consequences. Advantages of this method are that they provide a reliable estimate of cost-effectiveness within the trial and provide patient level data which may be useful for determining statistical relationships between events (Petrou and Gray, 2011). However, in circumstances where trials would be prohibitively expensive or unfeasible other options are needed. An alternative method, which synthesises evidence from a variety of sources, is to use a decision model.

Decision Models

A decision model is a representation of the world constructed to inform a decision. They are representations of the world, rather than scientific truth (Weinstein). More formally Sculpher et al (2006) see that decision models provide 'a structure within which evidence from a range of sources can be directed at a specific decision-problem (question) for a defined population and context'.

Decision modelling can be particularly useful in early economic evaluations where there is no data on the efficacy/safety of an intervention (Grutters, 2008). Another advantage is that they allow for testing of all alternatives (Sculpher et al., 2006).

Randomised control trials (RCTs) versus Decision Analytic models

There are a number of pros and cons of using RCTs evidence for the purposes of economic evaluation. The main advantage of RCTs is that they provide an unbiased estimate of the treatment effect. Furthermore, an economic evaluation based around a single RCT will be a consistent source of evidence, not only for providing an estimate of the treatment effect, but potentially for other parameters such as utilities and resource use (so long as this evidence was collected as per the trial protocol).

However, recently, there has been some dissent about the use of RCT evidence as the sole vehicle for decision making in economic evaluation (Shulpher et al. 2006). A key limitation of RCTs is concerned with the applicability of trial based analysis to the decision maker's setting. One reason for this is that there is a failure of RCT based economic evaluations to capture all the information that might be relevant to the decision maker. Whereas trials examine 'sub-sets' of relevant options, clinical practice is characterised by a 'range' of interventions that might be used in everyday practice in 'varying' degrees (Sculpher et al., 2006). This issue is particularly pertinent to the evaluation of the management of TIA patients where interventions are multifaceted. Other limitations with trials include the curtailed time horizon and an inadequate dealing with uncertainty.

Unlike trials, decision models have the ability to incorporate evidence from different sources. Since the decision model is an unconstrained framework, the model can more properly reflect reality, for instance by capturing all clinically relevant options. In addition, the model can capture the full information available to the decision make. The synthesis of evidence that this structure accommodates is desirable in that it does not rely on a single source of evidence. Providing that appropriate methods of evidence synthesis are used, the parameters used within the decision model should therefore be more robust.

The advantage of including all relevant parameters, using an appropriately structured decision model has a clear advantage in prospective (or pre-trial) modelling. In situations (including this thesis') where there is no option to use trial evidence, decision modelling may be of use in setting research priorities, specifically informing trial design. For instance, Sculpher et al. (2006) consider that pre-trial modelling can be used for a 'rough' estimation of cost-effectiveness of different alternatives, and to identify 'key' uncertainties in the model.

3.6. Models

A model is a simplified version of the real world which helps people make a better decision (Buxton et al., 1997). Within health care, there are many different types of mathematical or computer based models all of which make predictions for different purposes (e.g. capacity planning, management of hospital stock inventories, forecasting epidemics, mimicking disease progression). Models which estimate the effects of various choices are known as 'decision analytic models'. A basic type of decision analytic model

is the decision tree which postulates the outcome of a specific situation with specified choices and outcomes.

Decision trees

Perhaps the most common and basic type of model, the decision tree diagrammatically represents the probability and valuation (in terms of costs and QALYs) of various outcomes occurring (Brennan et al., 2006). It is a convention to represent decision trees diagrammatically with square nodes indicating a decision between particular strategies; circular nodes indicating points where two or more alternative outcomes are possible (Brennan et al., 2006). Particular characteristics of these model which become relevant in the later discussion of model selection are that the pathways followed by a particular patient is mutually exclusive; patients move along the tree from left to right and that the probabilities of an outcome occurring do not vary in a stochastic way.

Decision trees may not be the most elegant way of handling a situation where multiple events can occur either concomitantly or in a certain sequential order. Similarly the sequential moving of patients from left to right along the tree means that these models become laborious when the order in which events occur is not determined. (Related to this, these trees do not allow a looping back to earlier event states, so the representation can be encumbered by the number of nodes needed to represent possible outcomes). Finally, the lack of stochastic variation in outcomes means that this type of tree (unless this assumption is relaxed) assumes a homogeneous cohort of patients.

Therefore, other types of model are needed.

Markov models

Markov models are structured around mutually exclusive states rather than along patient pathways (Briggs et al., 2006). This potentially allows for a richer modelling of patient prognosis because a transition from one disease state to another may be modelled to reflect a change in disease progression. The Markov model also allows for a fuller representation of time because patient progression is measured in discrete time periods (cycles) which are usually of a fixed length. Normally, at the end of a cycle the patient may either move to another state (transition to a different state) or remain in the same state. The length of time that the patient is in each different disease state before becoming eligible for transition to another state therefore becomes an intrinsic part of the model, which is set by the modeller who should consider the nature of the disease.

A key limitation of using Markov models is that transitions to other states are mathematically independent of the length of time in state. They are therefore 'memoryless'. This means that they might not provide a realistic representation of disease history if the risk of relapse is non-constant over time or if the risk of relapse is dependent on the patient's former disease history. This assumption can be relaxed by creating additional states ('tunnel states') that consider the patient's time in state. These models are sometimes referred to as semi-Markov or state-transition.

Chambers et al. (2002) created a semi-Markov model to evaluate the long term care options following ischaemic stroke for a hypothetical population based on 30 day

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survivors of acute ischeamic stroke. The model presented by the authors was in fact presented as two linked 'modules'. The first module (model) was a decision tree detailing the treatment options after ischeamic stroke. Key health states included: recurrent stroke, on antiplatelet therapy, off antiplatelet therapy and dead. Non-fatal states were further stratified according to disability status (disabled or non). Deaths were categorised according to cause (acute stroke or other). Efficacy data was identified from trials and meta-analyses. Disability status was determined by the proportion of stroke survivors with a modified Rankin scale with a score in the range of 0-2 compared with 3-5 within the Oxfordshire Community Stroke Project cohort (Rothwell et al., 2005). Health state valuations were obtained from direct elicitation of patient's values (not preferences) for post-stroke states (Baruch et al., 2007). Key outcomes were recurrent strokes, costs, life years, QALYs and Disability free life years.

Individual sampling models (ISM)

Individual sampling models (sometimes referred to as patient level simulation models) track specific individuals along the path of care that each of them follow (Brennan et al., 2006). This approach enables the model to accommodate both heterogeneity in patient characteristics as well as the unexplained element of variability in patients' progression thorugh the care pathways in the model. Allowing for heterogeneity in patient characteristics means that patient attributes may more closely resemble actual patient histories which in turn may increase the model's validity. This might beuseful in the case of suspected TIA where different risk factors have been shown to enter additively in a prognostic risk score of stroke recurrence (see 'ABCD2 score' p. 17). However, this

approach might increase the complexity of the model without benefit if the relation between patient characteristics and treatment effect is imperfectly known.

Individual sampling models also allow for unexplained variation in the disease progression/pathways followed by patients who have same or similar characteristics. The accumulation of costs and QALYs depends on the unique pathways experienced by each individual, rather than an aggregate approximation for the whole cohort, as in decision trees and Markov models.

Brennan et al. (2006) also reported that one key advantage of this type of model is that ISM can incorporate 'time to next event' rather than being restricted to equal time periods as in Markov models.

The ISM can potetially improve the relevance of the model in terms of mirroring the real world situation. However, such models require indiviudal patient data, which may not be available.

Discrete Event Simulation (DES)

Discrete event simulation (DES) models are a special type of ISM. As cited by (Barton et al., 2004) the key distinguishing factor between ordinary ISM models and DES comes down to the issue of interaction between patients, which is useful in modelling the impact of treatments or vaccinations for infectious diseases. DES models were first used in systems engineering. Unlike the simpler structure of the ISM modelling described in section x.x, DES allows for a fuller representation of time. A DES can potentially be

designed to count (or simulate) 'clock' time, which it does in discrete units determined by the model's next event. There have been several examples of DES in stroke; the majority having been produced by the same author (Mant, 2008, National Audit Office, February 2010). These have been in decision analysis of complex interventions of stroke care, where a systems wide approach (i.e. to model competing resources) was needed. The advantage of a DES vs. a cohort level would be in evaluating the costs and consequences of initiating thrombolytic therapy in acute stroke. While possible in the simpler model, the DES has advantages in considering the trade-off between providing a hyper-acute service like thrombolysis and other services which might be cut back.

Model selection decision

In summarising the above model types, it is not possible to identify one as more valid than the other. However, certain characteristics might be difficult to implement in the decision tree or Markov structures assessed. The taxonomy of model structures by Brennan et al. (2006) provides a conceptual representation of the factors that are important to the selection decision. One factor that distinguishes between the models is whether time is important. Decision trees are essentially timeless, whereas markov models are arranged in discrete cycles of time. More sophisticated models such as DES can emulate clock time, which is useful if capacity constraints (and specifically the interaction of individuals competing for resource) needs to be explicitly modelled (Brennan et al., 2006).

3.7. Guidelines in economic evaluation

Given the role of economic evaluation in guiding and informing policy decisions, there is a need to establish that economic evaluations are of sufficient quality. Economic models that

aren't robust may result in erroneous decisions. In health care policy, the cost of making the wrong decision is reflected in the foregone benefits of the best alternative use of the resource. This has led to the preponderance of guidelines in the health economics arena for research and health technology assessment (e.g. British Medical Journal guidelines, the CHEERs statement) to assess the quality of economic evaluations (Husereau et al., 2013).

Areas of Methodological uncertainty regarding model structure

Aside from the areas previously documented, methodological enquiry is ongoing in certain areas of model development (particularly with respect to the early development (conceptualisation) stages (Chilcott et al., 2010). This is clearly important since, as previously stated, a poorly specified model could lead to a decision rule being applied that is sub-optimal/erroneous.

Model parsimony

This refers to the argument to keep the model as simple as possible without oversimplification of the essential elements of the intervention on both the patient pathway and disease process (Karnon et al., 2007, Weinstein et al., 2001). However, the precise specification of the model is something for the modeller to justify; by its very nature it remains subjective and not something that can undergo quality assurance via model checklists.

Within the context of the model considered here this may mean ensuring that relevant impact(s) of different modelling interventions are fully considered. This may mean that a model which accumulates costs and QALYs over its course is preferable to one which

relies on estimates of final outcome alone. This implicitly requires the model to consider the effectiveness of the timeliness of interventions (i.e. to model the effects of time in some way). However, the same approach may not be unnecessary for a disease area where time (in terms of time to treatment and time to disease progression) and consequence (in terms of costs and utility) do not vary across interventions.

Evidence from different sources/studies

The synthesis of evidence from different sources requires a systematic approach, and possibly the application of epidemiological methods such as meta-analysis. If data is to be synthesised from multiple sources then it is important that the effects of different populations and outcome measures used is considered as this may introduce bias. In the case where data from previously published systematic reviews or meta-analysis are to be used it remains important to consider the quality and applicability of these studies to the specific research question.

Selection of time horizon

An area requiring further methodological enquiry identified by Karnon et al (2007) is that of the selection of the time horizon. This is largely because the proliferation of models using different time horizons (and particularly non lifetime time horizons) may be sufficient to turn over policy decision rules.

Treatment of uncertainty

This requires careful consideration. The model's treatment of uncertainty will demand an understanding of what assumptions the model makes and where the evidence is weakest.

The way in which the model is initially specified and structured is a separate concern to the treatment of parameter uncertainty (the precision with which an input parameter is estimated) (Briggs et al., 2006).

3.8. Discussion

This chapter presented economic evaluation as a framework for evaluating the costs and consequences of an intervention. A rationale for performing decision analytic models was presented. This focussed on the salient features of the intervention being considered within this thesis.

CHAPTER 4. CRITICAL APPRAISAL OF ECONOMIC EVALUATIONS IN TIA

4.1. Introduction

The objective of this chapter is to review systematically and critically, economic models that have evaluated the management of acute stroke and/or TIA. This informs the methods used to structure and populate this thesis' economic model (Chapter 4).

To provide valid information for policy decisions, economic models should be based on realistic modelling of the health condition. Sculpher et al (2000) make a case for taking this further stating that 'the disease should be the underlying process of any model and should drive all decisions about service delivery'. In the context of TIA where symptoms have typically resolved by the time of presentation in Primary Care, the important aspect of the underlying process would be the risk (particularly the early risk) of a subsequent stroke and whether this is mediated by any form of secondary prevention (medical or surgical).

While reviews of economic evaluations in stroke exist, the approach and purpose of these studies reflects varied purposes for conducting reviews. Jones et al. (2004) undertook a systematic review of cost-effectiveness evidence focussing on the medical prevention of stroke (exclusively in the agents clopidogrel and modified release dipyridamole). Evers et al. (2000) chose to systematically review trial based economic evaluations in stroke research (excluding decision analytic models) and Guilhaume et al. (2010) performed a qualitative review of stroke management (excluding TIA). Other reviews in specific sub-sets of stroke prevention and management have also been carried out i.e. imaging

sequences prior to carotid endarterectomy, acute stroke treatments and the management of stroke in patients with atrial fibrillation (Benade and Warlow, 2002, Earnshaw et al., 2009); Sandercock et al. (2002). A de novo search was therefore necessary. The search protocol is now outlined.

4.2. Search Protocol

Search 1: How are models characterised in secondary stroke prevention?

Inclusion criteria

Population: Patients with TIA or minor stroke

Intervention: Any form of secondary stroke prevention (i.e. medical, surgical, care setting or protocol). Any change to service delivery from patient's presentation of symptoms through to treatment and follow-up. Included interventions will be 'complex' health service interventions where the term complex follows the convention adopted by the MRC as involving 'several interacting components' MRC Developing and evaluating complex interventions

Study type: Full economic evaluations (where a full economic evaluation is one comparing costs and consequences) published within the last ten years

Exclusion criteria: Studies in stroke rehabilitation, in special populations (e.g. atrial fibrillation), single technology appraisals.[5]

4.3. Search Strategy

The keyword search was based on the following strategy (including truncation of terms where appropriate): TIA, stroke, prevention, economic evaluation. Filters were not applied to isolate complex/policy models; a sift of abstracts was performed to exclude single technology appraisals.

In April 2010, five electronic bibliographic databases were searched: MEDLINE; EMBASE; Database of Abstracts of Reviews of Effectiveness (DARE); NHS Economic Evaluation Database (EED); Cochrane Library. In addition, the 'grey' literature was searched by exploring the Internet using keywords. The reference lists of idenitfied publications were also searched for further relevant modelling studies. In May 2013, the search was updated.

4.4. Results

A flow diagram detailing the selection of economic evaluations is provided in figure 4.1. A summary of the cost-effectiveness models included in this appraisal are presented in tables 1 and 2.

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[5] Note that a single technology appraisal usually only considers one technology and is therefore not likely to have applicability to the policy context of this thesis. NICE. 2004. *Guide to the Methods of Technology Appraisal.* [Online]. Available: http://www.nice.org.uk/niceMedia/pdf/TAP_Methods.pdf.

Figure 1: Flow diagram of selection of economic evaluations for service delivery models of stroke management
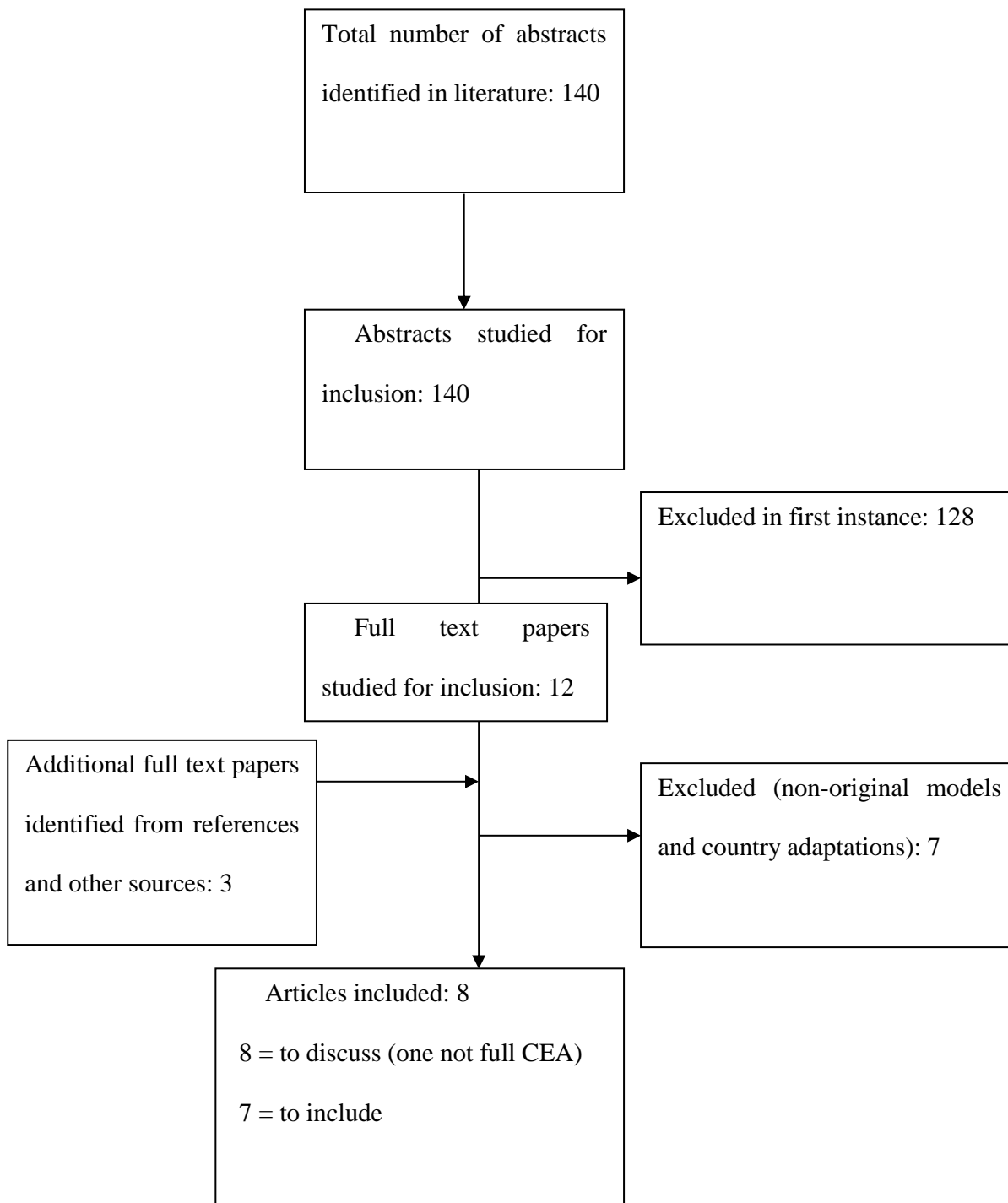
The criteria used to appraise quality were based on published checklists in economic evaluation described previously (Husereau et al., 2013, Philips et al., 2006, Drummond, 2005). The main checklist for this purpose was Philips et al. (2006).

For each included paper, the structure of the model and methods for identifying, analysing and incorporating data in models was assessed. In addition, the authors' handling of uncertainty and evaluation of consistency was considered. Data was extracted into evidence tables in the first instance; these tables informed the design of the summary tables and the subsequent discussion Table 10 and Table 11).

Table 10: Summary of published economic evaluations

Author (year), country	Comparators	Effectiveness	Resource use (price year)	Analytic approach	Model outcomes	Parameters driving cost-effectiveness
Chambers et al. (2002), US	**Viewpoint:** Societal and 3-rd party payer **Alternatives:** 'new' interventions: dual antiplatelet therapy, thrombolytic therapy and stroke unit care (all above compared to conventional practice).	Analysis of RCT, published meta-analysis cohort study for treatment efficacy, treatment discontinuations, and death.	Costs presented for four countries at 1996 prices, primarily from national sources.	Cost-effectiveness analysis. Linked decision analytic models – decision tree (short term); Markov (long term) **Time horizon:** Lifetime Uncertainty: Not reported.	Incremental cost/QALY in addition to incremental cost/stroke averted, incremental cost/life year gained. ICERs show that thrombolysis is cost saving, dual antiplatelets were cost-effective when compared to aspirin.	Stroke incidence, efficacy, long-term care cost, service cost associated with a service to diagnose and provide thrombolysis. **Sensitivity analysis:** not reported.

Author (year), country	Comparators	Effectiveness	Resource use (price year)	Analytic approach	Model outcomes	Parameters driving cost-effectiveness
Moodie et al. (2004), Australia	**Viewpoint:** third-party payer **Alternatives:** current practice,thromblytic therapy, asprin therapy.	Risk/ risk reduction of mortality, stroke and haemorrhage associated with therapy.	Australian 1997 prices converted to US $. Incremental resource use only identified (i.e. associated with reduction in beddays).	Cost-effectiveness analysis. Decision analytic model (not defined) Time horizon: lifetime Uncertainty: univariate and probabilistic.	Incremental cost/DALY. **ICER:** thrombolysis is cost-saving. Aspirin therapy is cost-effective.	Hospital discharge rate, access to stroke units for thrombytic therapy. **Sensitivity analysis:** no reported impact on decision.

Author (year), country	Comparators	Effectiveness	Resource use (price year)	Analytic approach	Model outcomes	Parameters driving cost-effectiveness
NICE (2008), UK	**Viewpoint:** third-party payer **Alternatives:** immediate access TIA clinics, weekly clinics, GP management (no referral). .	Based on therapeutic effect of dual antiplatelets (aspirin-dipyridamole). Applied a risk reduction to baseline stroke risk. Authors do not state that the risk reduction is absolute.	UK 2007 prices.	**Time horizon**: Lifetime (based on extrapolation of outcomes from a 90 day model) **Uncertainty:** Univariate. Extensive testing of assumptions used to populated model.	**ICER:** Immediate clinics dominate weekly clinics. Cost/QALY=£3330 when immediate clinics are compared to GP management.	Speed by which treatments are intiated. **Sensitivity analysis:** No effect on recommendation of immediate referral for patients with an ABCD2 score≥4 PSA not carried out.

Author (year), country	Comparators	Effectiveness	Resource use (price year)	Analytic approach	Model outcomes	Parameters driving cost-effectiveness
Birmingham TIA (2008)	**Viewpoint:** 3rd party payer **Alternatives:** Rapid assessment specialist clinics with different outpatient booking systems.	Regression methods applied to Oxford Vascular data to determine the recurrent stroke risk by ABCD2 score.	2007 or most recent available year. Non-recent years were inflated using relevant price index.	Discrete event simulation model **Time horizon:** 10 years (period of ongoing patient enrolment) with 1 year of follow-up. **Uncertainty:** deterministically tested.	Stokes averted. Cost/QALY (approximation) **ICER:** £1500/QALY for strategies where all suspected TIA are referred.	Use of emergency ambulances, alternative referral rules for GPs, improved GP diagnosis.

Author (year), country	Comparators	Effectiveness	Resource use (price year)	Analytic approach	Model outcomes	Parameters driving cost-effectiveness
Stahl et al. (2003), US	**Viewpoint:** 3rd party payer. **Alternatives:** Acute stroke treatments delivered according to protocol vs. routine clinical practice (where delivery is less timely).	Transition probabilities for recovery or worsening of functional outcome (by Rankin scale).	US $, 2000 prices.	**Model type:** Discrete event simulation model **Time horizon:** lifetime. **Uncertainty:** structural uncertainty tested by varying the incidence of stroke and costs.	Incremental cost US $/QALY **ICER:** Protocol complicant strategy was dominant when compared with current practice.	Model is sensitive to numbers of stroke and non stroke patients competing for use of imaging devices. **Sensitivity analysis:** model robust unless cost of implementation are prohibitive.

Author (year), country	Comparators	Effectiveness	Resource use (price year)	Analytic approach	Model outcomes	Parameters driving cost-effectiveness
Wardlaw et al. (2006), UK	**Viewpoint:** 3rd party payer **Alternatives:** 21 different imaging algorithms using 5 different diagnostic tests.	**Method used to estimate effectiveness:** meta-analysis of individual patient level data of tests used in the diagnosis of carotid stenosis.	UK 2003/4 prices.	**Model type:** State transition **Time horizon:** 20 years **Uncertainty:** testing of extreme values and using this to place confidence intervals around net benefit.	**ICER:** less invasive tests are cost-effective (have highest net benefit) at WTP thresholds of £20,000 - £30,000. Ultrasound should be used first in the sequence of tests (as the preferred strategy).	Cost of endarterectomy, time to surgery.

Author (year), country	Comparators	Effectiveness	Resource use (price year)	Analytic approach	Model outcomes	Parameters driving cost-effectiveness
NAO (2010)	**Viewpoint:** 3rd parrty **Alternatives:** current stroke care pathway versus more thromboblysis perfromed, and increased public awareness Stroke.	Population-based sources (South London Stroke register, National Audit).	UK 2008 prices.	**Model type:** Discrete event simulation **Time horizon:**10 years **Uncertainty:** model run multiple times to test uncertainty. Discount rates altered.	**ICER:** Further improvements were cost-effective at a cost/QALY of £2858.	**Sensitivity analysis:** Rerunning scenarios had no effect.

Table 11: Summary of key model inputs and assumptions

	Chambers et al.	Moodie et al.	Birmingham TIA (Mant et al.)	Stahl et al.	Wardlaw et al.	NICE	NAO
Method for modelling stroke recurrence	Constant risk per 3 month cycle.	Not described.	Parametric survival function (Weibull distribution) based on patient level survival data.	Constant annual transition probabilities after 1 year. (Prior to 1 year the model assumes transition associated with functional improvement or worsening only).	Variable cycle lengths within the model (shortest was daily, longest was four weekly).informed by cumulative stroke risks.	Parametric survival function (exponential) based on patient level data.	Not clear how probabilities (from observational study evidence were used as parameters in the model.

	Chambers et al.	Moodie et al.	Birmingham TIA (Mant et al.)	Stahl et al.	Wardlaw et al.	NICE	NAO
Data source for stroke recurrence	Secondary sources: RCT and meta-analysis of RCT data.	Secondary sources: systematic review and RCT data.	Authors analyse patient level data collected in Newcastle in the emergency setting.	Secondary sources:National lifetables. Risk constant for all patients after first year in model.	Relative risks by stenosis group used to adjust baseline risk of cumulative stroke in observational studies. .	Observational study data for baseline risk adjusted by therapeutic effect from RCT.	Secondary sources: observational registries.

	Chambers et al.	Moodie et al.	Birmingham TIA (Mant et al.)	Stahl et al.	Wardlaw et al.	NICE	NAO
Valuation of benefits	Gage et al. (1996) Direct elicitation of patient preferences using standard gamble and time trade off.	Dutch disability weights (2000) (Visual analogue scale and Time Trade Off)	Gage et al. (1996) (Values used in model do not match valuations with reference.)	Multiple published sources. Method unclear.	Dorman et al. (2000). EQ-5D to international stroke trial participants.	Dorman et al. (2000).	Van Exel et al. (2004) Based on published values. Converted from the Barthel index.

This review identifies relatively few (n=8) modelling studies in secondary stroke prevention. Most of these studies differed in terms of the precise decision problem(s) they were approaching and the interventions they were assessing. In general, all the studies suggested that interventions conferring even modest incremental benefit to the patient tended to be cost-effective. Comparison of results directly is not possible mainly because of differences in the specified populations, the range of alternatives and diseases modelled, and the assumptions relating to how the service pathway affects patient outcomes.

4.5. Structure

All models provided a clear indication of the research question, alternatives, time horizon and perspective. Most models adopted the perspective of the 3rd party payer; in a few instances, a societal perspective was adopted. The choice of perspective related to the purpose and context of the model.

A variety of different model types were used, from simple decision tree to discrete event simulation. As might be expected, simulation type models tended to be employed when the impact of capacity constraints (e.g. delay to a TIA clinic appointment) needed explicit modelling. In these cases, the queue was essentially determined by the inputs to the model. However, simple model structures were used to model the impact of assumed delays to treatment on service provision. For instance, in an acute stroke treatment model, Moodie et al. assume that a delay to investigation restricts the proportion of the population eligible for the intervention. A disadvantage of this approach is that, when the proportion of patients is arbitrarily set, the relationship between inputs (resource used) and outputs is no

longer reflective of actual usage. A more sophisticated model would consider the capital outlay associated with increasing the proportion of patients eligible for this service.

In all cases, the authors presented a "coherent theory of the health condition under evaluation", and explored a range of alternatives (Philips et al., 2006). However, the methods for modelling stroke recurrence were strikingly different (Table 11). Given that TIA and minor stroke are both associated with a heightened early risk of recurrence, it would seem important that a model capture the attenuation in stroke risk over time. Two models reported fitting parametric or semi-parametric curves to patient level data to capture this (Mant et al, 2008; NICE, 2008). In two instances, no reference to the methods used was made. Stahl et al report that they varied the cycle length within their state transition model to allow for an attenuation of risk over time; this suggests that the transition probabilities varied in discrete intervals of time. This may reflect the underlying data. Phillips et al. caution against allowing data availability to determine the structure of a model, but also acknowledge that is reasonable to accept that data availability can limit or refine model structure. The use of survival methods, variable cycle lengths and non-constant transition probabilities all appear to be suitable refinements.

Compared to trials, decision analytic models also have greater flexibility in the extent to which they can consider all alternatives. In the context of stoke/TIA prevention, examples of this include the mathematical model produced by Wardlaw et al. to test not only different imaging strategies but different imaging sequences for carotid endarterectomy. Two models appear to be constructed specifically for the purpose of being able to test policy interventions. For instance, Chambers et al. combined treatment and prevention

modules in their model. This enabled them to make simultaneous recommendations about thrombolysis, stroke unit care and aspirin therapy.

4.6. Data

All eight modelling studies used evidence synthesis from a variety of sources as opposed to being primarily based on a single trial. All models reported the data sources used to estimate parameters. However, the review methods used to select parameters were not always provided, so these studies failed to consider bias. All of the models faced challenges in determining the treatment effect associated with the service delivery intervention. The treatment effect tended to be determined by multiple inputs; these were often from different sources. For example, the NICE acute stroke model compared weekly TIA clinics, immediately accessible TIA clinics and an option of GP management alone. The treatment effect was determined by: the time when treatments were initiated, which treatments were initiated, the patient's ABCD2 risk score and the level of carotid stenosis.

Table 12 provides the short-term assumptions in the NICE model under each service pathway. Sources for the parameter inputs included meta-analysis of carotid surgery trials, a RCT of aspirin-dipyridamole versus aspirin alone, a population-based study of stroke incidence and secondary analysis of a database of GP prescribing.

Table 12: Assumptions (service pathways) made in NICE (2008a) and impacts

	Assumptions relating to service pathways	Impacts
Immediate TIA clinic	Optimal medical management initiated immediately. Majority of carotid surgeries performed within 2 weeks. Immediate clinics more expensive to run than weekly clinics.	Improved efficacy (risk reduction applied to baseline stroke rate). Higher costs associated with TIA clinic service. Higher drug costs.
Weekly TIA clinic	Optimal treatments initiated with delay. Majority of carotid surgeries performed within 2-4 weeks.	Lower efficacy compared to immediate TIA clinic.
GP management alone	Optimal treatments not offered. No imaging or referral for carotid surgery.	Least efficacious but no costs associated with running TIA service.

In the main, the measure of benefit was presented in terms of QALYs. Several modelling studies replicated approaches offered in other publications, which might point to publication bias. Certainly the methods for valuation of benefits were often not reported by the authors (Table 11), it was necessary to check the secondary source.

Typically the cost perspective used included healthcare as a minimum. In three of the models, an attempt to capture the long-term costs allowed for a broader representation of costs; however the paucity of data on informal care and indirect costs meant they were

often excluded. Another simplification was often that resources were assumed to be flexible and not capacity constrained. In the main, resources were presented in units, alongside costs. Unit costing tends to assume that there are constant returns to scale; it is easy to see that this assumption might not hold where the nth additional patient requires capital outlay (e.g. opening a new hospital ward). Other commentators have highlighted the dangers of the assumption of resource use flexibility and incomplete descriptions of costs in economic evaluations of service delivery (Godber et al., 1997, Coast et al., 2000).

4.7. Uncertainty

All models used some method for dealing with uncertainty. All performed univariate analysis as a minimum. To some extent, the model type dictated whether probabilistic analysis could be implemented, as this is non-straightforward in simulation based models which are typically set up to model patient (as opposed to parameter) variation as a random process. One Discrete Event simulation reported re-running its analysis several times for all scenarios to check that the results (with respect to randomness) were replicable.

4.8. Consistency

Five of the studies commented on at least one aspect of model consistency. Four of the five studies made reference to the generalisability of their findings, often via direct comparison with results in other modelling studies. Expert opinion appeared to feature highly in ensuring that the models had face validity with clinicians, but authors did not report the techniques used to achieve this.

There was a failure of all but one study to report detail on the checks used to control for model error, yet model error is a key risk to the credibility of the model (Chilcott et al., 2010).

4.9. Strengths and Weaknesses

The strength of this study is that it appears to be the only study that appraises a range of modelling studies in service delivery interventions without exclusion of TIA. The weakness is that often the data reporting of analytical methods (within the included studies) lacked transparency; this makes it difficult to appraise the suitability of the mathematical modelling techniques employed. In one case, the model type was not stated and the analytical method used was not otherwise obvious from the description of the model's scope. In general, the methods of pre-model data analysis were poorly documented. However, most papers adhered to the quality standards of the Philips' checklist in terms of a clear statement of the research question, detail on model structure and data inputs and appropriate methods for dealing with uncertainty.

4.10. Discussion

In order to inform the methods for structuring and populating a model in the TIA Primary Care setting, a critical appraisal of existing models in acute stroke/TIA was carried out. Critical appraisal was necessary to inform the selection of model type and the analytic methods for modelling in the TIA setting. Models identified within this critical appraisal varied from the simple decision tree to more complex discrete event simulations. Selection decisions were often not provided by the authors.

In terms of results, there was little to suggest that the different model types would result in different results. Perhaps unsurprisingly, given the high economic burden of disabling stroke, interventions that provided modest benefit to the patient were often cost-effective at willingness to pay thresholds typically accepted in the UK (NICE, 2004). Model selection decisions seemed to reflect the remit of the policy maker. More complex models tended to be used to establish the efficiency of the system of care (of which the intervention is part of) as opposed to the efficiency of the intervention per se.

CHAPTER 5: METHODS

5.1. Introduction

This chapter begins by stating the primary aim and the objectives of this thesis. The chapter then describes the methods to be used to address the objectives and involves two main approaches. Firstly, the chapter will describe the methods used to build and structure an economic model of alternative models of service delivery to manage TIA (see 5.4. Structuring the model methods). Secondly, the chapter will describe the methods used to identify cost-effectiveness data for use in the model (see 5.6. Identification of Evidence).

5.2. Study Aim

The primary aim of this thesis is to identify and quantify the incremental costs and benefits of GP initiation of treatment following a suspected TIA (hereafter referred to as The GPiT strategy) compared with best practice.

5.3. Study Objectives

The objectives of this thesis are to:

i. Build and structure an economic model to compare the GPiT strategy with best practice.

ii. Identify and quantify the incremental costs of the GPiT strategy model compared with best practice.

iii.   Identify and quantify the incremental benefits of the GPiT strategy model compared with best practice.

iv.   Analyse the incremental costs and benefits of the GPiT strategy compared with current practice.

v.   Perform a sub-group analysis to identify the impact of the management of patients who present with different clinical characteristics following TIA.

vi.   Identify and quantify the uncertainty around the incremental costs and benefits of the GP model compared with current practice.

vii.   Identify the need and type of future research.

5.4. Structuring the model methods

This section provides a specification of the model structure.

Purpose of the model

The purpose of the model is to identify and quantify the incremental costs and benefits of

GP initiation of treatment following a suspected TIA (hereafter referred to as The GPiT

strategy) compared with best practice (base-case). In the UK there is compelling evidence

from NICE and the Department of Health to suggest that prompt assessment and treatment

of suspected TIA in specialist rapid access neurovascular clinics is both effective and cost-

effective (NICE, 2008). One specific point of guidance made by both parties is that

suspected high–risk TIAs identified in primary care should be seen within 24 hours of

patient presentation, with the remainder within one week[6]. In spite of these

recommendations, there is less compelling guidance on how the NHS should arrange and

deliver its services to ensure that TIA patients are treated in such a timely manner; an issue

perhaps more pertinent given the results from a UK wide audit of TIA services

documenting far from timely responses (NICE 2008a, Mant 2008).

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[6] Note that the relevant time interval for patients seeking care in this model is limited to the delay between patient presentation and initiation of appropriate treatment. This model does not consider the delay between a patient's experience of symptoms and presentation with symptoms, which can be lengthy for some patients. Clearly, both forms of delay increase the risk of early recurrence due to untreated TIA. A natural extension of the GPiT model, not considered here, would be to consider delivering GPiT simultaneously with a public education campaign aimed at reducing time to patient presentation. Public awareness of symptoms suggestive of stroke have already been targeted by FAST, but there may be some reticence about patients seeking GP assistance, especially if symptoms are experienced outwith normal GP surgery hours (Lasserson, D. S., Chandratheva, A., Giles, M. F., Mant, D. & Rothwell, P. M. 2008. Influence of general practice opening hours on delay in seeking medical attention after transient ischaemic attack (TIA) and minor stroke: prospective population based study. *BMJ,* 337**,** a1569.)

Selection and justification of modelled alternatives

Identification of current practice

In order to identify current practice for the purposes of the modelled intervention, information from national audit was used to determine the timeliness of service provision and data from non-urgently treated TIA services was used to estimate risk (Giles and Rothwell, 2007a). The studies used for this purpose have been documented more fully elsewhere (see Chapter 2).

Identification of best practice

Giles and Rothwell (2007a) systematic review and meta-analysis identifies the most clinically effective TIA services (for which there is evidence) are rapid access, non-appointment based clinics run by specialists. The unambiguous finding reported here and elsewhere is that more timely specialist treatment very effectively reduces the risk of subsequent vascular events (in the region of the observed 80% relative risk reduction at 90 days documented in the EXPRESS study). In the most clinically effective TIA clinics in the UK the care pathways are unchanged from current practice previously documented. The crucial difference is that patients are placed on best medical treatment sooner.

Description of care pathways

The base-case comparison is between the intervention, the GPiT strategy (Figure 2) and the comparator, best practice (Figure 3).

In both cases, the focus is on what has happened once the patient has presented with symptoms to the GP and the GP makes a diagnosis equivalent to 'suspected TIA'. Patients in whom the GP does not suspect TIA are diverted away from the care pathways for TIA.

Intervention, the GPiT strategy:

Figure 2 is a diagram of the care pathway associated with the GPiT strategy. In this care pathway, the GP initiates treatment and then refers the patient to a rapid access clinic for specialist assessment and review of medication.

Comparator, best practice:

Figure 3 is a diagram of the care pathway associated with best practice. In this care pathway, the GP does not treat but assesses the patient and refers to a rapid access clinic for specialist assessment and initiation of treatment.

Note that the term 'care pathways' adopted here refers uniquely to the patient routing associated with the respective strategies.

GP action	Specialist action	GP action
• initiates treatment	• reviews	• follow-up

Figure 2: The patient care pathway associated with the intervention (GP initiation of treatment)
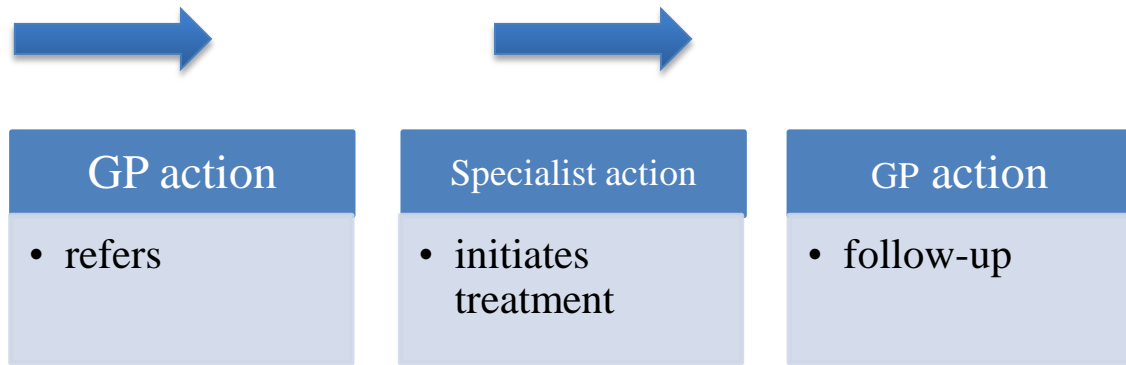
Figure 3: The patient care pathway associated with the comparator (best practice)

Population

The population is defined as all presenting patients in primary care in whom the GP suspects TIA. In order to reflect the clinical situation, the population includes non-true TIA cases which the GP misdiagnoses as suspected TIA (i.e. TIA mimics).

The proportion of true TIA relative to TIA mimic is set at a level based on results from systematic review of diagnostic accuracy studies in primary care (see Chapter 6). Patients not presenting to their GP, missed TIA diagnoses (i.e. the false negatives) and those with unresolved symptoms at time of presentation (i.e. potential strokes) are excluded for reasons previously outlined. In addition, it is assumed that specialists are perfectly accurate i.e. have 100% sensitivity and specificity.

Timing of care pathways (base-case)

Table 13 details the distinction in the timeliness associated with the care pathways in the base-case model. The care pathways and their associated timings allow for a fuller description of the alternative models of health service delivery of this thesis' enquiry.

Table 13: Strategies to be compared

The base-case comparison is between the comparator, best practice, and GPiT.

Best practice

Best practice is assumed to be analogous to that exemplified in the 2007 publication of the National Stroke Strategy. This means that all patients with suspected TIA who have an ABCD2 score of 4 (hereafter high risk) or above are assessed by a specialist within 24 hours or within 7 days for the remainder (i.e. patients with ABCD2 scores 3 and below (hereafter low risk)). Patients who have their diagnosis of TIA confirmed by a specialist will be started on a treatment regimen that includes dual antiplatelet therapy (aspirin – dipyridamole) in addition to statins and antihypertensives.

GPiT

As for the best practice, the alternative model sets to achieve the same standard of care regarding the timeliness for referral to a specialist. However, in the baseline analysis, treatment is initiated in *all* patients (i.e. including TIA mimics) on the day they present to the GP, i.e. a mean 24 hours sooner (high risk) or up to 7 days sooner (low risk). Patients continue to be referred to a specialist for assessment and review of treatment; at this point, TIA mimics will have their treatment discontinued.

Identification of the model base-case

The base-case comparison is GPiT versus best practice. A secondary analysis will compare GPiT with the performance of current practice.

The base-case of the economic model assumes that a proportion of all suspected TIAs identified by GPs will be TIA mimics. The assumption that GPs are not perfect diagnosticians of TIA has been shown to be a very valid one in the findings of several population based studies in suspected TIA (Chandratheva et al., 2011). This is unsurprising

given the clinical nature of TIA, which has no 'gold standard' test in diagnosis. The economic model assumes that all patients who see specialists are appropriately imaged and receive the correct diagnosis. In addition, the model implicitly knows the true diagnoses and ratio of TIA: TIA mimic.

Rationale for choosing intervention/comparator(s)

The rationale for GPiT is that initiation of treatment at the earliest possible opportunity[7] may confer extra benefit to the TIA patient, given the heightened early risk of stroke following TIA. However, quantifying this benefit will depend entirely on the accuracy with which GPs correctly identify suspected TIA since there is a possible risk associated with inappropriate treatment in TIA mimics. (Precisely, this risk will depend on the non-stroke pathologies that GPs mislabel as suspected TIA). Decision analysis allows for quantification of this trade-off in terms of incremental costs and benefits to assess the feasibility of a trial.

5.5. The economic model

The objective of this section is to explain why an economic evaluation has been carried out, why CEA is the chosen form of economic evaluation and why a Markov model has been selected. i.e. to outline the purpose for the summary description and structure of the economic model.

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[7] For the patient presenting in Primary Care.

Summary Description of the economic model

A Markov (state transition) model was developed in Microsoft Excel (Microsoft Corporation) to simulate outcomes following a suspected TIA. The structure of the model was informed by current literature and expert opinion (a steering group of clinicians and health economists) on the early management of TIA (TIA steering group, 2008).

In the base-case, the model estimates the incremental cost and incremental benefit (in terms of QALYS) of GP initiation of secondary prevention agents (relative to the next best strategy) at 90 days and via extrapolation of outcomes at 90 days to a lifetime horizon. The model also makes a projection about the sequelae of clinical events (e.g. stroke free survival, major haemorrhagic events and carotid surgeries) following TIA up to 90 days.

Within the Markov model, a 90 day time horizon was selected in order to provide a projection of the clinical outcomes of a strategy of GP initiation of treatment. This was to allow for comparison with published outcomes corresponding to best practice in the EXPRESS study 90 days from follow-up (Rothwell et al., 2007). Model predictions that coincide with clinical follow-up may have more face validity with clinical experts in the field (Briggs and Sculpher, 1998).

As well as estimating the ICER at 90 days, the model also makes a projection about the risk of major haemorrhage occurring in the GPiT strategy that is not available elsewhere. In the acute phase, the model calculates the number of patients transferring from a state where the patient has had a suspected TIA to each of four non fatal health states and five fatal states. Table 14 lists these states.

The model employs a fixed cycle of one day. The cycle length chosen was deliberately short in order to capture the potential benefit from GP initiation of treatment being at least a day sooner. This cycle length was informed by epidemiologic review and modelling on the benefit of early treated TIA in terms of recurrent stroke risk.

In the base-case, a hypothetical cohort of 1000 TIA patients with suspected TIA is modelled for 90 days. In the initial development of the model, it was assumed that GPs are perfectly accurate, i.e that there are no 'mimics'. In further iterations of the model development, this assumption was changed to allow GPs to make false positive TIA diagnoses (of suspected TIA). This was on the basis of clinical opinion and the findings on a review of the diagnostic accuracy of primary care practitioners in TIA. Note that the model does not account for false negatives in the analysis. As discussed in Chapter 2, the diagnosis of TIA in Primary Care is essentially clinical, where a diagnosis is essentially made by ruling out other conditions rather than ruling out TIA. This means that negative cases will not routinely come to light (there is likely to be no record). However, it is important to recognise that false negatives represent a susceptible patient group who may face a higher risk of recurrence (as they are not identified for timely treatment), and that if GPiT was implemented nationally it would be worthwhile to consider investing in an appropriate supporting program of clinical education (Lasserson, 2013).

The reference year for costs was 2011/2012. The viewpoint of the analysis is the UK NHS. The viewpoint of the analysis is the UK NHS. This perspective is narrower in the sense that it does not include the costs associated with personal and social care, which are likely

to be a major component of the economic burden of stroke. The rationale for the narrower perspective was twofold: 1) the 3rd party healthcare payer needs to be persuaded of the healthcare outcomes within its own budgetary domain; 2) estimates of personal and social care costs over the remaining lifetime are difficult to obtain and subject to widespread variation depending on the methods used to value care costs.

Using the UK NHS perspective is conservative, in that it will be ignoring social care costs: if the GPiT model leads to reduced risk of stroke, then the lower social care costs associated with fewer strokes will not be incorporated in the final results. Thus, overall, the effect will be to under-estimate the cost effectiveness of the GPiT model.

In the acute phase of the model, there is no discount factor. This is because the modelled time horizon is only 90 days, which was chosen to reflect the differences in outcome following the intiation of antiplatelet therapies. No half cycle correction was applied, again because of the very short cycle duration. In the lifetime analyses of the extended model, a discount rate of 3.5% per annum on costs and benefits which is in line with that currently recommended by NICE methods guidance (NICE, 2004).

Structure of the economic model

Table 14 describes the health states used in the model. These health states are: TIA, Ischaemic stroke, Haemorrhagic stroke, Carotid surgery, Major haemorrhage, Fatal ischaemic stroke, Fatal haemorrhagic stroke, Surgical death, Fatal major haemorrhage and other cause death. Figure 4 shows the possible transitions between health states in the Markov model. The boxes are the health states and the arrows represent the possible

transitions between them. The circular arrows represent the possibility of remaining in that particular state over each cycle. In the initial development of the model complications of carotid surgery other than death were not considered; however, extension of the model to consider these outcomes was later introduced. This allowed patients to move from the carotid surgery states to experience major haemorrhage and haemorrhagic stroke. Within the model structure, a simplification was that any death following a major event (stroke, major haemorrhage, or carotid surgery) was counted as cause-specific.

Table 14: Description of health states used in the acute phase of the model

State	Description
TIA	Patient has had a suspected TIA, and the acute symptoms (relating to the TIA) have resolved. All patients enter the model in this state, and remain in this state so long as they do not have an event.
Ischaemic Stroke	Patient has an ischaemic Stoke
Haemorrhagic Stroke	Patient has a haemorrhagic stroke (includes any haemorrhage within the cerebral cortex of the brain?)
Carotid surgery	Patient undergoes surgery for carotid stenosis
Major haemorrhage	Patient has had a non fatal major haemorrhage
Fatal ischaemic stroke	Underlying cause of death is ischaemic stroke*
Fatal haemorrhagic stroke	Underlying cause of death is haemorrhagic stroke*
Carotid surgery death	Patient dies following surgical complications. Surgical deaths include all deaths during or after surgery attributable to carotid surgery.

Fatal major haemorrhage	Underlying cause of death is major haemorrhage
Other cause death	Underlying cause of death is non-vascular

† Patients entering these states continue to reside in these states until death or 90 days, whichever is the sooner. States therefore include the rehabilitation period post-event.
*Underlying cause of death is defined as any death within 90 days of a major event (stroke, major haemorrhage or surgery)
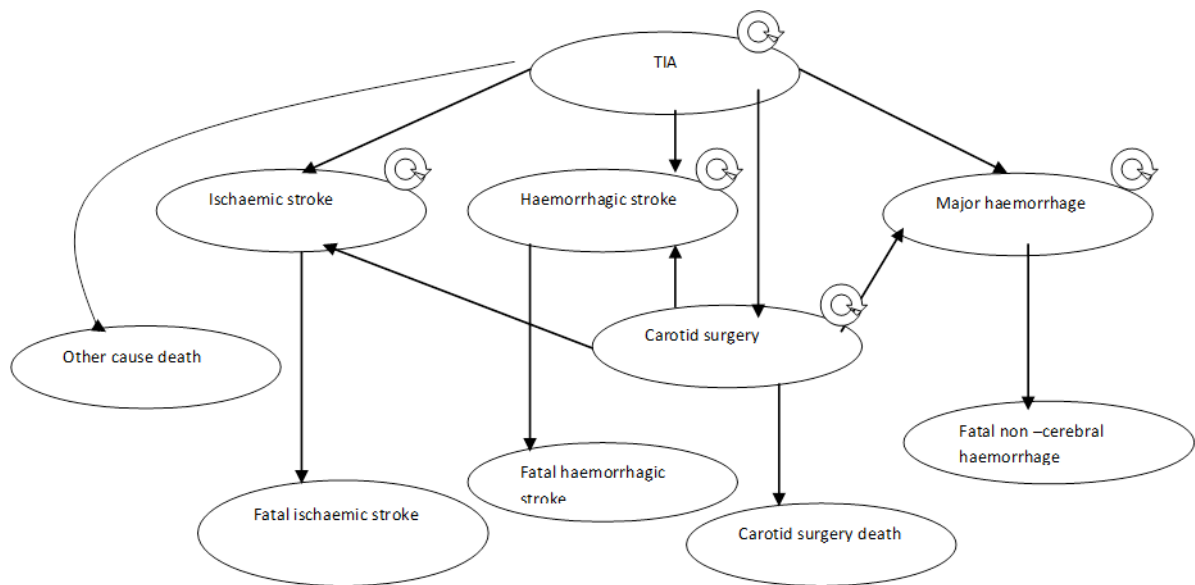
Figure 4: Markov cohort simulation model

The risk of transition from the initial state to each of the other states is determined by a unique transition probability associated with that transfer. Patients remaining in a particular health state are represented by the circular arrows.

Within the model, the entire population begins in the suspected TIA health state. The model assumes heterogeneity in patient's risk of recurrent vascular events; chiefly patients are characterised according to whether they are high or low risk, and these clinical characteristics (as ABCD2 scores) are observed by GPs.

The model assumes errors in the accuracy of TIA diagnoses by GPs via false positive referrals to TIA services. A TIA mimic is defined as a patient who experiences symptoms suggestive to the GP as TIA but whose symptoms are the result of another pathology. The main source of evidence for intervention effectiveness is observational study evidence derived from the OXVASC cohort, so distribution of risk factors are similar to those reported elsewhere (Rothwell, Coull et al. 2004a). In order to reflect the age/gender balance nationally (and to make a nationally applicable recommendation to policy) as opposed to Oxfordshire alone, the calculation of mean age was adjusted to reflect the UK demographic using the methods of Wardlaw et al. (2006). (See also 'Calculation of life expectancy'; Table 15, p.97).

As a simplification, recurrent TIA (within 90 days of patient entry) was not modelled as a possible complication following TIA. Patients could only experience one stroke or major haemorrhage within the 90 day timeframe. A further simplification was to exclude myocardial infarction and other cardiovascular outcomes from the analysis. (Patients with previous stroke and MI could be excluded as they should be on treatment). The purpose of this model was to determine the cost-effectiveness of GPiT in TIA; extending the research question to include cardiovascular diseases would greatly increase the complexity of the model. Within the simple model structure here, cardiovascular outcomes are part of other cause death.

Following suspected TIA, the risk of transfer to each of the other states is estimated, conditional on treatment status. For the case of stroke outcomes, the risk of transfer to any stroke state is conditional both on treatment status and the time since presentation with

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TIA. The transition from TIA to carotid surgery is only permitted if the patient is referred to a specialist.

The model incorporates time-dependent probabilities by varying the risk of stroke (ischaemic and haemorrhagic) at three discrete time intervals, 0-2 days, 2-7 days and 7-90 days. The baseline assumption is of constant hazards within these intervals.

The advantage of this relatively simple model structure is that re-parameterisation of the transition probabilities is sufficient for exploring variations in the case-mix of patients. This extends to variation in the case-mix of patients, including the proportion of true TIA relative to minor and serious pathology mimic states.

In the base-case analysis it was assumed that the course of combined secondary preventive medications lasted at least 90 days. Patients were assumed to have no known contraindication to dual antiplatelet therapy (for instance, on anticoagulation) or any other drugs at point of presentation to GP i.e. there would be no reason for the GP not to prescribe a combined course. The effect of discontinuations due to minor side-effects and or patient adherence were not modelled. It was assumed that certain drugs would however be stopped following the patient experiencing one of the life-threatening event represented in the model. These included discontinuations of statins and antiplatelet agents following haemorrhagic stroke and discontinuation of antiplatelet agents following major haemorrhage.

Costs are accumulated for each day that the patient spends in any non-fatal health state. In addition, there are some 'one-off' transition costs associated with the patient moving health states (as the patient experiences an event). For instance, the unit cost of a GP clinic or an emergency medical procedure in the case of major haemorrhage.

Quality adjusted life days (QALDs) are accumulated for every day that the patient spends in each non-fatal health state. The model assumes that the patient experiences static utility for the time in state i.e. the model does not attempt to capture the within state fluctuations in the health of the patient associated with diurnal variation. It follows that the accumulation of QALDS can be divided by 365 to derive the total QALYs for the purposes of reporting results in the standard metric of cost/QALY.

While it is common to employ a half-cycle correction when using a Markov cycle when cycle lengths are relatively long (e.g one year), this adjustment was not made on the grounds of the daily cycle length used for this model. Patients dying with a cycle were only counted as dead in the next cycle, so this leads to a negligible but potential overestimation of survival within the 90 day model by up to one day.

Extrapolation to lifetime time horizon

Costs and benefits of the surviving cohort for the remainder of their lifetime were estimated. This was done by a simple extrapolation of outcomes from the 90 day survivors for both costs and benefits. In order to establish a measure of benefit, the mean life expectancy for the fraction of the original cohort was estimated and multiplied by the associated QALY weight associated with that health state. For costs, the direct health

service costs to the NHS are again calculated. In addition a discount factor of 3.5% is applied to both costs and benefits. The summary measure reported is now the discounted cost/QALY, and this reflects the lifetime time horizon.

Calculation of life expectancy

The average life expectancy for the surviving cohort at 90 days was assumed to be state specific. For survivors of TIA, the life expectancy was taken from published UK lifetables, adjusted to reflect the age/sex profile of the original cohort (Office for National Statistics, Wardlaw et al., 2006). For survivors of stroke (either haemorrhagic or ischaemic) this life expectancy was assumed to be half that of patients with TIA, which corresponds to an assumption made in the NICE guidance for acute stroke and TIA (NICE, 2008a).

For the other non-fatal model outcomes at 90 days, estimates were guided by rapid review (where the general methods for a rapid review have been previously described). Survivors of major haemorrhage face a higher risk of all cause death than survivors of TIA, in line with evidence on study follow up of survivors of acute GI bleeds (Moukarbel et al., 2009), in order to be conservative the life expectancy was assumed to be one third of 10.8 years. Patients who had a TIA mimic were assumed to have the same average life expectancy as for genuine TIA. Patients who had no complications or events following carotid endarterectomy were assumed to have the same average life expectancy as those patients with incident TIA.

Table 15: Expected number (percentage) of TIAs and minor strokes in a standard population of 500,000 people

	55-64	65-74	75-84	85+
male	22.5 (4.6%)	66.3 (13.5%	63.4 (12.9%)	25.7 (5.2%)
female	30.1 (6.1%)	65.3 (13.3%)	130.7 (26.7%)	86.0 (17.6%)

Table 16: Life expectancy [unadjusted] (median) 2004-06 lifetables

	55-64	65-74	75-84	85+
male	20.81	13.36	7.57	3.10
female	23.94	15.78	9.03	3.695

Table 17: Life expectancy [adjusted by age of presenting patient] (median) 2004-06 lifetables

	Average life expectancy (years)
Representative cohort	10.53
male	10.75
female	10.41

Table 18: Model parameters for fatal health states

Parameter	Assumption made in model	Source	Basis of estimate
Other cause death	All cause mortality minus ICD60-69 (Calculated as 49,472 per million) Annual probability of death = 0.0495	ONS lifetables (ONS 2013)	Estimate based on age and sex profile of presenting cohort of the OXVASC study
Life expectancy post TIA	As per general population (calculated as 10.5 years)	Birmingham TIA model (Mant et al. 2008)	Assumes that patients will be well if no event post 90 days
Life expectancy post stroke	Life expectancy half as per general population (5.25 years)	NICE acute stroke and TIA guidance (NICE 2008a)	Assume two-fold increase in risk of death.
Life expectancy post major haemorrhage	Life expectancy half as per general population (5.25 years)		Assumes that major haemorrhage is associated with some frailty. (TIA steering group, 2008)

Scenario analysis

Unlike a trial, decision analytic modelling allows for the testing of a number of different strategies with relative ease. The desirability of carrying out a scenario analysis is that it allows for consideration of all relevant alternatives and therefore provides a more comprehensive analysis of the research question.

In the extended scenario analysis, three further strategies were introduced. current practice was included (in contrast to best practice). In addition, variations on the GPiT strategy were introduced: one with specialist referral limited to high-risk patients; the other equivalent to no onward referral. In both cases, all suspected TIA cases are treated. The justification for the inclusion of the GPiT alternative strategies was to explore the cost-effectiveness of alternative configurations of GPiT.

Table 19: Description of strategies considered in Scenario Analysis

Strategy	Patient pathway	Service Delivery
Current practice	GP referral to a specialist TIA clinic for imaging, assessment and treatment. Specialist prescribes optimal treatment. GP follows-up.	**Delay to treatment** –- currently implemented into model via different stroke free survival curves derived from Giles et al. (2007) systematic review. See assumed and projected survival curve below. **Delay to surgery** - patients have surgery within 2 weeks. The remainder face a delay consistent with the findings of Halliday et al. on behalf of the RCP Carotid Endarterectomy Steering Group (Halliday et al., 2009) 2-4 weeks – 14% >4-12 – 34% >12 – 30%

Strategy	Patient pathway	Service Delivery
GPiT alternative (No subsequent specialist referral)	GP initiates treatment in all patients and then does not refer suspected TIA patients to a specialist. GP follows-up all patients. This strategy is equivalent to GP management of TIA patients.	All patients receive immediate initiation of treatment.
GPiT alternative (High risk only referred on to a specialist)	GP initiates treatment in all/ high risk patients (see note above regarding 2 applications of this strategy and then refers only patients identified as high risk to a rapid access clinic for specialist assessment (including imaging) and review of medication. GP follows-up all patients.	High-risk patients face the same benefit and risk as those on GPiT. Low-risk patients receive immediate initiation of treatment, equivalent to GPiT alternative (No subsequent specialist referral).

Sensitivity Analysis

The model considered the joint uncertainty in the input parameter point estimates. For each parameter, an appropriate candidate probability distribution on the basis of the type of data was selected following Briggs et al. The model was run 1000 times, as determined to minimize Monte Carlo error each time randomly selecting a value for all parameters from a respective distribution resulting in 1000 Cost/QALY pairs which provided simulation

output in scattergraph plots (Briggs et al., 2006). The model calculated the mean costs and QALYs over the 1000 simulations, which averaged resulted in the mean net monetary benefit by strategy for different values of the threshold ratio. This allowed the construction of cost-effectiveness acceptability curves summarizing the evidence in support of the intervention for multiple strategies for different thresholds.

In addition, further sensitivity analysis was carried out to test the underlying assumptions of the model. Deterministic analysis (using the point estimates and not probabilistic distributions) was initially performed to establish which parameters were most sensitive on the results. Parameters judged to be sensitive to the results of the model were then subjected to probabilistic testing to further test this, i.e. by re-running the Monte Carlo simulation 1000 times for the input parameter and comparing the probabilistic and deterministic results.

5.6. Identification of Evidence

In order to populate the model searches were conducted to identify the best available sources of evidence from the literature. A decision about the parameters requiring estimation followed from previous decisions regarding the structure of the. The data requirements of the model are organized by the nature of input parameter (i.e. Clinical, Cost and Resource Use, Utilities and Life Expectancy).

Data search methods

Two types of search/review were performed (rapid review and structured literature review). [Here, I use the term rapid review to refer to a quick, restricted and focussed search of published evidence.] Compared to the standard structured literature review, the rapid search/reviews adopted here were restricted to a single database (Embase) and were restricted to high quality systematic review, meta-analysis and RCTs. The aim was to provide a consistent and transparent search that could be replicated by another reviewer.

Justification for a rapid review process

In the absence of an established convention for a 'rapid review' process to populate economic models in Health Economics, this section aims to provide a rationale.

The suitability of performing a rapid review (versus a structured literature review) followed pre-defined criteria. Since it is beyond the scope of this thesis to comprehensively review all evidence, the aim was again to provide a clear rationale for limiting the number of included studies where rapid reviews were performed. Table 20 reports the criteria for assessing if a rapid review can be justified.

Table 20 : Criteria for assessing if a Rapid Review is justified

A rapid review can be carried out if...

At least one recent systematic review (or meta-analysis) or RCT has been previously carried out in the same population as per this thesis (ideally in a UK population).[8]

or:

The results of the model are not likely to be sensitive to this parameter. (Where there is doubt, this is to be determined by logical testing of the model, once constructed, by allowing the parameter to be at maximal and minimal values and comparing the ICER against the commonly applied ceiling threshold in the UK of £20,000-£30,000)

Rapid review

The rationale for these reviews is to identify the clinical, cost and QALY valuations necessary for populating the economic model. The search strategy searched the EMBASE database. The search was restricted to published studies in the English language in the last 10 years, up to 01 Jan 2013. Prior to searching, an explicit statement of the question relating to participants, interventions, comparisons, outcomes and study design was formed. The search strategy combined free text terms. The search terms used (including any limits) and dates searched are reproduced in 'Appendix 3: Rapid Reviews'. Eligibility criteria for included studies were defined a priori.

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[8] Where a similar population was a priori determined to be TIA or minor stroke patients. Preference was given to studies that recruited from patients living in the UK.

Structured literature review

In the single case where these criteria in Table 20 (p.104) were not met, a more extensive approach was sometimes required. The methods for the structured literature review in these instances are documented in the full in the next chapter (see Chapter 6).

5.7. Estimation of Effectiveness

Clinical transition probabilities

Patient progression is determined by simulating the movement of the cohort through health states, starting with the patient's presentation with suspected TIA in primary care in cycle 0; patients then are assigned into other health states based on the probability of the event occurring in the next cycle - this is the clinical transition probability associated with the event.

Time dependent transitions for all stroke [combined ischaemic/ haemorrhagic] following true TIA

Survival analysis was used to implement time dependency, using a similar approach to NICE (2008). Using the pooled analysis of time to event data at 2,7 and 90 days from the Giles and Rothwell (2007a, p.1068) dataset an estimate of the daily stroke rate (h) for projected treated and untreated risk[9] can be made using the following formula:

$$h = (-1/t) \ln (S/So)$$

---

[9] Strictly speaking, untreated ('Proj. no Rx' on graph) risk is non-optimally treated risk. The time to event data for the projected no treatment curve corresponds to the pooled result for ' population based, face to face follow-up'; the projected early treatment curve corresponds to the 'pooled specialist stroke service' (Giles, M. F. & Rothwell, P. M. 2007a. Risk of stroke early after transient ischaemic attack: a systematic review and meta-analysis. *Lancet Neurol*, 6**,** 1063-72.

where **t** is the number of days follow-up since the TIA, **S**=the number of patients who survived the follow up period without a stroke and **So**=the number of patients in the group.

The technique for determining the baseline stroke rate and effects of treatment initiation are next considered graphically. A technical summary is provided at the end of this chapter. These calculations result in the projected early ('Proj Early') and projected untreated ('Proj no Rx') curves in Figure 5 and Figure 6, which illustrates modelled stroke free survival.
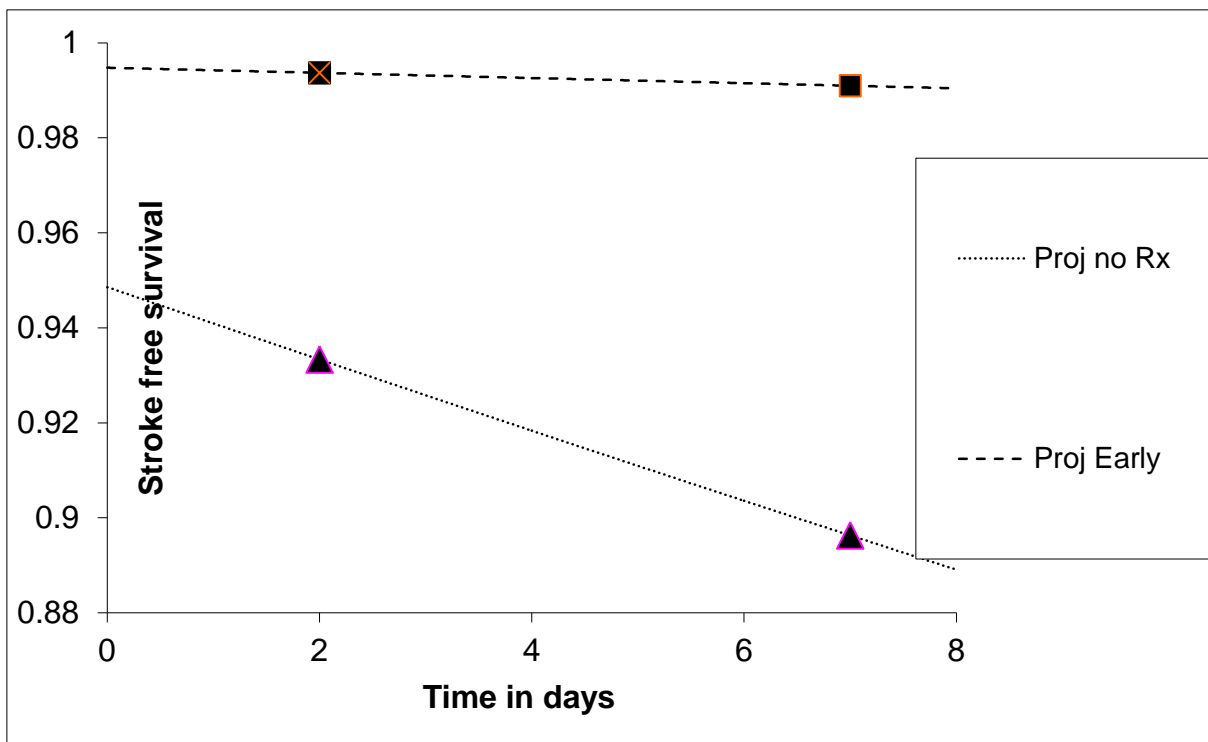
Figure 5: Modelling stroke free survival following TIA

The blocked squares relate to the observed data points within specialist stroke clinics. The blocked triangles relate to the observed data point within less urgently treated TIA. The proportion of the cohort remaining event free (stroke free survival) subject to treatment status is shown by the dotted curves joining the data points.

It was assumed that constant hazards applied within the intervals from 2-7 and 7-90 days. Inspection of Figure 6 reveals that extrapolation of the daily stroke rate as applied within the interval of 2 to 7 days back to day zero underestimates the true risk of events since Stroke free survival for both curves is less than one (as indicated by the y axis intercepts). A correction was therefore applied such that survival is maximum and equal to 1 at time zero, equivalent to the assumption that everyone in the cohort is alive at the point of presentation to the GP.

To do this, assumption of a constant daily stroke rate was made to extrapolate the survival data backwards from day two to the start (time zero) where survival is at a maximum and consequently equal to one. The resulting assumed early treatment curve (solid line) between days 0 to 2 in Figure 6 accounts for the excess risk within the hyper-acute period, before treatment is initiated.
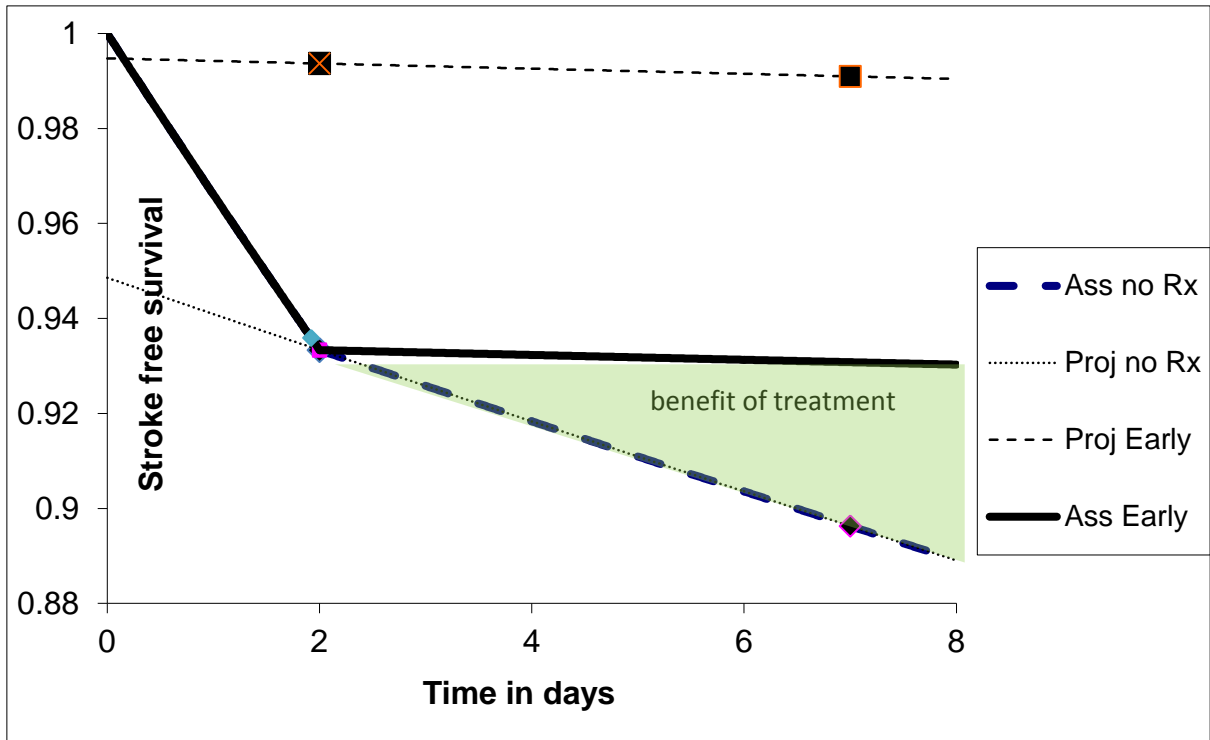
Figure 6: All stroke survival by strategy (first 8 days) under the strategy of best practice.

The blocked squares relate to the observed data points within specialist stroke clinics. The blocked rhombus shape relate to the observed data point within less urgently treated TIA. The proportion of the cohort remaining event free (stroke free survival) is shown by the solid line curve.

In turn, the modelled risk associated with the 'assumed early treatment curve' (solid dashed line) can be modified by the initiation of secondary preventive agents. Therefore, if treatment commences at the beginning of cycle 2, the daily stroke rate calculated from the 'specialist stroke clinic' data is immediately applied, modifying the underlying stoke risk. The benefit of treatment at day 2 is therefore shaded area between these curves. The 'assumed early treatment curve' in this instance corresponds to the model's strategy of best practice.

Note that while the lines appear to be straight line, a distribution using the exponential model was fitted. In addition the graphs have been truncated at 8 days for presentation purposes.

The technique allows for the initiation of treatments at different time points along a continuum. In all cases the baseline stroke risk is associated with the 'assumed no Rx' curve and treatment initiation modifies risk by applying a reduction in the daily stroke rate at the point of treatment initiation. Notice that at present this modelling assumes that all treatment is initiated uniformly either at day 1 (GPiT), day 2 (best practice) or day 7 (current practice) and that the benefit of treatment is instantaenous.

All stroke survival by date of treatment initiation

The estimates for all stroke survival for the first 10 days for by date of treatment initiation are shown in table x below (full 90 days for all strategies in technical appendix).

Time (in days)	(day 1) [values used in GPiT]	(day 2) [values used for base-case analysis best practice]	(day 7) [values used in current practice]
0	1	1	1
1	0.984481	0.984481	0.984481
2	0.983943	0.969203	0.969203
3	0.983406	0.968674	0.954162
4	0.982869	0.968145	0.939354
5	0.982333	0.967616	0.924777
6	0.981796	0.967088	0.910425
7	0.98126	0.96656	0.896296
8	0.981131	0.966432	0.896178
9	0.981001	0.966305	0.89606
10	0.980872	0.966178	0.895942

Adjustment by ABCD2 scores

The time dependent risks of stroke were then adjusted to accommodate the heterogeneity in the data with respect to ABCD2 scores. This was to enable important differences in the treatment effect across sub-groups to be interpreted at a policy level.

The incidence rates for high and low ABCD2 scores from the Johnston et al (2007) study were pooled. The stratified relative risk of these rates was then calculated. This allowed for

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disaggregation of the combined stroke risk curve by high and low risk sub-groups. The pooled analysis in Table 25 suggests that the relative risk in the low risk (relative to high risk) population might be relatively constant over time, and was therefore set at 0.2 in the base-case. Given that the underlying relative risk is affected by the incidence of patients with ABCD2 scores of 4 or above in the study population, disaggregation assumed that the proportion of patients with ABCD2≥4 was =0.5 (corresponding to a proportion of patients with ABCD2≥4 = 0.5). This is in line with the proportion of high risk cases observed in the Oxford cohorts used to derive and validate the ABCD2 score (Johnston et al., 2007).

Table 21: Strokes experienced by time point and ABCD2 score.

 (Observed frequencies within both clinic and validation cohorts are combined to increase sample size)

ABCD2 score	by day 2	by day 7	by day 90
0-3 incidence (n=1628)	17	20	40
4+ incidence (n=3171)	171	246	391

Table 22: Pooled analysis – relative risk of stroke for low risk populations

(Johnston et al. 2007)

ABCD2 score	by day 2	by day 7	by day 90
0-3 incidence rate (a)	0.0104	0.0123	0.0246
4+ incidence rate (b)	0.0539	0.0776	0.1233
relative risk (a/b)	0.1936	0.1584	0.1993

Mathematically, the disaggregation of stroke free survival followed from solution of a pair of simultaneous equations where L is the stroke free survival rate in the low risk sub-group and H is the stroke free survival rate in the high risk subgroup and S(t) is the Stroke free survival rate.

On the assumption that 70% of the cohort are low risk:

$$0.7L + 0.3H = S(t) \tag{1}$$

Using the incidence rate (where the proportion of the population at risk is given as 1-S(t)) gives the relative risk approximation of 0.2:

$$(1-L)/(1-H) = 0.2 \tag{2}$$

Rearranging:

$$(1-L) = 0.2 \, (1-H)$$

$$L = 0.8 + 0.2H \tag{3}$$

Substituting (3) into (1) gives:

$$0.7(0.8 \times 0.2H) + 0.3H = S(t)$$

Solving provides the rule for disaggregating S(t)

$$H = (S(t) - 0.56)/0.44$$

Application of this result can then be viewed on survival plots (next section).
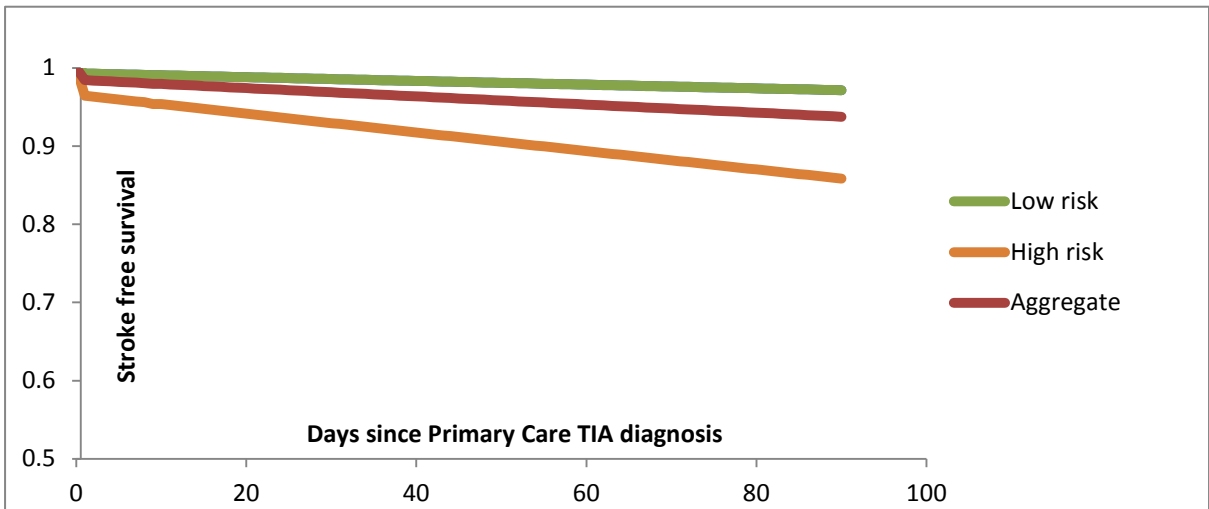
Figure 7: Stroke free-survival following TIA by risk group: initiation of treatment following GPiT
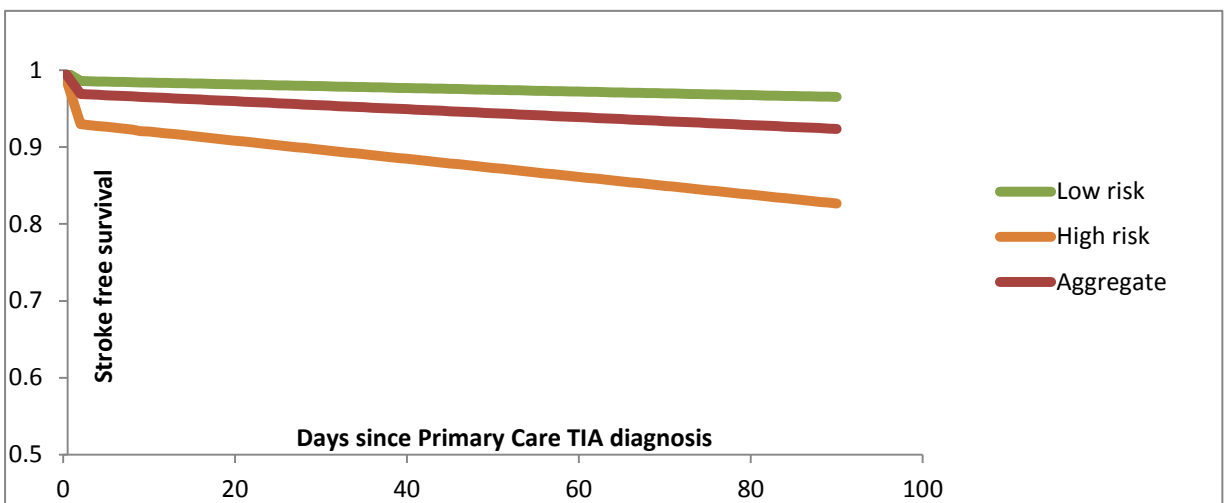
Figure 8: Stroke free-survival following TIA by risk group: corresponding to initiation of treatment following best practice
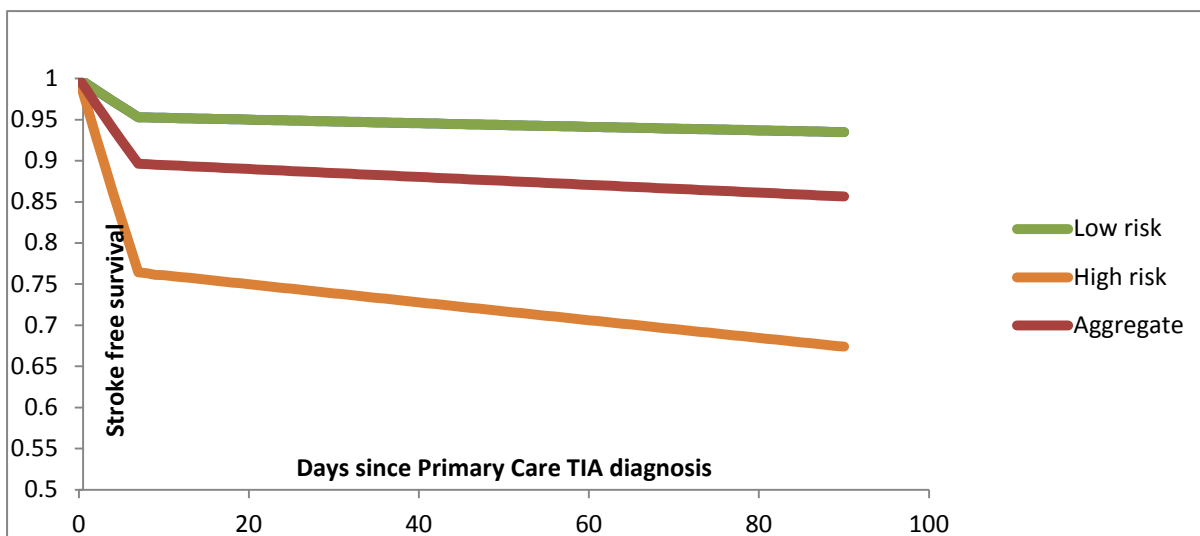
Figure 9: Stroke free-survival following TIA by risk group: corresponding to initiation of treatment following current practice

Table 23: Disaggregated survival by date of treatment initiation

Days since TIA	Low risk: Day 1	High risk: Day 1	Low risk: Day 2	High risk: Day 2	Low risk: Day 7	High risk: Day 7
1	0.984587	0.922936	0.984587	0.922936	0.984587	0.922936
2	0.984347	0.921737	0.969697	0.848485	0.969697	0.848485
3	0.984108	0.920539	0.969465	0.847327	0.955312	0.776558
4	0.983868	0.919341	0.969234	0.846169	0.941414	0.707071
5	0.983629	0.918144	0.969002	0.845012	0.927988	0.639939
6	0.98339	0.916948	0.968771	0.843855	0.915017	0.575084
7	0.98315	0.915752	0.96854	0.8427	0.902486	0.512428
8	0.982936	0.914679	0.968333	0.841663	0.902311	0.511553
9	0.982507	0.912535	0.967918	0.83959	0.901961	0.509804
10	0.982434	0.912169	0.967847	0.839236	0.901901	0.509505

Type of stroke experienced

In the model base-case, it was assumed that the proportion of ischaemic to haemorrhagic strokes experienced following TIA was 1.42/0.010 (Antithrombotic Trialists' Collaboration, 2002). This proportion was considered to be constant across all populations, i.e. for true TIA and mimic states, as well as for high and low risk individuals.

5.8. Mortality and risk of events (acute model)

Table 24: Model parameters for true TIA

	Data	Unit of data	Daily transition probability (where applicable)	Assumption
Probability of all stroke (at 2, 7 and 30 days)	Time and treatment dependent. **See separate survival analysis**			Pooled event rate data from specialist study clinics. (Giles and Rothwell, 2007a)
Relative risk of all stroke for low risk populations ABCD2<4 compared with ABCD2>-4 (at 2,7, and 30 days)	Estimated to be constant at 0.2	Relative risk	N/A	**Pooled analysis** of data (Johnston et al., 2007).

	Data	Unit of data	Daily transition probability (where applicable)	Assumption
Proportion of haemorrhagic strokes (as proportion of all stroke)	Incidence per 1000 per year Primary Intracerebral Haemorrhage/ Incidence per 1000 per year Ischaemic stroke = 0.10/1.42	Ratio	N/A	Calculated as a proportion of time dependent transition probabilities for stroke, Antithrombotic Trialists' Collaboration (ATC), (2002).
Probability of major haemorrhage (at 90 days)	Treated: 2.42% per annum Untreated: 0.10% per annum	Rate	0.0000671	ActiveW 2006 (Connolly et al., 2006) and ATC (2002).
Probability of other cause death	Age and sex dependent	Risk	(Standardised mean=) 0.0001608	UK lifetables (adjusted for mean age and sex of assumed cohort) with within model stroke and major haemorrhage deaths excluded.
Conditional probability of fatal ischaemic stroke (given ischaemic	6%	Ratio	0.0029926	Based on Lothian stroke registry (Counsell et al., 2002), reporting of outcomes at 6 months (2-10% with the risk

	Data	Unit of data	Daily transition probability (where applicable)	Assumption
stroke)				of fatality increasing in age deciles) and ATC 2002.
Conditional probability of fatal haemorrhagic stroke (given haemorrhagic stroke)	15%	Ratio	0.0039552	Based on the above sources (Lothian stroke register was for <u>all</u> stroke), but with the assumption that prognosis tends to be worse. Birmingham TIA model had conditional probability of death at 20%.
Conditional probability of fatal major haemorrhage (given major haemorrhage)	0.17% per annum	7	0.0000047	ACTIVE W trial (for dual antiplatelet arm).

Complications of carotid surgery, risk at 30 days

Expert opinion obtained within a model steering group meeting suggested that the risk modification (other than surgical death at 30 days) of carotid surgery could be explicitly modelled. A pragmatic decision was taken to not add in additional non fatal health states post complication (e.g. cranial nerve palsy). Data transitions from carotid surgery to

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ischaemic, haemorrhagic stroke and major haemorrhage were allowed. Data was obtained to see how surgery modified the risk of events, both at 30 days, and for the lifetime horizon. It was a model assumption that only symoptomatic stenosis of 70% or more would be treated, as this is the level that corresponds to current recommendation.

The risk of events post carotid surgery are provided as conditional probabilities in the literature. These were converted these to daily transition probabilities using an exponential model (see general formula under 'mortality rates' p.138)

Table 25: Model parameters for carotid surgery

	Data	Statistic type	Daily transition probability %	Assumption
Conditional probability of haemorrhagic stroke given carotid surgery (30 days from surgery)	0.018	Ratio	0.0597	Rothwell et al., (2004b), proportion ischaemic (2/3)
Conditional probability of ischaemic stroke given carotid surgery (30 days from surgery)	0.036	Ratio	0.1205	Rothwell et al., (2004b), proportion ischaemic (2/3).
Conditional probability of major haemorrhage given carotid surgery (30 days from surgery)	Assumed to be unchanged from treated TIA, not considered a significant outcome in the carotid triallists' collaboration	Ratio	-	Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST, 1998).
Conditional probability of surgical death given carotid surgery (30 days from surgery)	0.09	Ratio	0.3096	Rothwell et al. (2003)

Model parameters for TIA mimic

This table presents the parameters estimated for the TIA cohort presenting who are false positive, with a relatively minor other diagnosis. From the review of diagnostic accuracy, the likely explanation for this are likely to include: vertigo and dizziness, migraine, syncope. It was therefore felt that such sequelae were benign and would not be harmed by the initiation of inappropriate treatment. It was felt that this cohort might show some modest benefit from initiation of antiplatelet therapy.

Table 26: Model parameters for TIA mimic

	Data	Daily transition probability, %	Assumption
Probability of all stroke (90 days)	sum of haemorrhagic and ischaemic stroke	N/A - calculation	see below
Probability of ischaemic stroke (90 days)	Treated: 80% CI reduction in the risk of all stroke in a population aged 55-64 Untreated: standardised incidence per thousand per year 1.42.	Treated risk reduction = 0.00008 Untreated: 0.00039	Assumed same as per primary prevention populations of similar age to cohort. Treated: Wald and Law (2003); Untreated: Rothwell et al. (2004a).

Probability of haemorrhagic stroke (90 days)	All stroke – ischaemic stroke cases	N/A - calculation	Treated: Wald and Law (2003) Untreated: Rothwell et al. (2004a)
Probability of major haemorrhage (90 days)	Treated: Excess risk expressed as a prevalence per 100 people 2.3%	0.00027	From meta analysis of aspirin trials, Wald and Law (2003). This does not confer an excess risk of fatal major haemorrhage (prevalence per 100 people was -0.01 (0.07-0.05)
Probability of other cause death (90 days)	Age and sex dependent	Not varied	UK lifetables (adjusted for mean age and sex of assumed cohort) with stroke outcomes (ICD60-69) excluded

Transition probabilities for mortality

These rates were then converted to daily transition probabilities assuming constant hazards applied. Since no patients started in any of these states, the constant hazards were calculated on the basis of mean length of time in state using:

$$risk = 1\text{-exp}^{(\text{-rate})}$$

$$rate = \text{-ln} (1\text{-risk})$$

	Data	Daily transition probability	Sources
Conditional probability of fatal ischaemic stroke (given ischaemic stroke)	0.25 (at 90 days)	0.0030	ECST (1998); Rothwell et al., (2004b).

Conditional probability of fatal haemorrhagic stroke (given haemorrhagic stroke)	0.40 (at 90 days)	0.0040	Estimate based on Mant et al., (2004).
Conditional probability of fatal major haemorrhage (given major haemorrhage)	0.15 (at 90 days)	0.000005	Conservative assumption based on low fatality rate, ACTIVE-W

5.9. Estimation of Utility Data

The main outcome for the modelwas the QALY. The estimates provided were based on the Dorman et al. (2000) which elicited the quality of life in 867 UK patients who were participants in the International Stroke Trial using the EQ-5D. This study assessed health states by dependent 0.31 (95% CI 0.29-0.34), independent 0.71 (95% CI 0.68-.84) and fully recovered health states 0.88 (95% CI 0.84-0.92). Since all patients in this trial had had a minor stroke, not a TIA, the figure of 0.88 may under-estimate the utility of a patient in the TIA health state. In addition, as the Dorman study classified stroke according to the level of disability, there was no mean measure for Stroke. This was calculated by assuming that one third of all strokes are disabling (resulting in dependent health states), and the remainder non disabling (resulting in independent health states) i.e. 1/3 (0.31) x 2/3(0.71)=0.443 QALDS. This is the same assumption as applied in the NICE model. (NICE, 2008a).

The Dorman study did not report health states specific to carotid surgery and major haemorrhage. In addition, to date there appears to be no referencable single source of utilities for the health states included within the economic model. For these states (which

affect small numbers of the population) estimates were made about the health status (in QALDs) and plausible range. This followed from a search of the Centre for Reviews and Dissemination and PUBMED using the key word terms (i. carotid surgery or carotid endarterectomy, ii. major heamorhage, Quality of life, utility, EQ-5D) allowing for possible truncations to inform the estimate.

As the population moves through the 90 day acute model, patients accumulate QALDs as they remain in or transit to other health states. The assumption was made that patients who die within the 90 day period experience accumulate QALYs in the cycle in which they die. In the absence of a half cycle correction, this might lead to a negligible over-estimation of total QALDs in all arms (by a maximum 1 QALD per patient).

Table 27: Quality of life values used in the model

	Data	Plausible range	Sources
Post confirmed TIA	0.88	0.84-0.92	Dorman et al., (1997).
Stroke	0.44	0.33-0.55	Estimate obtained from Dorman with the assumption that 1/3 of all strokes are disabling i.e. 1/3(.31) x 2/3 (.71)=.443
Major haemorrhage	0.31	0.29-0.34	Assumption, TIA steering group, (2008).
Post carotid surgery	0.71	0.68-0.84	Assumption (as per dependent stroke).
Non stroke mimic (benign)	0.88	0.84-0.92	Assumption (as per TIA).

Non stroke mimic (serious)	0.31	0.29-0.34	Dorman et al. (1997).

An alternative source of QALYs commonly used in models of stroke that has been argued to have more face validity with clinicians, are those provided by van Exel et al. (2004). These utility values are based on direct comparison of proxy report on functional status (using the Barthel index) and self-report (by EQ-5D) in 598 stroke patients in the Netherlands. The authors found evidence in support of a stable relationship between the Barthel Index and EQ-5D. From this, it is possible to make a projection about the HRQoL on the basis of stroke severity. The values from the linear regression are shown in Table 28.

Table 28: Utility values by Barthel index, van Exel (2004)

Health status (Barthel index)	Utility	s.d.
independent (20)	0.75	0.00
mild (15-19)	0.63	0.07
moderate (10-14)	0.36	0.07
severe (5-9)	0.11	0.07
very severe (0-4)	-0.15	0.06

s.d. = standard deviation

5.10. Estimation of Cost and Resource Use data

Identification of cost and resource use estimates had three components. First, a rapid review of the costs of TIA and stroke in the UK was carried out. This identified one recent critical review on the cost of stroke in developed world countries, which reported the mean cost of stroke from 27 UK studies as US $22 377, the median as $15,720 and the range as $5026-107,860 (Luengo-Fernandez et al., 2009a). Adjustment using the appropriate purchasing power parity index for the year in question, the amount in US dollars equates to a mean in the region of £15,000. The Luengo-Fernandez study did not provide evidence on the cost of TIA, or non Stroke health states.

Second, the results from the included studies in this thesis' critical review of models following TIA in Chapter 3 were re-analysed. For each included model, the costing methods were appraised using quality criteria established by the Philips et al. (2006). Data was extracted in the following fields:

- Perspective and costing principles
- Resource use included in analysis

Finally a costing exercise was carried out to identify the most recent costs of capital and drugs from standard sources. (Department of Health, November 2012, British National Formulary, March, 2013).

Table 29: Data searches undertaken – Cost and Resource Use

Costs of care
GP clinic (per patient clinic)
Specialist daily clinic (per patient clinic)
Specialist weekly clinic (per patient clinic)
Mean length of inpatient stay and associated cost for all modelled outcomes: ischaemic, haemorrhagic, major haemorrhage, CE surgery
Capital expenditure by NHS associated with change in strategy
Medication costs based on prescribing (by strategy)
Pack price, dosage of medications used in the EXPRESS study drug algorithm (by class)
Length of course (by drug class)
Mean cost /per person/ per day (combined medication) for each alive state in model

Costs

Costs are calculated assuming an NHS perspective, inflated using the 2011 hospital pay and price index information from the PSSRU as necessary (Curtis, 2012). The main costs relate to the time in hospital, surgical procedures, and drug costs. A basic cost for a high-dependency hospital bed in a stroke unit, and the cost of in-hospital costs associated with carotid endarterectomy were obtained from the latest available NHS reference costs (2009/2010). The costs of medication were obtained from the British National Formulary 2011, and are summarised in Table 30.

Table 30: Drug costs included in the model

	Dose/ day					
Drug costs	(mg)	pack price	tabs/ pack	tabs/ mg	Cost/ mg	cost/ day
aspirin	75	£ 0.85	28	75	0.0004	£0.03
simvastatin	40	£ 1.17	28	40	0.0010	£0.04
dipyridamole	400	£ 2.87	84	100	0.0003	£0.14
lisinopril	10	£ 0.95	28	10	0.0034	£0.03
bendrofluazide	2.5	£ 0.81	60	2.50	0.0054	£0.01
Total estimated cost						£0.26

For simplicity the model assumed a standard drug regimen was applied, based on the most commonly prescribed statins and blood pressure lowering agents. The model assumed that all patients would be suitable for treatment of cerebrovascular risk factors with the full regimen (i.e. dual anitplatelets, blood pressure lowering agents and a statin).

This results in a combined cost of aspirin, dipyridamole, blood-pressure and lipid lowering drugs of £0.26 per patient per day. This combined cost, as well as those associated with GP and Rapid Access visits, inpatient stays, and carotid endarterectomy are those reported in Table 31. In the base-case analysis it was assumed that the course of secondary preventive medications was continued over the patient's remaining lifetime, however, current UK guidance is not explicit in recommending the duration of treatment with respect to dual antiplatelets. At the time of writing there appears to be no recommendation from the Royal College of Physicians on the optimal length of antiplatelet therapy for TIA and stroke, and NICE recommends that treatment should continue unless there is joint agreement on the

appropriateness of stopping (NICE, 2005). The model therefore assumes that the course of treatment would continue for 90 days; this corresponds to the length of follow-up in a number of trials and cohort studies of dual antiplatelets in TIA/stroke populations (NICE, 2005). The additional costs associated with the capital expenditure as the intervention was felt to be potentially resource saving. However, it is possible that such an intervention might shift the balance of care from specialty stroke services to GP providers of care.

Resource Use

GP follow-up identical in all scenarios, and is assumed to occur once within the 90 day model.

Table 31: Unit costs in the GPiT strategy model

	Data	Plausible range	Sources
Acute costs (90 days)			
Cost of secondary prevention medicines (combined/day)	£0.26	Not varied	BNF, price year 2012
Cost of GP clinic	£43.00	Not varied	PSSRU, 2012 (Curtis, 2012)
Cost of specialist clinic (daily/weekly)	£246.00	Not varied	NHS reference costs, year 2011/12
Cost of carotid surgery	£4,017.00	Not varied	NHS reference costs, year 2011/12
Lifetime costs			
Dependent after a stroke at 90 days	£57,378	(43,033-71,722)	NICE (2008a), inflated to current year using the Hospital and Community Health index (HCHI) (Curtis, 2012).
Independent after a stroke at 90 days	£8,415	(6,312-10,519)	NICE (2008a), inflated using HCHI
Recovered (GP follow-up) at 90 days	£887	(665-1109)	NICE (2008a), inflated using HCHI
Recovered (specialist follow-up) at 90 days	£1475	(1106-1844)	NICE (2008a), inflated using HCHI

5.11. Model assumptions

The objective of this section is to outline the methods relevant to the service delivery aspects of the model. Whereas the previous section was concerned with the derivation of transition probabilities for clinical patient progressions within the model (for the 2 patient populations: True TIA, TIA mimic) this section considers how the alternative TIA management strategies* impact on clinical patient progressions.

* i.e. best practice, current practice, GPiT (baseline), GPiT (high risk referral only) and GPiT (no referral).

Table 32: Assumptions for the base-case model

	Data (used in model)	Plausible range	Sources
Prevalence of true TIA in a primary care population suspected of having TIA	0.60	0.4-0.8	Estimated by review of **diagnostic accuracy**
Proportion of cohort with ABCD2 scores > 4 or above	0.30	-	From a prospectively identified cohort in the OXVASC study (Rothwell et al., 2004a)
Proportion of true TIA requiring carotid surgery	0.05	0.01-0.10	Estimated from (Wardlaw et al., 2004) Assumed 80% of people eligible will have surgery
Proportion of false positive TIA requiring carotid surgery	0.00	Not varied	Definition of benign TIA excludes patients with occlusion
Positive predictive value of a GP	0.50	0.3-0.7	Review of diagnostic accuracy (Chapter 6)
Positive predictive value of a stroke specialist	1.00	Not varied	Assumption

5.12. Sensitivity analysis for increased risk of major haemorrhage

An additional threshold analysis was carried out (for the base-case comparison, GPiT vs. best practice) to determine the robustness of the model to an increase in the rate of major extracranial bleeding in the TIA mimic population. This was intended to test the uncertainty surrounding the harm of inappropriate treatment in a population with misdiagnosed TIA in Primary Care. An analysis was performed in Excel by holding the other parameters within the model constant, and varying the daily transition probability TIA-major extracranial haemorrhage such that a maximum ceiling ratio of £20,000 per QALY was attained.[10] This provides detail of the maximum acceptable rate of major haemorrhage at which GPiT remained cost-effective.

Sensitivity analysis for poor prognosis in carotid surgeries foregone

An additional sensitivity analysis was carried out to adjust the model results for carotid surgeries foregone in the alternative GPiT strategies involving no referral for specialist assessment. This was to examine the impact of medical management of patients with significant stenosis. This adjustment applies to the GPiT alternative strategy with no subsequent referral and the alternative strategy with partial referral by ABCD2 risk score. In the latter case, carotid surgeries are only foregone in patients in the low risk group. No adjustment was made to the current practice scenario as the average treatment effect with

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[10] Formally this was done by using the EXCEL add-in 'goal seek'.

current practice is likely to already reflect poor prognosis as a result of delayed carotid surgeries.

Wardlaw et al. (2007) identify the cumulative risk of recurrent stroke as 29% at 90 days in the affected sub-group with carotid stenosis (defined as 70% occlusion according to ECST criteria). The equivalent rate in the period of 90 days to three years was 48%. The above figures suggest that in a cohort of 1000 suspected TIA cases, of which 500 are true positive, and 25 (5% of 500) are candidates for surgery. If no surgeries were offered, this would suggest that there would be approximately 7 recurrent events at 90 days and a further 5 events at 3 years, i.e. 12 recurrent events. These results do not indicate the excess risk of stenosis over and above patients without significant stenosis but the absolute risk. However evidence presented to date indicates that the risk is low in those without significant stenosis and on optimal medical management. There is an issue of which data source to use to control/adjust for a population without stenosis as there are problems with data reporting stroke rates stratified by degree of artery occlusion. Wardlaw et al. pool results for patients with no stenosis with those of complete artery occlusion (Wardlaw et al., 2006). The excess risk up to 90 days was therefore assumed to be the stroke rate from the best performing stroke clinics, and equivalent to the aggregate risk estimated using survival methods. i.e. about 0.2%. To be conservative, a sensitivity analysis was carried out on the short and long-term model predictions when the proportion of the cohort with stroke was assumed to increase by 7 (at 90 days) and 12 (for the lifetime horizon). The corresponding increases for the GPiT strategy with referral of the high risk cases only assumed that the excess risk of medically treated stenosis were 1.4 at 90 days and 1 at lifetime.

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5.13. Technical summary: Stroke free survival

Stroke free survival rates (proportion of the original cohort who are alive) at t=2, t=7 and t=90 (i.e. from the figures above 0.93, 0.90 and 0.83). In addition, it can be assumed that the entire cohort is alive at t=0 (i.e. where survival is at a maximum i.e. 1)

To calculate the proportion of the cohort free from stroke between the intervals of 2 and 7 days you need the stroke free survival rates (proportion of the original cohort event free) at t=2, and t=7 (i.e. from the figures above, using notation $S(t_2)=0.93$ and $S(t_7)=0.90$).

In order to estimate the proportion of the cohort event free at other points in time (t_i) within the interval for which we have data (i.e. $t_i=2,3,\ldots\leq 90$ etc.) one option is to calculate and apply survival methods.

An exponential function was used to implement time dependency in the model. It would be possible to use other functional forms here but the rationale for using this function was suggested by the clinical evidence on recurrence. To calculate this, the natural log of the ratio of the above survival rates is used to calculate the hazard or (instantaneous event rate) for any timepoint within the interval. In this case, t evaluates to 5 (the interval, in days, corresponding to the follow-up period relating to the data)

$$h_t= -\ln(0.90/0.93)/(5) = -0.0066.$$

(Note this evaluates to a constant hazard rate for all time points within the above interval)

    i.   The above four steps were repeated (substituting in for $S(t_{90})$ and $S(t_7)$) to estimate the hazard rate between 7 and 90 days.

ii.   Therefore the relation between the hazard rate and the survival function can be used to calculate continuous (stroke free) survival rates for the TIA population for any S_i within the interval for which data is required by the model, i.e. for days 2-90.

iii. To estimate points earlier in time, the above steps (i-ii) were repeated for the interval 0 and 2 where the stroke free survival rates were $S_0=100\%$ and $S_2=0.93\%$. (Note that $t=0$ is taken to be the point at which the patient presents to the GP).

iv.   This provides the modelling method for the non-urgently treated TIA.

v.   This exercise was repeated for specialist study clinics initiating optimal secondary prevention agents urgently to derive the hazard rates under optimum service delivery.

vi.   The two curves were used to implement treatment status. Patients faced the non-urgently treated TIA curve until treatment is initiated. At this point, the hazard rate from urgently treated TIA is applied.

Table 33: Cumulative event free survival: by strategy (first 9 days)

Time (days)	GPiT (corresponds to treatment on day 1)	Best practice (corresponds to treatment on day 2)	Current practice (corresponds to treatment on day
0	1	1	1
1	0.984481	0.984481	0.984481
2	0.983943	0.969203	0.969203
3	0.983406	0.968674	0.954162
4	0.982869	0.968145	0.939354
5	0.982333	0.967616	0.924777
6	0.981796	0.967088	0.910425
7	0.98126	0.96656	0.896296
8	0.981131	0.966432	0.896178
9	0.981001	0.966305	0.89606

<u>Discussion</u>

This chapter has outlined the methods for the identification and application of data to build and structure the GPiT strategy model. In one area, GP diagnostic accuracy, the need for a more structured literature review was necessitated. This is the focus of the next chapter.

CHAPTER 6: NARRATIVE REVIEW OF STUDIES ASSESSING THE DIAGNOSTIC ACCURACY OF GPS IN THE DIAGNOSIS OF TIA

6.1 Introduction

The rationale for this narrative review is to establish the accuracy of GPs in making the diagnosis of TIA. Previously, Chapter 5 identified GP accuracy as an important model parameter requiring a more structured and in-depth review. The need for a review on this subject was also highlighted in the discussion of the published Birmingham TIA report (Mant, 2008). The review question that the review is seeking to consider is 'What is the accuracy of GP diagnosis in patients with first-ever TIA?' The question is further refined by inclusion/exclusion criteria (section 6.2).

Given that the diagnosis of TIA is essentially clinical, a strategy of GPiT will correspond to an increase in unnecessary prescribing (one extra patient treated) for every false positive GP diagnoses made. It therefore follows that the ability of the GP to identify and treat just the true positives could be a key driver of the cost-effectiveness of the intervention strategy.

A linked aim of the review is that it will also record what the final diagnoses of non true TIA are, i.e. those diagnoses suspected by the GP as TIA but ultimately receiving non-stroke diagnoses. The clinical outcomes of the false positive diagnoses will be important in identifying the potential harm of early initiation of GP treatment. From the answer to the review question it will be possible to determine the number of false positive diagnoses in a

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hypothetical population. Additional information on the underlying pathologies of stroke mimics will enable judgements to be made on the harms posed by treatment.

One contribution of this review is therefore that it will help define the profile of patients receiving the GPiT intervention. This is of clear import to policy makers. Methods for the review are provided overleaf, starting with the search questions.

6.2 Methods

Search 1a: What is the accuracy of the primary care doctor's diagnosis in patients TIA?

Inclusion criteria:

- Studies reporting details of diagnostic accuracy of TIA/minor stroke (ischaemic or all stroke)

- Studies reporting diagnostic accuracy of clinicians in Primary or pre-hospital care

- Study design: any original research papers or secondary reviews of diagnosis of stroke in the community

- Year 2000 onwards

- Reference standard: usually specialist diagnosis (will include and report other methods of verification)

Exclusion criteria:

- Studies designed only to test accuracy of a diagnostic instrument (for instance screening tool) where no evidence on the accuracy of the clinician is provided

- Studies which do not include strokes or TIA first triaged in Primary or pre-hospital care

- Studies with incomplete or missing description of the methods for verifying diagnosis

- Studies which do not quantify accuracy (or allow for quantification of accuracy), for example by not reporting sensitivity, specificity, positive

predictive or negative predictive values (or allowing them to be calculated from detail provided)

Seach 1b: What differential diagnoses occur in TIA/mini stroke first assessed in Primary Care?

Inclusion criteria:

- Studies reporting details on differential diagnoses where TIA is initially suspected

- Quantification of differential diagnoses must be provided, for instance in percentage terms or absolute frequencies

- Any setting (preference to Stroke/TIA presenting in Primary or pre-hospital care)

- Study design: original research or secondary reviews

- Year 2000 onwards

Documentation of search strategy

As evidenced above and by the search strategy reproduced in Appendix 2 (p.210). Where possible, standardised subject terms were used with additional keyword searches. A review of the papers identified in the earlier Birmingham TIA report with a focus on index words informed this process. The specific search words included the following (allowing for possible truncations) "Diagnostic accuracy", "Predictive Value of Tests" "Sensitivity" "Specificity" and "Transient Ischaemic Attack".

The Embase/Medline databases were searched on 02/06/2009 and were too limited to those published between 1989-2009 week 19 (initially), updated to 2013 week 12. In addition a review of the Cochrane Library (including DARE database) and MEDION database was conducted to identify any additional studies in diagnostic accuracy of TIA/stroke. None were found. References of included studies were also checked.

201 identified studies

↓

201 abstracts for first review

↓

n =11 for main search (includes information on accuracy)

Of which n=5 (information on alternative stroke diagnoses)

Figure 10: Study flow

Table 34: Study methods

Author (year) [country/ study type]	Study population and size	Index test	Reference standard	Verification method
(Fischer et al., 2008) [Denmark/ retrospective cohort]	All (n=583) patients classified as having acute cerebrovascular accident at a mobile emergency care unit.	Physician trained in advanced life support but with no specialist training in neurology.	Diagnosis applied was the primary diagnosis at point of discharge from hospital.	Screening of hospital information systems at 6 hospitals. Non randomised comparison of consistency between all referred medical records and hospital information system at the study author's hospital.
(Mant et al., 2003) [UK/ retrospective cohort]	All registered participants (n=5801) at participating GP practices.	GP	Study authors. Confirmed TIA.	Authors applied a set of reference criteria to decide if the TIA or stroke was substantiated based on the evidence. TIA diagnosis required a record by the GP corroborated by the specialist and Stroke diagnosis was only made where there was evidence from 2 sources (or 1 source and patient record).

Author (year) [country/ study type]	Study population and size	Index test	Reference standard	Verification method
(Gibbs et al., 2001) [UK/ prospective cohort]	Random sample (n=60) of patients referred to TIA clinic.	GP	Specialist	Case note review. (Random but limited sample of referred TIA and stroke suspects was selected (n=60) from General Practice Research Database for case note review).
(Harbison et al., 2003) [UK/ prospective cohort]	All (n=487) patients referred to the stroke unit, of which (n=216) were referred from Primary Care.	Primary care physicians, A&E doctors and ambulance staff using the Face Arms Speech Test.	Specialist. (Time based definition for TIA).	Independent review of medical records by two study authors (neurologists in training). Areas of disagreement were discussed with lead study neurologist.

Author (year) [country/ study type]	Study population and size	Index test	Reference standard	Verification method
Tomasik et al. (2003) [Poland/ GP survey]	N/A (survey, n=100 GPs).	GP	Two GPs with special interest in vascular diseases. (Not indicated whether there was independent verification by two study authors for each questionnaire. If this was not the case study may lack agreement between verifiers).	GPs with special interest in vascular diseases identified if proposed diagnosis/management was: i. correct ii. probably correct or iii. Incorrect.
McNeill (2008) [UK/ prospective cohort]	Patients admitted to the stroke unit (n=72) on the basis of primary care doctor's referral letter.	Primary care doctor.	Admissions doctor at stroke unit (Senior House Officer).	Hospital notes and study author's opinion. It is not stated explicitly that the study author and the admitting Senior House Officer were the same person.

Author (year) [country/ study type]	Study population and size	Index test	Reference standard	Verification method
Kidwell (2000) [US/prospective cohort]	Consecutive transfers (n=1298) to a medical centre	Paramedic (using the Los Angeles Prehospital Stroke Screen)	Specialist	Medical review and case discussion by two neurologists.
Bos et al. (2007) [Netherlands] [prospective cohort].	Population based (n=6062) in those without disease with no relevant prior comorbidities (stroke/MI/ dementia).	Not directly applicable. Study objective was to identify the incidence and prognosis of different types of transient neurological attacks. Study therefore aimed to ascertain all transient neurological attacks within community.	Not directly applicable. Study classified transient neurological attacks into 3 categories: focal (i.e. equivalent to TIA), non-focal and mixed (for TIAs with focal and non-focal symptoms).	Electronic linkage of data sources from General practices, Mental health outpatients and face to face survey methods.

Author (year) [country/ study type]	Study population and size	Index test	Reference standard	Verification method
Fonseca et al. (2011) [Portugal/ prospective cohort]]	Cohort of consecutive referrals (n=578) [suspected TIA time-based definition] patients attending a once weekly TIA clinic.	GP or A&E diagnosed TIA, referred to clinic.	Specialist diagnosis.	Data collected on neurological, laboratory and imaging exams. Two independent observers classified patients into groups: TIA, Mimic, TNA: difficult to classify). Kappa statistics showed good inter-observer agreement (k=0.89, 95% CI: 0.8509.93).
Magin et al. (2013) [Australia/ prospective cohort]	All referrals with suspected TIA [time-based definition] (n=344) from GP or Emergency departments.	Referred to TIA clinic.	Specialist stroke physician. Most cases informed by MRI.	Clinico-radiological assessment.

Author (year) [country/ study type]	Study population and size	Index test	Reference standard	Verification method
Cameron et al. (2011) [UK/ prospective cohort: with suspected TIA]	Consecutive referrals (n=3553) to acute access TIA clinic.	Referred to TIA clinic (source not discussed). TIA was not further defined.	Clinical diagnosis of cerebrovascular (TIA). Authors acknowledge outcome includes some minor stroke.	Standardised assessment verified by senior stroke physician.
Murray et al. [UK] (2007)	All new referrals (n=813) to TIA clinics.	Referred to TIA clinic.	Specialist diagnosis.	Not discussed.

Table 35: Summary of results

Note: These tables detail summary data. A detailed view of the data extracted with a view to the graphical presentation of results are tabulated in Table 47 and Table 48 (p.212-214).

Author (year)	Study purpose	Estimate of clinician accuracy	Estimates of other diagnoses (accounting for >5% of non-stroke diagnoses)
Fischer et al. (2008)	To calculate the proportion of patients admitted with a suspected stroke who had a final diagnosis at hospital discharge of 'acute cerebrovascular incident'.	Positive predictive value of initial diagnosis of stroke = 30.1% (95% CI 26.3-34.1).	Unclear reporting. Specific diagnoses not detailed. Authors refer to non-stroke neurologic disease, systemic and non-systemic disease without further explanation.
Mant et al. (2003)	Comparison of three different methods for identifying prevalent cases of cerebrovascular disease in the community: GP database systems; population surveys and hospital information systems.	Sensitivity of GP (the GP database records) = 80%, specificity = 97% and the positive predictive value = 70% (95% CI: not reported).	Not provided.

Author (year)	Study purpose	Estimate of clinician accuracy	Estimates of other diagnoses (accounting for >5% of non-stroke diagnoses)
Gibbs (2001)	Stated aim 'to establish the difference in burden of cerebrovascular disease across the different health regions of the UK and to determine the initial management of new cases of stroke and TIA was uniform across the UK'.	Of those (n=30) cases coded as TIA on the General Practice Research Databasen (GPRD), 48% were confirmed as correct by specialist. A further 18% of TIA diagnoses received a stroke diagnosis. Of those coded as stroke 64% were correct and 16% were given a final diagnosis of TIA. These suggest an overall GPRD PPV of approximately 48% (66% if all CVA) and 64% (80 if all CVA). (CI: not reported).	Limited information due to small study size (n=60). No non-stroke diagnoses were observed in more than 5% of patients.
Harbison (2003)	To assess the diagnostic accuracy of stroke referrals from Primary Care and Emergency Room physicians, and ambulance staff using the Face Arm Speech Test?	Primary care physicians had a PPV = 71% (95% CI: 65-77%).	Information on non strokes and other diagnoses recorded by primary care doctors with a greater than 10% incidence were: infections and sepsis 14%, malignant tumour 11%; seizures 10% and deteriorating dementia 10%.

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Author (year)	Study purpose	Estimate of clinician accuracy	Estimates of other diagnoses (accounting for >5% of non-stroke diagnoses)
Tomasik (2003)	How competent are Polish primary care physicians in diagnosing and managing patients with transient ischaemic attacks in the carotid territory?	Standard test statistics not reported or calculable. (Authors state that proportion of patients receiving correct diagnosis ranged from 20-78%: this includes true positives and true negatives. Incorrect diagnoses occurred in 3-42% of cases: this includes false positives and false negatives).	Not applicable.
McNeil (2008)	How accurate are primary care referral letters for presumed acute stroke?	Standard test statistics not reported or calculable. Author's state 'Primary care doctor's diagnosis was correct in approximately 30% of cases'.	Identified as falling mainly into 2 groups: elderly patients which typically have general medical conditions such as sepsis or delirium and present with features such as: confusion (16%), falls/poor mobility (12%) and vertigo (7%). Second group: patients with functional neurological disorders (detail not provided) displaying focal neurological signs.

Author (year)	Study purpose	Estimate of clinician accuracy	Estimates of other diagnoses (accounting for >5% of non-stroke diagnoses)
Kidwell (2000)	To validate an instrument used by paramedics to detect ischaemic stroke, currently symptomatic TIA and intracerebral haemorrhage.	Paramedics trained in a screening instrument (non adjusted for documentation errors) resulted in sensitivity=91% (95% CI: 71-98), specificity=97% (95% CI: 93-99), PPV=86% (95% CI: 70-95) NPV=98% (95% CI: 95-99).	Not reported.
Bos (2007)	To incidence and prognosis of focal Transient neurological attacks (TIA), non focal Transient Neurological Attacks (TNA) and mixed Transient Neurological Attacks.	Standard test statistics not reported. 282 of the 554 (51%) Transient Neurological Attacks (TNA) that occurred were TIA, 228 were non-focal and 38 were mixed. 12 TNAs did not fit into any category. This study had higher ascertainment of TIA in the community (i.e. false negative TIA was detected) due to the use of survey methods.	Underlying pathologies for non-focal and mixed TNA not reported, but the long-term prognosis was assessed by Kaplan-Meier survival analysis. There was a high risk of vascular death and dementia in non-focal TNA.

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Author (year)	Study purpose	Estimate of clinician accuracy	Estimates of other diagnoses (accounting for >5% of non-stroke diagnoses)
Fonseca et al. (2011)	To classify patients with transient neurological attacks (TNA) and identify frequent problems in establishing diagnosis.	PPV (TIA or possible TIA)= 65.2% PPV (confirmed TIA with recent ischaemic lesion on imaging)= 19.7%	Not reported.
Magin et al. (2013)	To establish paths and care for patients referred by GPs and emergency departments to an acute access TIA clinic.	PPV (all referrals to clinic, TIA) = 52%	Not reported.
Cameron et al. (2011)	To describe long-term outcome following attendance at a TIA clinic.	PPV (all referrals to clinic, TIA)= 52%	Not reported.
Murray et al. (2007)	To describe profile of referrals to TIA clinic.	PPV (all referrals to clinic, TIA)= 26.8% PPV (all referrals to clinic, composite stroke)= 47.3 PPV (GP referrals, TIA)= 28.2% PPV (GP referrals, composite stroke)= 49.7%	Migraine 8.9%, syncope 7.7%.

6.3. Quality Assessment of Studies

The QUADAS-2 checklist for the purposes of assessing the quality of primary diagnostic accuracy studies was used to inform the rigour and validity of the review process (Whiting et al. 2011).

Since assessing the accuracy of GP diagnosis is distinct from the usual test accuracy studies for which the checklist was developed, some of the QUADAS-2 criteria were less applicable to the specific review considered here. These items were omitted, and the descriptive tool is therefore not included either.

It is nevertheless interesting to consider the ways in which this test accuracy studies considered in this review are different from the traditional test accuracy studies (Table 36).

Table 36: Differences between GP clinical accuracy studies, and more standard studies of test accuracy

Inclusion of test characteristics

Full results on the accuracy of the test were often not presented, as there was no follow-up on participants receiving a negative diagnosis. This excludes all but the potential to report the proportion of people with a positive test who have the condition (positive predictive value, hereafter PPV). It would, in fact, be interesting to have information on false negatives and true negatives (to enable sensitivity and specificity to be calculated),

Index test

As stated in Chapter 2, the diagnosis of TIA is essentially clinical, unless supported by facilities for imaging and interpretation. These services are not currently available for mainstream use in the UK NHS, so the diagnosis of TIA in Primary Care is entirely clinical.

Reference standard

Although specialists have access to imaging, the reference standard still rests on a clinical diagnosis which may not correctly identify true positives. In addition, the reference standard might be more prone to vary across studies, as there may be disparity in how studies classify/define TIA (as it is currently unclear if there is concensus on the 'new' tissue-based definition of TIA) and whether they consider a stroke misdiagnosed as a TIA as incorrect diagnosis.

Sequence of tests

It follows from the above point also that the reference standard is only routine in patients with a positive diagnosis, therefore the diagnostician in the reference case can not (normally) be blind to the results of the index test.

Appropriacy of meta-analysis

Meta-analysis is useful in generating an overall measure of tendency from multiple studies, by quantitatively pooling results from individual studies. While it may be appropriate to meta-analyse estimates of sensitivity and specificity from diagnostic accuracy studies, the same is not conventionally undertaken in studies of positive and negative predictive values. This is because the latter measures are heavily influenced by the prevalence of disease in the population, and therefore meta-analysis in these cases would be of limited value, unless the studies were all drawn from study populations with the same prevalence of TIA. Given the essentially clinical diagnosis of TIA, it seems unlikely that studies will be able to discriminate between true and false negative cases that would be required to determine sensitivity and specificity. (For one thing, in routine clinical practice, it is unlikely that the negative cases would come to light). For this reason, no attempt to meta-analyse PPVs (or any other aspects of diagnostic accuracy) will be made, however, Forest plots will be used to indicate the 95% CI ranges corresponding to the point estimates of effect size.

6.4. Results

The search identified 201 studies. Of these, 11 met the eligibility criteria (Figure 6.1 flow).

The majority of the studies were conducted in the UK, one in each of Portugal, the Netherlands, Australia, Denmark and Poland. Of the included studies recruiting patients, the smallest study size was 72 in a prospectively identified TIA clinic cohort, the largest 6062 in a prospective, population-based cohort of participants with no history of TIA.

However, the majority of studies used a prospective cohort. Usually the cohort would be composed of consecutive referrals to a TIA clinic (to avoid bias); so the index test was the GPs clinical evaluation of the patient resulting in referral. The study would then compare the results of the index with the reference standard (typically specialist diagnosis). This study design is therefore analogous to how diagnoses are made in practice, and would appear applicable to this thesis' review question.

In the main, patients were recruited on the basis of having TIA clinic referrals for suspected TIA or stroke. Exceptions to the rule included a study looking at the rapid transfer of patients to hospital by ambulance, a population-based study of the incidence of TIA in the community and a study designs looking at the consistency in different methods of record linkage. One postal survey of GPs asked them to consider their diagnosis in response to a series of vignettes.

Three studies focused on pre-hospital emergency setting whereas others focused on TIA and stroke in the community. This suggests that there may be have been differences in the

way the diagnosis was made. For instance, paramedics attending a TIA may use a specific screening tool to establish patient's risk (Kidwell et al., 2000). Across these 2 groups it would also be likely that there would be some differences in the acuteness and severity of the patient's symptoms. It seems plausible that the condition be more severe in the former, but also the presence of non-TIA diagnoses may be different. As these factors could account for plausible differences in test statistics presented, descriptive presentation of results was restricted to settings which were predominantly composed of suspected TIAs identified in Primary Care. Full details of all studies is provided in 'Appendix 4: Data extracted on Diagnostic accuracy and alternative stroke/TIA diagnoses' (p212).

The proportion of study participants with a suspected TIA and a final diagnosis of TIA ranged from 4% to 57% (figure 1). The proportion of study participants with a suspected TIA and a final composite outcome of TIA or stroke ranged from 20% to 86% (figure 2). These results appear to be symptomatic of the heterogeneity in the selection of participants and the method by which the reference diagnosis was established. Note that a full results table is provided in the appendix.

With a final diagnosis of TIA:
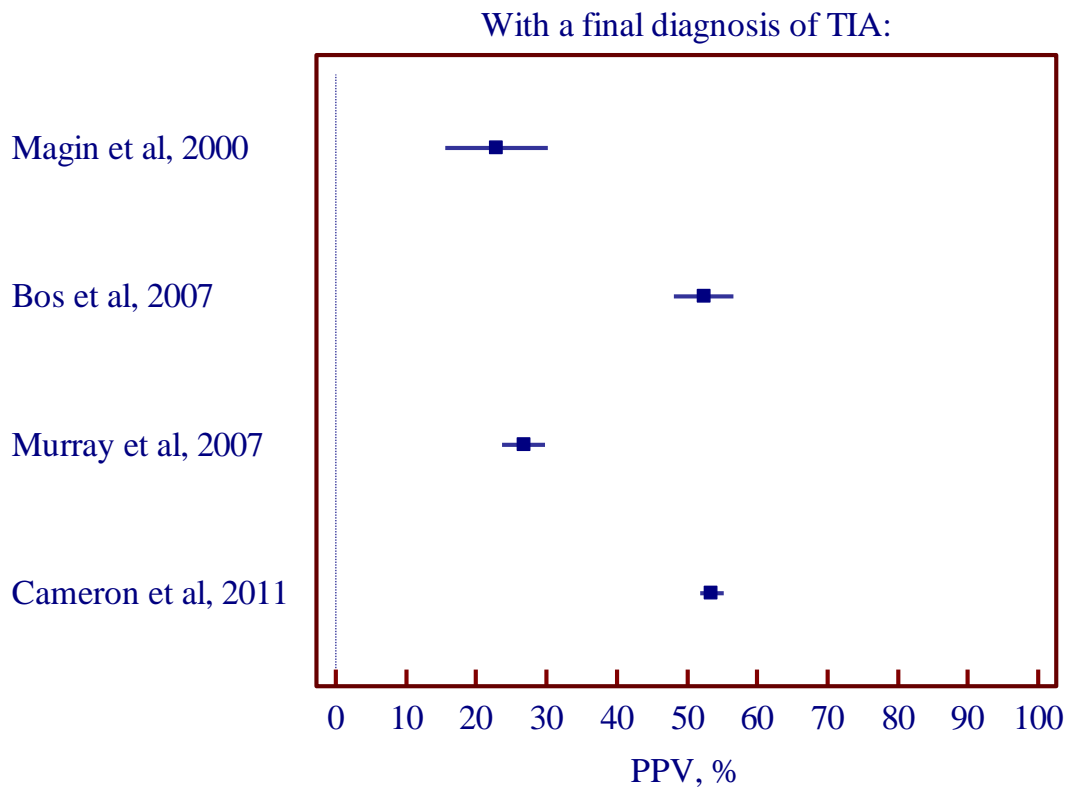
Figure 11: Positive predictive values of GP diagnosis in TIA‡

‡ Where not reported in the primary paper, 95% confidence intervals were estimated using the estimate of standard error for a proportion (Bland, 2000).

With a final diagnosis of TIA or Stroke:
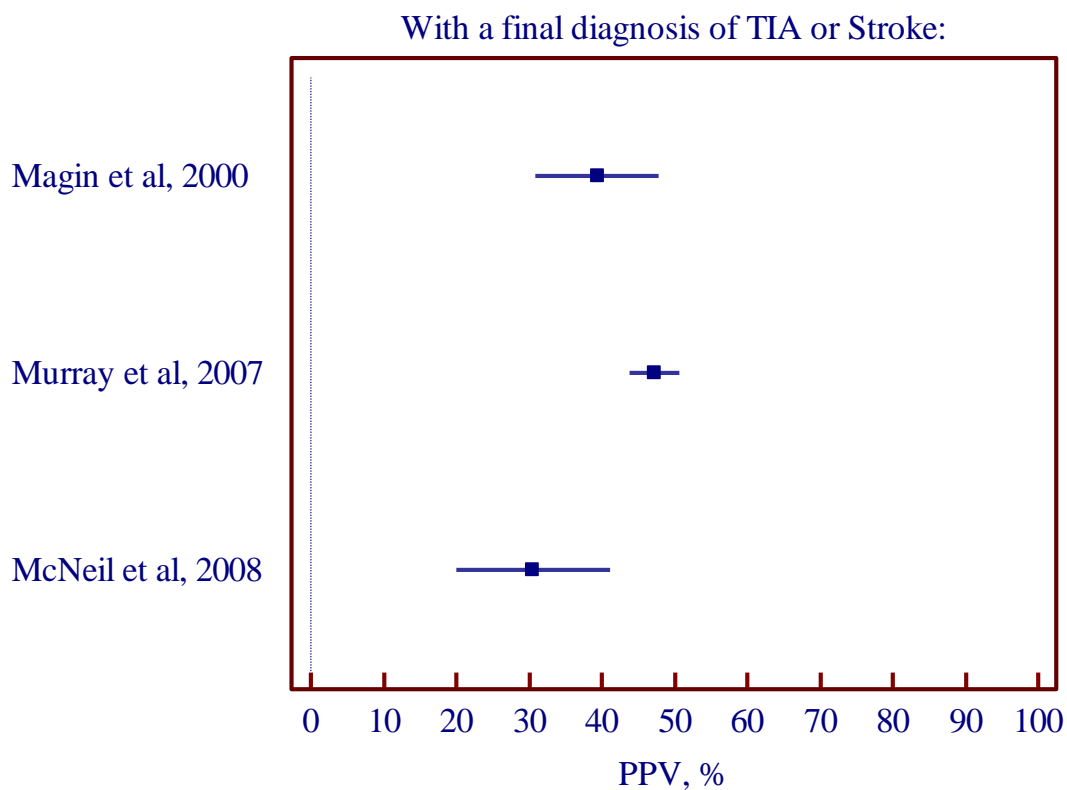
Figure 12: Positive predictive values of GP diagnosis in TIA or stroke‡

‡ Where not reported in the primary paper, 95% confidence intervals were estimated using the estimate of standard error for a proportion (Bland, 2000).

The linked aim of this review was to record the diagnosis of the false positive TIA cases. Only 5 of the studies reported on the final diagnoses received by patients (Gibbs et al., 2001). Of these, the study by Fischer et al was excluded from analysis (but not extraction) because it did not identify alternative TIA/Stroke diagnoses in Primary Care, and inclusion would therefore bias results. The details of all non TIA/stroke diagnoses were tabulated using the author's classification system initially. Following this, diagnoses were sorted by pathological cause, and results were pooled to provide the mean incidence.

The most common alternative diagnoses are presented in Figure 13. Few alternative diagnoses would be worsened by the initiation of secondary preventive drugs. Clinical Knowledge summaries (NICE) identify no specific contraindications for dipyridamole and that the risk of bleeding is no greater than with low dose aspirin alone (NICE, 2013). For this reason, the main contraindication would be active pathological bleeding. Therefore, Figure 19 presents detail on the alternative circulatory diagnoses. Full detail on all alternative diagnoses are presented in Appendix 4: Data extracted on Diagnostic accuracy and alternative stroke/TIA diagnoses.
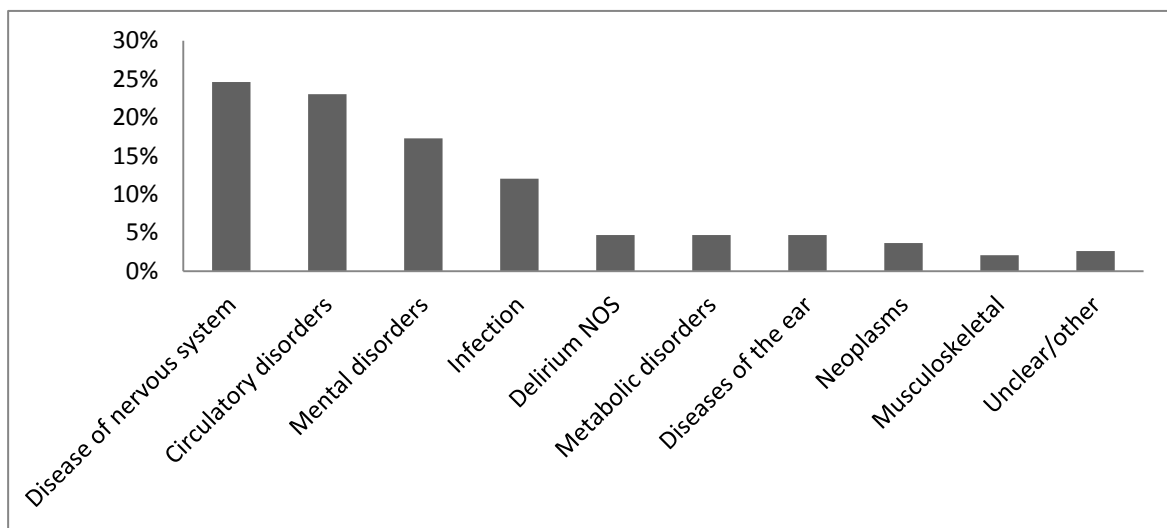
Figure 13: Alternative pathological cause in false positive GP diagnosed TIA (n=185) (NOS = not otherwise specified.)
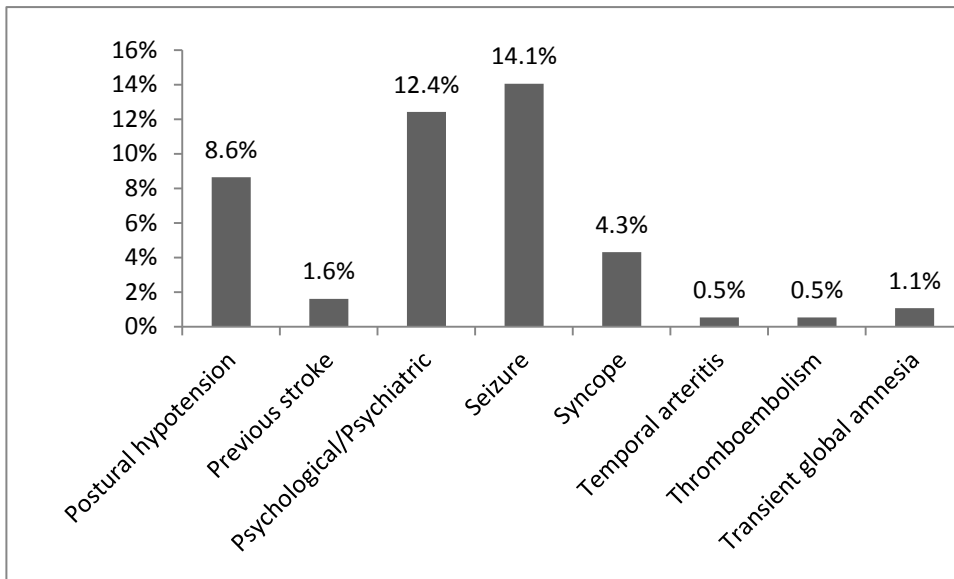
Figure 14 Percentage of all non-stroke diagnoses† observed in at least 0.5% of the sample

† Excludes [ICD-10 60-64 inclusive and TIA]; Psychological/psychiatric also includes dementia.

Within these studies, there were some characteristic differences in the way the alternative diagnoses were defined. For instance, in some cases the diagnoses seemed to relate to well-known category codes used in hospitals, whereas in others the authors seemed to have grouped diagnosis together. There were pitfalls of both methods. The first method resulted in a myriad of alternative diagnoses such that no diagnoses was recorded in more than 5% of participants whereas the second resulted in a loss of precision. An unexpected finding was that two studies (identified for this test accuracy review) used longitudinal follow-up to examine the prognosis of false positive TIAs, but did not report the alternative diagnosis causing the TIA (Bos et al., 2007).

However, half of the non-stroke diagnoses were explained by an underlying neurological or circulatory pathology (Figure 13) and over a third were explained by either seizure,

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syncope, hypotension or mental, behavioural or neurodevelopmental disorders (such as dementia, see Figure 14). There was therefore limited evidence to suggest a heightened risk of adverse events under the GPiT strategy.

6.5. Discussion

Summary of key findings

A review of studies in the diagnostic accuracy of TIA found that the majority of studies did not identify/report on negative cases. This review has therefore focussed on reviewing the positive predictive values presented in primary studies. Quality assessment suggested there was substantial concern about the risk of bias and applicability when comparing test statistics obtained in different settings and study designs.

A stratified analysis (presented using descriptive forest plots) was performed to demonstrate the positive predictive values in two instances: i. GP referred TIA receiving a final TIA diagnosis ii. GP referred TIA receiving a diagnosis of TIA or stroke. Meta-analysis was not performed for fear that the underlying prevalence of TIA could bias results.

A subsidary aim of this review was to identify the typical diagnoses in fase positive TIAs in a subset of studies identified within the main search. Common alternative diagnoses (defined as occuring in at least 5% of TIA or combined TIA/ minor stroke referrals) included syncope, dementia and migraine. In the main, this is consisent with the generally reported finding that most false positive TIAs had other neurological or vascular

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explanation. In two studies looking at outcomes over a longer period of follow-up, there was more convincing evidence that false positive TIA are associated with poor prognosis in terms of cardiovascular and neurological outcomes.

Limitations

There was a general question over the applicability of test-accuracy review methods to the accuracy of diagnoses made by GPs. This review did not provide the level of information to inform estimates on the precision of the positive predictive values, nor did it provide any robust information on the numbers of false negatives. The latter is of interest to policy makers as missed diagnoses constitute a susceptible group of patients that warrant the intervention but are missed in all the modelled scenarios. In practice, it might be that the GPiT intervention could also include some training of GPs to better recognise the symptoms of TIA. There may also be more attention given to training the public to better recognise symptoms and take appropriate action. Of course, both these measures will only be effective if they ensure that more of the target population are identified for treatment and remain to be tested in TIA.

Recommendations to future research

It may have been insightful to consider the accuracy of GPs in other conditions more generally as part of this research question. It might be interesting to compare referrals for chest pain or asthma, for instance. This might provide some guidance on how susceptible patients are identified in other disease areas where there is a similar speed of onset and opportunity for effective treatment. It was not possible to apply standard test accuracy

appraisal methods to primary studies which, in the main, restricted the reporting of results to PPVs. The methods used within the diagnostic review here, and elsewhere, offer possible approaches (Shapley et al., 2010, Astin et al., 2011).

Implications for the model

In conclusion, this review suggests a significant proportion (at least 50%) of suspected TIA cases identified by GPs ultimately receive some other (non-stroke) diagnosis, and therefore represent the broader population for a service delivery intervention in Primary Care. In addition, this review has highlighted something possibly unexpected: potentially high vascular risk (and so a likely benefit from treatment) in the false positive cohort.

CHAPTER 7: RESULTS OF THE COST-EFFECTIVENESS ANALYSIS

7.1. Introduction

The objective of this chapter is to present the results of the model based economic evaluation. The overarching aim of this thesis is to examine the cost-effectiveness of GPiT when compared to existing strategies based on current clinical practice and guidelines. Along with the key summary-level information (incremental costs and benefits), data is also presented on the sequelae of clinical events (e.g. stroke-free survival, major haemorrhagic events and carotid surgeries) following TIA at 90 days.

7.2. Approach

As discussed in Chapter 2, the budget for healthcare is finite. In order for healthcare purchasers to maximize health gains from a limited resource, the framework of economic evaluation was used to compare the costs and consequences of GP initiation of treatment versus strategies based on existing clinical practice. A decision-analytic Markov type model was developed to make a projection about the cost-effectiveness of GPiT relative to existing options. The main comparison compares GPiT to: i. best practice (base-case) ii. current practice (this is a "secondary" analysis). Comparisons are made at 90 days and over a lifetime time horizon. The chapter concludes with a summary of findings.

7.3. Clinical outcomes

The following outcomes are presented for a cohort of 1000 people with suspected TIA at 90 days: number of non-fatal or fatal ischaemic stroke, haemorrhagic stroke, major haemorrhage and carotid surgery events. In addition, figures 15-17 plots the event status

over the 90 days corresponding to the Markov model time period. These categorise the number of persons according to event status: well (for TIA and recovered carotid surgery states); non-fatal major event (for non-fatal stroke and major haemorrhage states) and dead. The contrast between strategies appears in the gradient of the curve for major events in the first 10 days of the model corresponding to differences in timings of treatment initiation over this period.

For reference, in the model time period of 90 days, the number of strokes anticipated in the best performing Oxford Vascular study cohort would be 6 per 1000; compared with 104 per 1000 in less urgently treated cohorts (Rothwell et al., 2007). Furthermore, assuming that 5% of the population are eligible candidates for surgery and the proportion of the population with true TIA is 50%, a maximum of (0.05 x 50=) 25 carotid surgeries could be anticipated (Wardlaw et al., 2006, Sudlow and Warlow, 2009).

The base-case model projections for rate of stroke (17.4 per 1000) in best practice are higher than the rate observed in the best performing stroke clinic, but the projections are within the anticipated bounds of other rapid access stroke clinics. Comparison of the number of strokes experienced at 90 days under best practice with that of current practice reveals a 75% reduction in the stroke rate which is also consistent with evidence on rapid access stroke clinics reviewed (Luengo-Fernandez et al., 2009b, Lavallee et al., 2007).

Table 37: Model health state occupancy at 90 days per 1000 cases of suspected TIA presenting in Primary Care

	No further event	Stroke Ischaemic		Haemorrhagic stroke		Carotid Surgery		Major haemorrhage		Other cause death
		Non-fatal	Fatal	Non-fatal	Fatal	Non-fatal	Fatal	Non-fatal	Fatal	
GPiT	953.59	11.90	2.78	0.08	0.03	14.47	0.05	2.96	0.00	14.14
Best practice	945.65	17.44	4.47	0.11	0.04	15.32	0.06	2.87	0.00	14.04
Current practice	918.73	44.12	12.26	0.29	0.11	8.37	0.03	2.52	0.00	13.56

Figure 15: Event status by time point within the Markov model for a notional population of 1000 suspected TIA cases, best practice
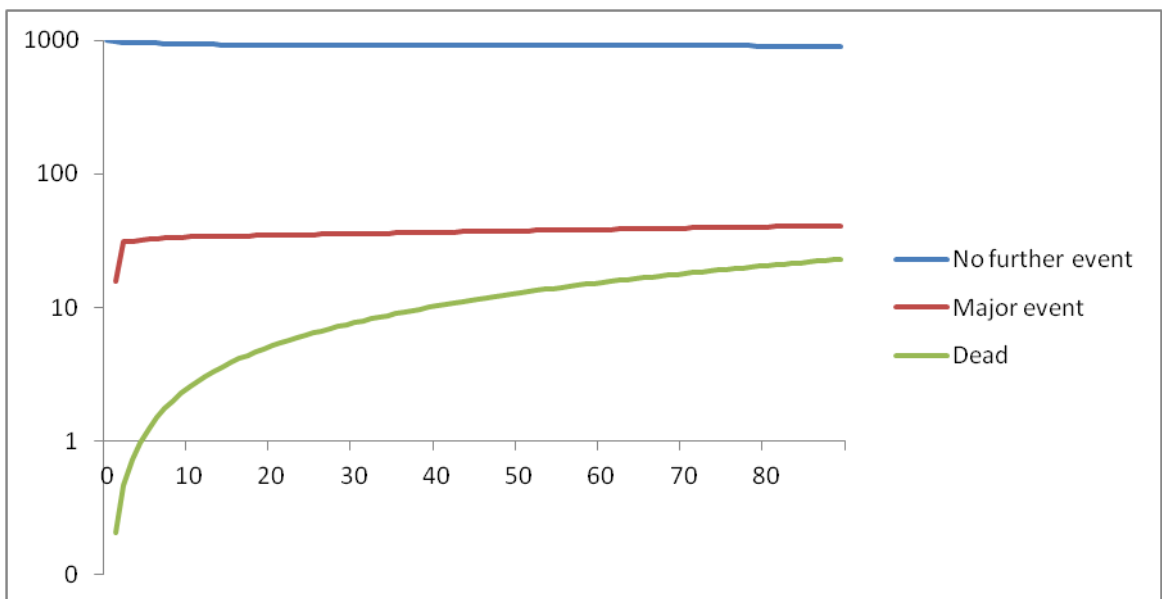
Figure 16: Event status by time point within the Markov model for a notional population of 1000 suspected TIA cases, GPiT
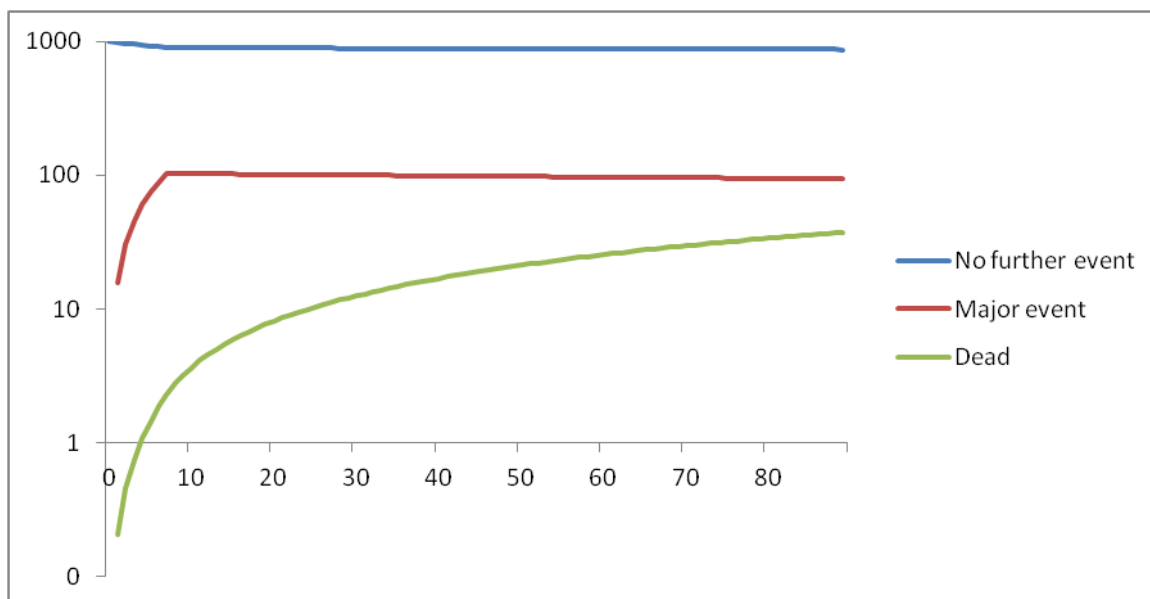
Figure 17: Event status by time point within the Markov model for a notional population of 1000 suspected TIA cases, current practice

7.4. Cost-effectiveness outcomes

The base-case comparison presents results from the pair-wise comparison of GPiT versus best practice. Total and incremental costs and effects are reported in addition to cost/QALY (where applicable). The secondary analysis reports the findings from a pair-wise comparison of GPiT vs. current practice. For both analyses, results are presented over two time points: 90 days and lifetime.

Table 38 presents the findings from the base-case comparison at 90 days from the deterministic analysis. The results suggest no difference between GPiT and best practice. Table 39 presents the results when the modelled outcomes are extrapolated to a lifetime

horizon. These results show that the incremental QALY gain is now approximately 0.0538 and the cost saving is £551.[11]

Table 38: Results of the base-case analysis (pair-wise comparison of GPiT vs. best practice) [90 day time horizon]

	Total QALYs/ patient	Total cost/ patient (£)	Incremental QALYs	Incremental cost (£)	Cost/QALY (£)
Best practice	0.2100	£190	-	-	-
GPiT	0.2108	£187	0.0009	-£3	No difference

Table 39: Results of the base-case analysis (pair-wise comparison of GPiT vs. best practice) [lifetime horizon]

	Total QALYs/ patient	Total cost/ patient (£)	Incremental QALYs	Incremental cost (£)	Cost/QALY (£)
Best practice	9.1439	£1,477	-	-	-
GPiT	9.1977	£926	0.0538	-£551	Dominant

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[11] Results for QALYs are expressed to 4 decimal places; results for costs are presented correct to the nearest integer. Incremental cost/QALYs presented may reflect rounding.

Table 40 and Table 41 present the secondary comparison for the 90 day model and the lifetime horizon respectively. The direction of results are similar to that of best practice, but as might be expected the magnitude of the effect gains and cost savings are greater.

Table 40: Results of the secondary analysis (pair-wise comparison of GPiT vs. current practice) [90 day time horizon]

	Total QALYs/ patient	Total cost/ patient (£)	Incremental QALYs	Incremental cost (£)	Cost/QALY (£)
Current practice	0.2053	£293	-	-	-
GPiT	0.2108	£187	0.0055	-£107	Dominant

Table 41: Results of the secondary analysis (pair-wise comparison of GPiT vs. current practice) [lifetime horizon]

	Total QALYs/ patient	Total cost/ patient (£)	Incremental QALYs	Incremental cost (£)	Cost/QALY (£)
Current practice	8.8870	£2,055	-	-	-
GPiT	9.1977	£926	0.3107	-£1,129	Dominant

In order to examine the robustness of these results to parameter uncertainty, probabilistic sensitivity analysis (PSA) was performed. Results of the 1,000 Monte Carlo simulations of the model are presented on cost-effectiveness scatter plots. Each point within the scatter plot corresponds to an incremental cost/effect pair resulting from random sampling of the inputs. Additionally, comparison of the mean outcome of the probabilistic modelling (mean incremental costs and QALYs) were compared with the incremental estimates from the deterministic analysis. Results appeared to be similar and are considered further in A.6.2. Scenario analysis for the base-case comparison.

The mean incremental QALYs and costs (of GPiT relative to the comparator) from PSA were calculated as part of the approach for constructing cost-effectiveness acceptability curves (CEAC). The CEAC curve shows the probability of a positive net benefit over a continuum of threshold values for different values of the ceiling ratio.

Specifically this is calculated as:

$$\textbf{Net benefit} \ = \ \lambda \, \textbf{Q} - \textbf{C}$$

Where **Q** is the incremental QALY gain of the intervention

And **C** is the incremental cost

And λ is the ceiling ratio of the ICER

Figure 18 shows a cost-effectiveness scatter plot and generated cost-effectiveness acceptability curve of GPiT vs best practice for the 90 day Markov model. The CEAC shows that GPiT is the preferred strategy in all simulations, at WTP conventionally adopted by NICE. All points within the scatter plot are associated with a net incremental QALY gain suggesting that GPiT is the more effective option. The results show considerable uncertainty as to the incremental cost. At the highest plausible gain of 0.0007 QALY an incremental cost of $0.0018 \times £20,000 = £36$ is the maximum acceptable incremental cost with a threshold ICER of £20,000/QALY. However, all points lie inside of the south east quadrant, indicating that GPiT appears to have a small but consistent benefit over and above GPiT. This result is likely to reflect the structuring of the GPiT strategy which is essentially identical to best practice, albeit with earlier initiation of treatment. Averaged over a cohort of individuals, the benefit appears somewhat modest and it is therefore difficult to identify if the margin of difference amounts to clinically significant difference in effect.
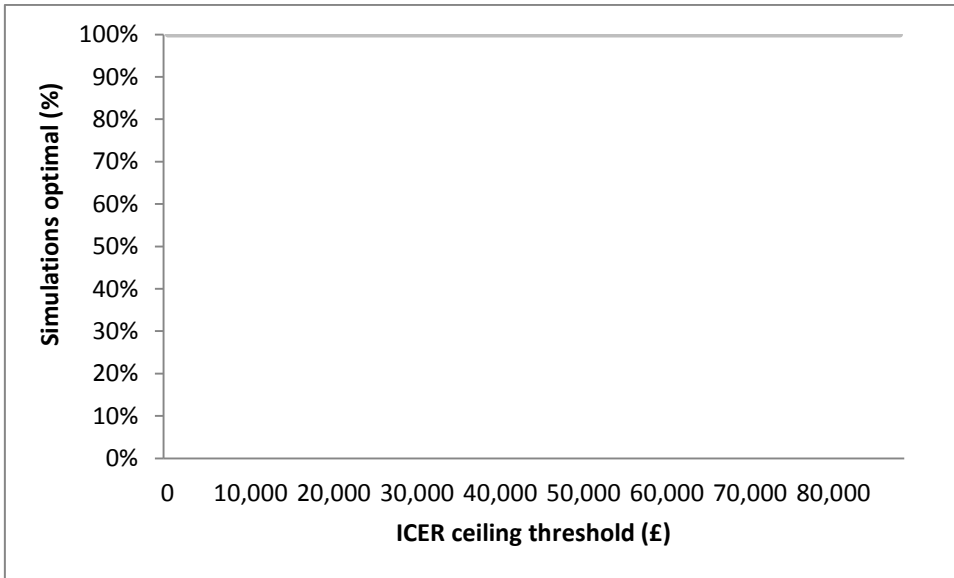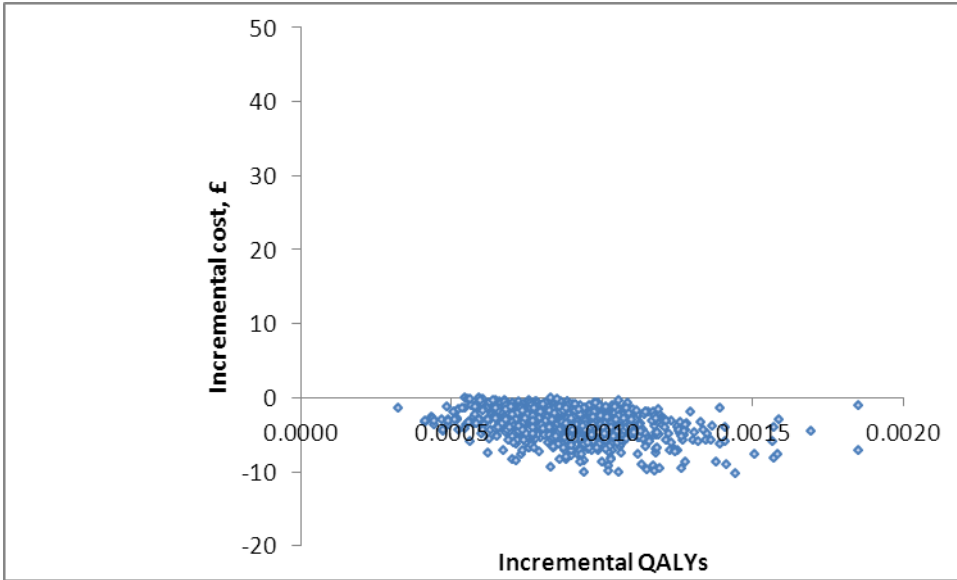
Figure 18: Cost-effectiveness scatter plot and cost-effectiveness acceptability curve at 90 days, GPiT vs. best practice

Cost-effectiveness results at lifetime

Figure 19 shows a CEAC scatterplot for GPiT compared to best practice when a lifetime horizon is adopted. The CEAC shows that GPiT has the highest probability of being cost-effective in all simulations over the continuum of ceiling ratios. As before, all points within is the scatter plot show an incremental benefit, however, now the mean plausible gain is approximately 0.05 QALY per suspected TIA case.
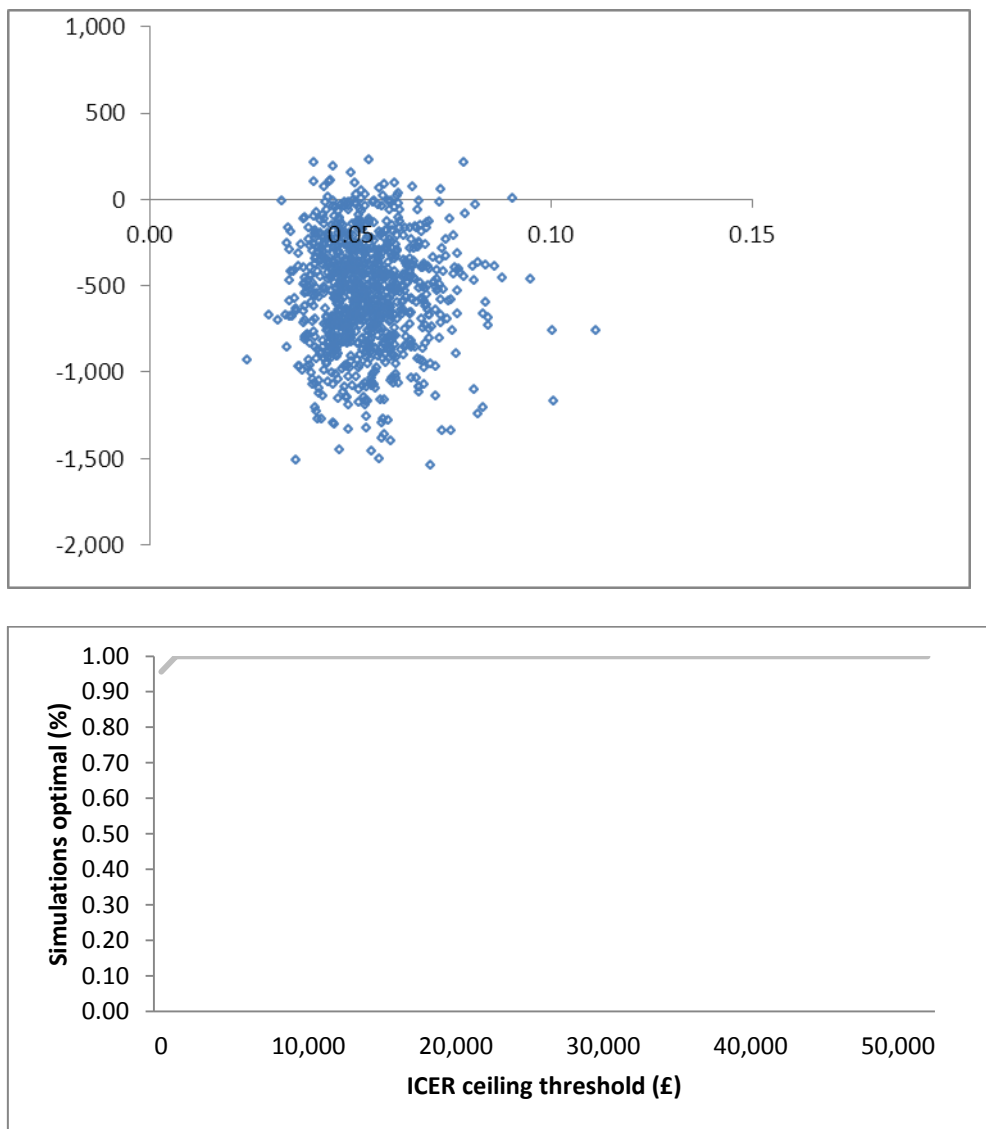
Figure 19: Cost-effectiveness scatter plot and cost-effectiveness acceptability curve when a lifetime horizon is adopted, GPiT vs. best practice

Figure 20 and **21** provide the second pair wise comparison within the base-case: GPiT vs. current practice for the 90 day and lifetime time horizons respectively. Inspection of the cost-effectiveness plane in Figure 20 shows that there is no uncertainty as to the effectiveness of GPiT but some uncertainty about the cost-savings. This is consistent with the CEAC which shows that GPiT is the preferred strategy in approximately 80% of simulations.
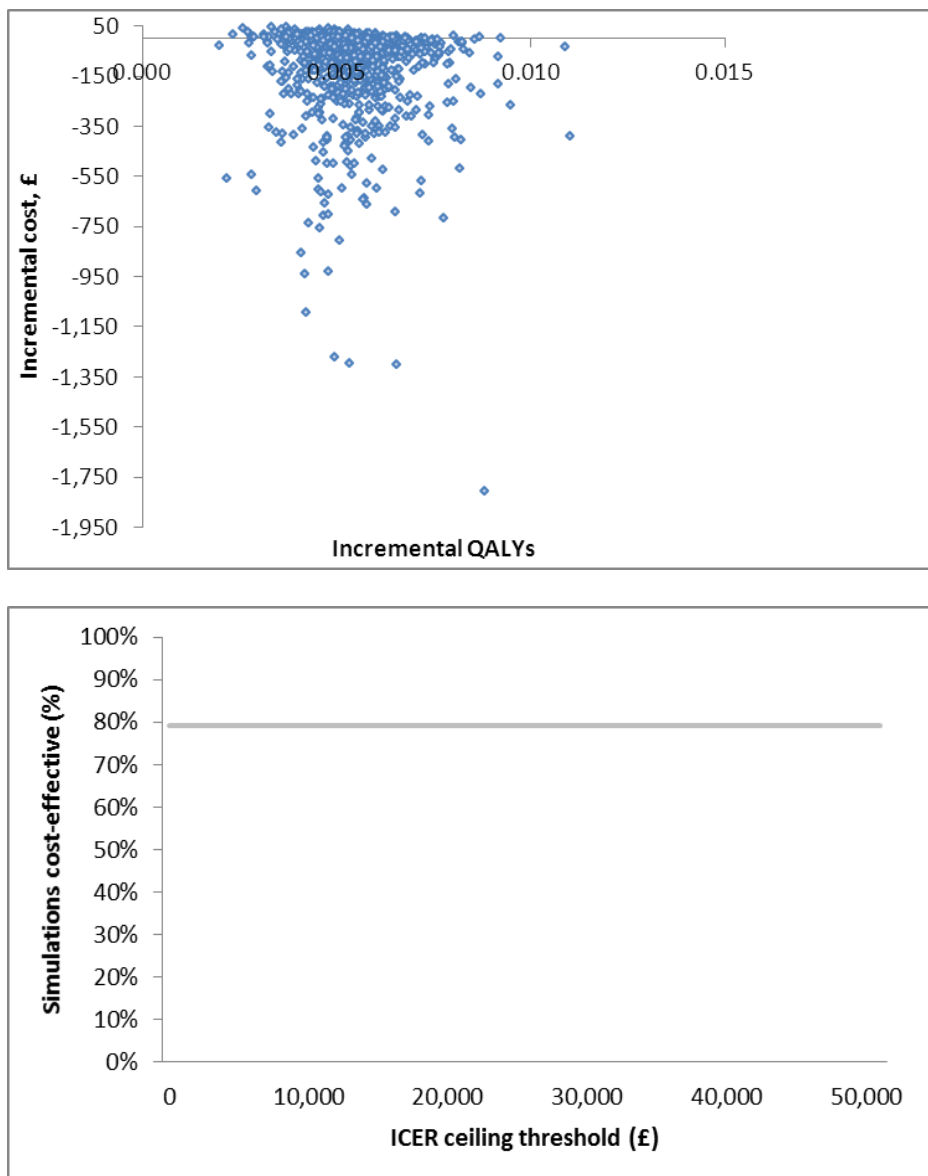
Figure 20: Cost-effectiveness scatter plot and cost-effectiveness acceptability curve at 90 days, GPiT vs. current practice
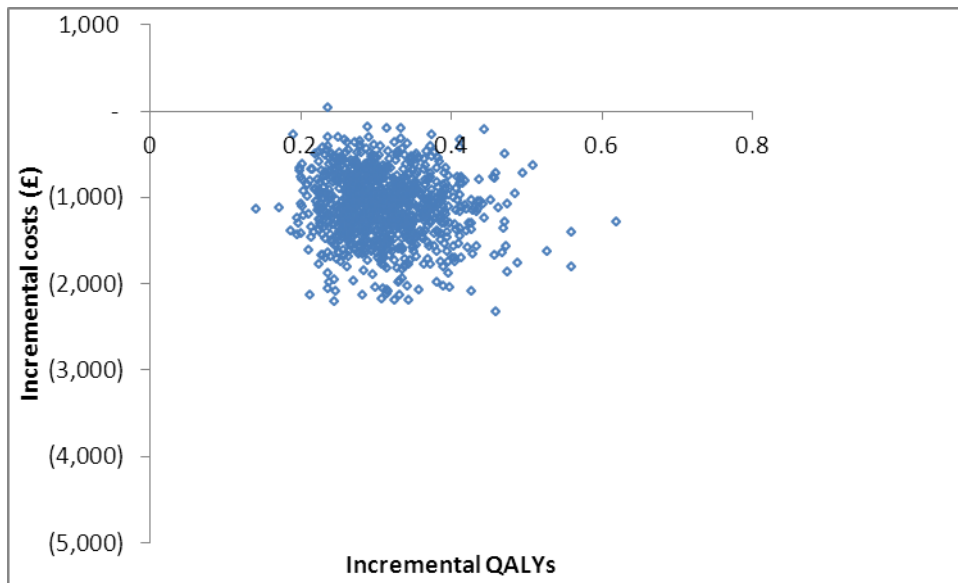
Figure 21: GPiT vs. current practice: Cost-effectiveness scatter plot when a lifetime horizon is adopted

The CEAC associated with points in the scatter plot shows that 100% of simulations are cost-effective at WTP according to thresholds conventionally adopted by NICE i.e. the CEAC associated with this scatter-plot would look identical to Figure 18 and is not reproduced for this reason.

7.5. Scenario Analysis: Other options for GP initiation of treatment

For the scenario analysis, results are presented in terms of the net benefit statistic. As discussed in Chapter 3, when considering multiple strategies (scenarios) the net benefit option allows for the direct comparison of options, without having to consider strict or extended dominance. As previously stated, the net benefit was calculated as

$$NB = \lambda\, Q - C$$

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Where **Q** is the incremental QALY gain of the intervention

And **C** is the incremental cost

And λ is the ceiling ratio of the ICER

Scenarios tested: a reminder

In addition to the main comparison of the three strategies, a scenario analysis was undertaken to evaluate the cost-effectiveness of alternative routing of patients after the GP has initiated secondary prevention. Different configurations of GPiT are now examined to explore different options for implementation, for instance, including strategies based on part or no onward referral (i.e. alternative GPiT 1: high risk group only referred and alternative GPiT 2: no subsequent referral). Findings are summarised in terms of incremental costs and effects relative to current practice, [where choice of comparator has been chosen for presentational purposes]. Preferred strategies were identified on the basis of (mean) expected net benefit for each comparison at ceiling ratio of the ICER at £20,000, computed from incremental costs and QALYs (Table 42). Using expected mean net benefit, the preferred strategy at both 90 days and for the lifetime horizon was GP initiation of treatment with no subsequent follow-up. These correspond to the scenarios preferred when the model is run deterministically.

Table 42 Comparison of main results: deterministic and probabilistic output

	Incremental QALYS vs current practice				Incremental costs vs current practice (£)				Maximum incremental net benefit at a ceiling ratio of (£20,000)	Most CE strategy (corresponding to strategy maximum incremental net benefit)
	Best practice	GPiT	GPiT refer only high risk	GPiT no subsequ-ent referral	Best practice	GPiT	GPiT refer only high risk	GPiT no subsequ-ent referral		
Base-case (probabilistic): 90 days	0.0046	0.0055	0.0059	0.0063	-95	-99	-115	-131	257	GPiT no referral
Base-case (determinisitic): 90 days	0.0047	0.0055	0.0059	0.0062	-104	-107	-120	-134	257	GPiT no referral
Base-case (probabilistic): lifetime	0.2573	0.3113	0.3118	0.3126	-560	-1115	-1109	-1115	7366	GPiT no referral
Base-case (determinisitic): lifetime	0.2569	0.3107	0.3112	0.3109	-578	-1129	-1123	-1130	7354	GPiT no referral

The probabilistic modelling also presents the results in terms of multiple cost-effectiveness acceptability curves at 90 days (Figure 22) and over the lifetime horizon (Figure 23). As before, each curve shows the probability that each intervention is most optimal; which has a slightly distinct interpretation from basis of mean net benefit above (Table 42). At typically applied ceiling ratios, Figure 23 shows that GPiT with no subsequent referral is associated with the greatest probability of each simulation/run being cost-effective (96% of model runs at a WTP threshold of £20,000/QALY). This finding is consistent with the recommendation on the basis of maximising expected mean net benefit; i.e. identifying GPiT with no subsequent specialist referral is the most cost-effective option at 90 days.
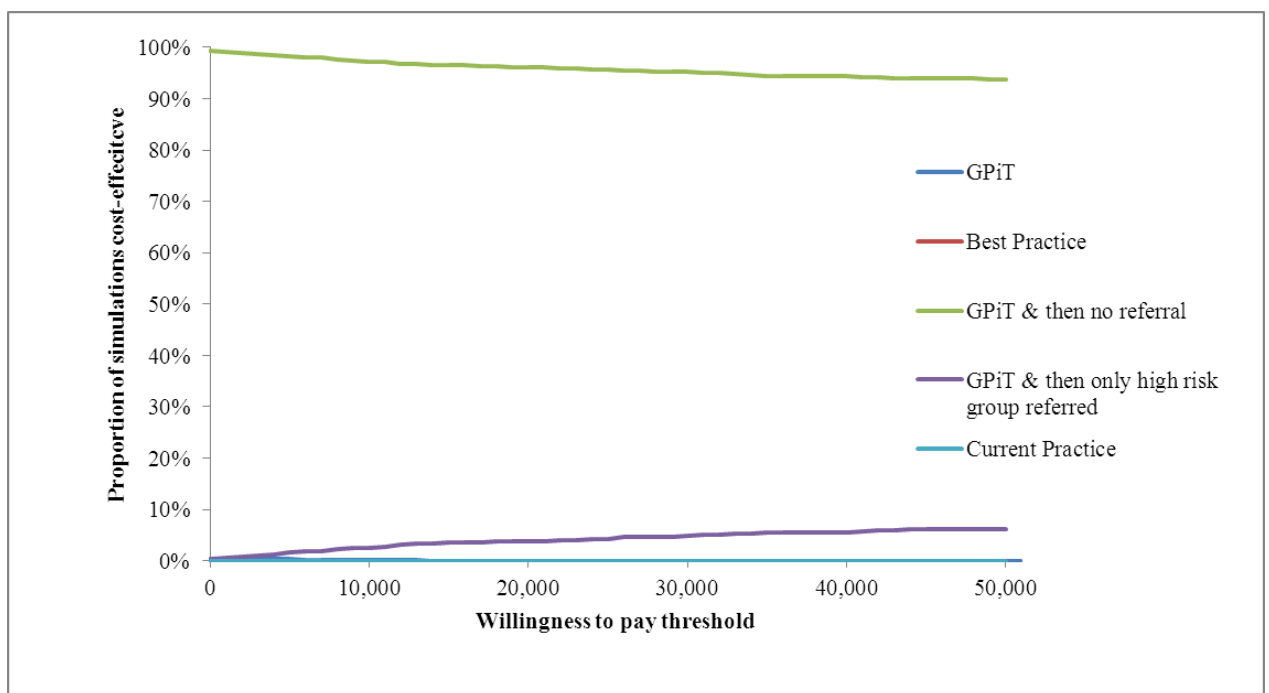
Figure 22: Cost-effectiveness acceptability curve for multiple strategies (90 days)

When the analysis horizon becomes lifetime, results from extrapolation of model outcomes suggest that the alternative GPiT with no subsequent referral is preferred (has a higher probability of being cost-effective) for all credible ranges of the ceiling ratio shown (Figure 23). Again, this is consistent with the preferred strategy on the basis of expected mean net benefit

Table 42).
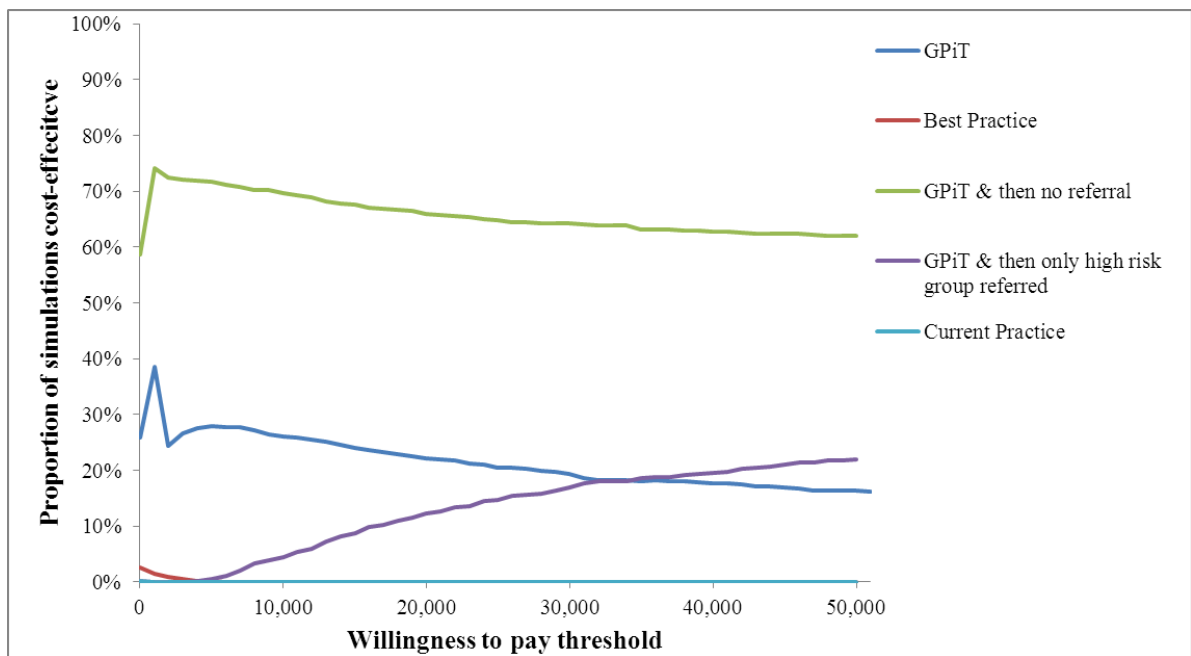
Figure 23: Cost-effectiveness acceptability curve for multiple strategies (lifetime)

7.6. Sensitivity analysis

Additional one-way sensitivity analysis was undertaken to further test the uncertainty within the model with respect to both the uncertainty in the data inputs (parameter uncertainty) and the methodological/structural assumptions. While parameter uncertainty has been tested by probabilistic modelling by allowing for variation around the point

estimates, it was desirable to test the robustness of the model results (in terms of preferred strategies) to alternative assumptions other than which the base-case model was founded. Following this, it was possible to re-run the probabilistic analyses for the alternative assumptions. A summary of the results from the sensitivity analysis is provided in Table 43. For information on total as well as incremental costs and QALYs, and net benefit at various thresholds, tables are provided in Appendix 6: Model results (Detailed view).

Table 43: Overview of results from sensitivity analysis (deterministic analysis results): note other assumptions relating to model remain unchanged, and as per the base-case.

Assumption		Incremental QALYS (vs. current practice)				Incremental Costs, £ (vs. current practice)				Incremental net benefit (corresponding to most CE strategy)	Most CE strategy [12]
		Best Practice	GPiT	GPiT high risk referral	GPiT: no subsequent referral	Best Practice	GPiT	GPiT: high risk referral	GPiT: no subsequent referral		
Standard model assumptions	90 day	0.0047	0.0055	0.0059	0.0062	-104	-107	-120	-134	257	GPiT no referral
	Lifetime	0.2569	0.3107	0.3112	0.3109	-578	-1129	-1123	-1130	7354	GPiT no referral

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[12] On the basis of net-benefit at a WTP of £20,000.

Assumption		Incremental QALYS (vs. current practice)				Incremental Costs, £ (vs. current practice)				Incremental net benefit (corresponding to most CE strategy)	Most CE strategy [12]
		Best Practice	GPiT	GPiT high risk referral	GPiT: no subsequent referral	Best Practice	GPiT	GPiT: high risk referral	GPiT: no subsequent referral		
Variation in accuracy of GP diagnosis (PPV =75%)	90 day	0.0070	0.0083	0.0088	0.0093	-155	-160	-181	-202	387	GPiT no referral
	Lifetime	0.3854	0.4661	0.4674	0.4659	-867	-1474	-1471	-1475	10823	GPiT no referral

Assumption		Incremental QALYS (vs. current practice)				Incremental Costs, £ (vs. current practice)				Incremental net benefit (corresponding to most CE strategy)	Most CE strategy [12]
		Best Practice	GPiT	GPiT high risk referral	GPiT: no subsequent referral	Best Practice	GPiT	GPiT: high risk referral	GPiT: no subsequent referral		
Variation in accuracy of GP diagnosis (PPV=25%)	90 day	0.0023	0.0028	0.0030	0.0031	-52	-53	-60	-67	128	GPiT no referral
	Lifetime	0.1285	0.1553	0.1550	0.1558	-289	-784	-775	-784	3892	GPiT refer only high risk
Increased risk of major haemorrhage	90 day	0.0047	0.0055	0.0059	0.0062	-104	-107	-120	-134	257	GPiT no referral

Assumption		Incremental QALYS (vs. current practice)				Incremental Costs, £ (vs. current practice)				Incremental net benefit (corresponding to most CE strategy)	Most CE strategy [12]
		Best Practice	GPiT	GPiT high risk referral	GPiT: no subsequent referral	Best Practice	GPiT	GPiT: high risk referral	GPiT: no subsequent referral		
in TIA mimic population	Lifetime	0.2569	0.3106	0.3106	0.3106	-578	-1129	-1123	-1130	7343	GPiT no referral
Adjustment for poor prognosis in medically treated severe carotid stenosis	90 day	0.0047	0.0055	0.0059	0.0062	-104	-107	-120	-134	258	GPiT no referral
	Lifetime	0.2569	0.3107	0.3228	0.3132	-578	-1129	-1100	-1015	7472	GPiT no referral

Assumption		Incremental QALYS (vs. current practice)				Incremental Costs, £ (vs. current practice)				Incremental net benefit (corresponding to most CE strategy)	Most CE strategy [12]
		Best Practice	GPiT	GPiT high risk referral	GPiT: no subsequent referral	Best Practice	GPiT	GPiT: high risk referral	GPiT: no subsequent referral		
Variation in utility values used (van Exel et al.)	90 day	0.0022	0.0026	0.0029	0.0030	-104	-107	-120	-134	195	GPiT no referral
	Lifetime	0.1817	0.2197	0.2201	0.2207	-578	-1129	-1123	-1130	5537	GPiT refer only high risk

Assumption		Incremental QALYS (vs. current practice)				Incremental Costs, £ (vs. current practice)				Incremental net benefit (corresponding to most CE strategy)	Most CE strategy [12]
		Best Practice	GPiT	GPiT high risk referral	GPiT: no subsequent referral	Best Practice	GPiT	GPiT: high risk referral	GPiT: no subsequent referral		
Variation in lifetime cost of stroke (50% increase in all long-term care costs)	Lifetime	0.2569	0.3107	0.3112	0.3109	-1156	-2258	-2246	-2260	8484	GPiT no referral

Assumption		Incremental QALYS (vs. current practice)				Incremental Costs, £ (vs. current practice)				Incremental net benefit (corresponding to most CE strategy)	Most CE strategy [12]
		Best Practice	GPiT	GPiT high risk referral	GPiT: no subsequent referral	Best Practice	GPiT	GPiT: high risk referral	GPiT: no subsequent referral		
Varying the discount rate (costs and benefits)	0% discount rate, lifetime horizon	0.3070	0.3713	0.3719	0.3715	-686	-1341	-1334	-1342	8780	GPiT no referral
	6% discount rate, lifetime horizon	0.1920	0.2322	0.2326	0.2323	-513	-1002	-997	-1003	5654	GPiT no referral

† This analysis is outlined in the following section, 'Sensitivity analysis' p. 101

The most conservative estimate from the analysis of the acute model suggested that GPiT would still be the preferred strategy if a daily transition probability of 0.14% was not exceeded. This is approximately equivalent to a 40% annual probability of an extracranial bleed, i.e. a four-fold increase in the annual rate of bleeding compared with the base-case assumption. The maximum rate of bleeding that was cost-effective at lifetime was considerably higher, probably due to the impact on cost savings from a reduction in the risk of recurrent stroke.

Table 44: Outcomes following adjustment for poor prognosis in medically managed patients with carotid stenosis who would otherwise have been eligible for carotid surgery (90 day time horizon)

	Total QALY/ patient	Total costs/ patient	Inc. QALYS vs. best practice	Inc. costs vs. best practice	Net benefit at a £10,000 ceiling ratio	Net benefit at a £20,000 ceiling ratio	Net benefit at a £30,000 ceiling ratio
Current practice	0.2053	£293	-0.0047	£104	-£150	-£197	-£243
Best practice	0.2100	£190					
GPiT	0.2108	£187	0.0009	-£3	£12	£21	£29
GPiT refer only high risk	0.2112	£173	0.0012	-£17	£29	£41	£54
GPiT no referral	0.2115	£159	0.0015	-£31	**£45**	**£60**	**£75**

Table 45 Outcomes following adjustment for poor prognosis in medically managed patients with carotid stenosis who would otherwise have been eligible for carotid surgery (lifetime time horizon)

	Total QALY/ patient	Total costs, £ /patient	Inc. QALYS vs. best practice	Inc. costs vs. best practice	Net benefit at a £10,000 ceiling ratio	Net benefit at a £20,000 ceiling ratio	Net benefit at a £30,000 ceiling ratio
Current practice	8.8870	£2,055	-0.2569	£578	-£3,147	-£5,717	-£8,286
Best practice	9.1439	£1,477					
GPiT	9.1977	£926	0.0538	-£551	£1,089	£1,626	£2,164
GPiT refer only high risk	9.2002	£955	0.0563	-£522	£1,085	£1,648	£2,211
GPiT no referral	9.2098	£1,040	0.0659	-£437	**£1,096**	**£1,755**	**£2,415**

7.7. Expected value of perfect information (EVPI)

For the base-case analysis, the uncertainty surrounding the decision whether or not to implement GPiT resulted in an individual EVPI of £2,251 at a WTP of £20,000. Implementing GPiT affects the entire population with an index (first in a lifetime) TIA or

resolved minor stroke presenting in Primary Care; this equates to a total 'effective' population of 208,761 when the intervention is rolled out for 10 years. The calculated population EVPI is therefore £470 million at a WTP of £20,000. This value equates to the upper bound of eliminating all uncertainty within the model. The population EVPI at different values of the ceiling threshold is presented in Figure 24. The EVPI curve is of the expected shape[13], given that GPiT dominates the comparator in the mean analysis but there is uncertainty about which strategy is more costly (so non-zero EVPI at zero WTP) and also uncertainty about which strategy is more clinically effective (so EVPI remains positive at large WTP values).
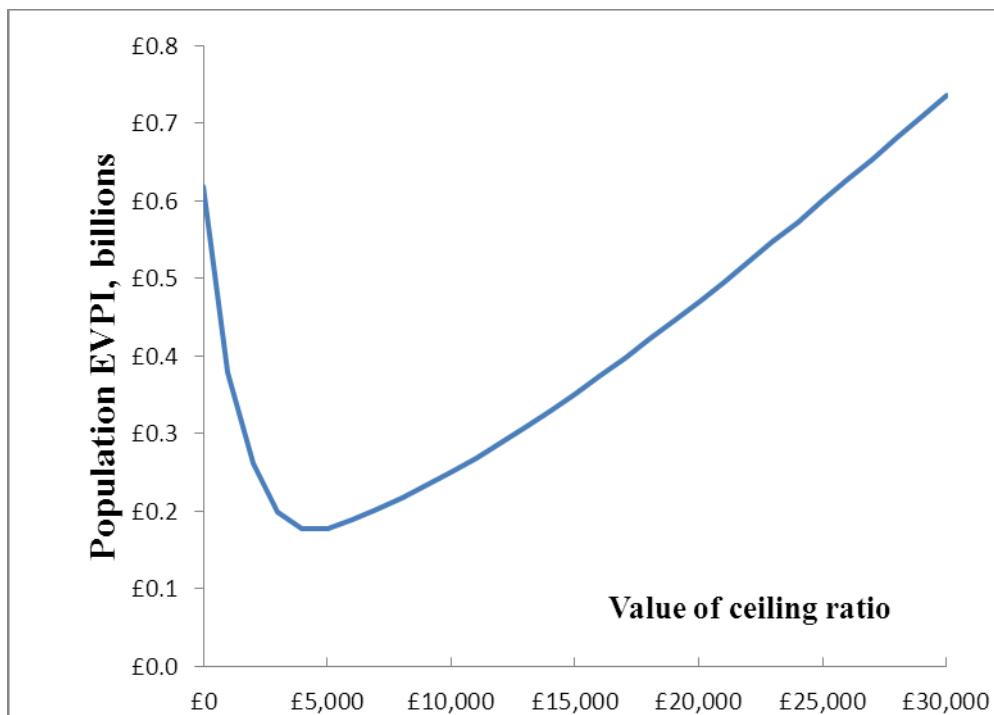
Figure 24: Population EVPI at different levels of the ceiling threshold

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[13] i.e. positive values of EVPI and no sharp point where the 'a priori' decision changes.

Additionally it would be desirable to explore the EVPI for subsets of parameters, for instance, around the effectiveness of the intervention, utilities, costs and important to this model, parameters relating to the safety of care: in particular, the positive predictive value of GP diagnosis of TIA and the risk of adverse events. This would inform which parameters were most valuable to further research. In particular, if the partial EVPI associated with safety parameters is low, this would potentially allow for a case to be made for implementation of GPiT based on current evidence.

7.8. Summary of results

Results from the base-case analysis at 90 days demonstrate that in comparison with best practice, GPiT is both more effective and less costly. When outcomes at 90 days are extrapolated to a lifetime horizon, there is an increase in both incremental cost savings and QALYs gained. Secondary analysis shows that the magnitude of benefit is greater when GPiT is compared to current practice. Comparison of deterministic and probabilistic results suggests that the results of the model are robust to parameter uncertainty.

Results from scenario analysis identify that the alternative GPiT strategies (with fully or partially restricted specialist follow-up) are also cost saving and beneficial when compared to both best and current practice. At both 90 days and over a lifetime horizon, 'GPiT: no subsequent referral' was preferred. However, an observation was that the difference in net benefit between all three GPiT strategies was small. Furthermore, univariate sensitivity analysis showed that these findings hold under the structural/methodological sensitivity analysis performed.

The next chapter considers the model implications in more detail. Limitations of the approach used and recommendations to future research are also made.

CHAPTER 8: DISCUSSION – GP INITIATION OF TREATMENT IN THE CASE OF SUSPECTED TIA

8.1. Introduction

This chapter discusses the implications of the model results. Finally, it considers the implications of these results in terms of recommendations for clinical practice and research.

8.2 Interpretation of results

Findings from the model show that a strategy based on GP initiation of treatment (and subsequent referral) is less costly and more effective compared with strategies based on existing practice. This result appears robust for the range of sensitivity analysis performed. In terms of budget impact, the model suggests that GPiT strategies could save NHS resources in the long-term by reducing the economic burden of stroke and its sequelae. In terms of the population of England with suspected TIA, the model predicts total long-term savings of between £14 - £30 million per annum depending on the current level of service provision.[14] The only exception was if the adverse effects of inappropriate treatment in the TIA mimic population are considerably higher than conjectured. Threshold analysis suggests that this risk could be up to four times higher and GPiT would still be preferred.

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[14] Estimate based on incidence of TIA from the TIA commissioning guide for England (0.05%) and cost-savings predicted in the long-term model (NICE 2008b). Range presented corresponds to the anticipated cost saving for current practice (£1,129) versus optimised (scenario referred to as best practice in the model) (£551) and correspond to the steady state prediction associated with long-term roll out of GPiT. Note that the projected savings in the first year of implementation alone will be significantly lower than these projections. However, the 90 day model suggests that the effect on the budget should be no worse, and possibly a little more favourable (cost-saving), than best practice in this time period. All analysis assumes that GPiT is associated with no additional staffing or other costs of implementation.

In addition, scenario analysis performed identified that there may still be a question with respect to the most efficient configuration of a service involving GP initiation of treatments, as results are sensitive to the time horizon. The finding that GPiT 'no subsequent referral' was most cost-effective at 90 days is not surprising given the cost-savings (TIA clinic and carotid endarterectomy surgeries) in secondary care. When the perhaps more relevant (since it considers the sequelae of stroke) lifetime horizon is considered, the preferred strategy remains GPiT 'no subsequent referral' but the difference in net benefit between other configurations of GPiT ('GPiT' base case) and GPiT: refer only high risk was small.

One implication of this service innovation is that if 'GPiT: refer only high risk' is preferred, the purpose for which the ABCD2 score is used changes. Currently the ABCD2 threshold of four and above is used to identify the population at highest risk of recurrence for expedited treatment. However, under a strategy of GPiT, where everyone is treated irrespective, ABCD2 appears to have a role in identifying more of the population with severe carotid stenosis. As might be expected, the maximum (lifetime) benefit from carotid endarterectomy occurs with (the main GPiT) 'refer all' strategy but 'GPiT refer only high risk' appears to have application in cost-effective identification of those most likely to have stenosis.

If either GPiT or 'GPiT: subsequent referral high risk group only' are preferred strategies, this would suggest that the role of the TIA clinic becomes more about diagnosing as opposed to treating, a view also put forward by Mant et al. (2007, p.121). Furthermore, as

patients with genuine TIA will be on the correct treatment, the benefit of the strategies which still refer to clinic would also appear to be due to the potential for providing an alternative diagnosis. In the model developed here, only the effect of treatment discontinuation in TIA mimics was operationalised. However, over and above the direct treatment effects (beneficial or harmful) there is also a diagnostic dimension to be considered. It is not implausible that the TIA mimic cases may significantly benefit from attending a specialist TIA clinic, as the investigations might prompt the correct diagnosis.[15] If this is the case, results here underestimate the benefit of GPiT with subsequent referral.

Results would appear to indicate that it is difficult to form a recommendation on which GPiT strategy is optimal (especially as the difference between strategies, in terms of net benefit, is small). However, over a lifetime horizon, the base-case GPiT strategy may be the most efficacious assuming there is a benefit to carotid endarterectomy and getting the right diagnosis. If this strategy would place too great a burden on the health system, in terms of additional demand for specialist clinics, GPiT (refer high risk) or even GPiT (refer none) would also appear to be good options. However, the latter strategy means that there is no referral at all for carotid endarterectomy which might not be well accepted by health professionals or patients.

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[15] Indeed, this would seem to especially apply to TIA which is typically diagnosed by 'ruling out' other differential diagnoses.

8.3 Generalisability

In trying to structure a model around current and best UK practice, there was widespread variation in TIA practices across the UK and that current practice was difficult to characterize. However, the model's characterization of current practice was based on the findings of clinical audit into TIA services, and other parameters from the model (utilities, drug and long—term care costs) were drawn from UK sources. In addition the modelling of best practice drew on the EXPRESS study, a high quality before and after nested cohort study within the Oxford Vascular population, in Oxfordshire, UK.

The results of the model appear to show good external consistency. For instance, as previously discussed, the number of strokes anticipated by the strategies appear to be consistent with the projections based on individual patient data on stroke recurrence. It is also not unusual for a stroke prevention intervention to be identified to be both less costly and more effective than comparator in the long run. This is largely because of the significant economic burden and poor health outcomes following stroke. However, there is an important contrast between this and the other modelling studies reviewed previously (Chapter 4). All these models considered service developments that would be likely to require an increase in TIA clinic capacity. Initially, these interventions result in cost increases. In contrast, GPiT potentially allows for some specialist resources to be released, and is therefore cost-saving.

The only study that has examined a similar strategy to GPiT was the Birmingham TIA model. This model considered a strategy analogous to GPiT (no subsequent referral) but no strategy directly analogous to the base-case GPiT strategy.[16] The strategy based on no subsequent referral identified that referring all suspects was the most effective strategy and was potentially the most cost-effective (ICER £35,000 per major stroke averted). It is possibly inappropriate to make a direct comparison of the outcome (clinical/ cost-effective) of this study with the model developed in this thesis. First of all, the models had different methodological/structural assumptions, these included: notable differences in the modelling of the treatment effect; choice of parameters within the model and the time horizon adopted. Nevertheless, in terms of the recommendations made across models recommendations are similar. For instance, both models suggest that if GPs are better at correctly identifying stroke, a strategy of partial referral (high risk group only) may be preferred, depending on the value of the ceiling ratio adopted.

8.4 Model limitations

Findings are preliminary, based on limited evidence in relation to the introduction of a new role for GPs in the management of TIA.

Limitations of the model structure include the failure of the Markov model to consider repeat or co-morbid events. In addition, cardiac events are not modelled. All are clinically

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[16] The name given to this is 'optimal management by GPs'. Mant et al. p.102.

significant events with obvious impacts in terms of costs and QALYS, so the reasons for exclusion need to be considered a little more.

First of all, expanding the model to include more outcomes might have improved its face validity with clinicians. However, a more comprehensive model is only a better model if it succeeds in offering a more realistic modelling of the disease process (Philips et al., 2006). In recent years, the recommendations of a stroke costing model commissioned by the NAO have been questioned on the basis of a lack of transparency in the model methods and overly optimistic benefits relating to thrombolysis treatment (Sudlow and Warlow, 2009, National Audit Office, 2005). In the field, this has resulted in some discussion about whether hyper-acute services following stroke have been wrongly prioritised.

Secondly, it is plausible that extending the model to include cardiac events would provide more support in favour of the intervention if GP initiation identifies and treats more people with high general vascular risks, so the exclusion of cardiac events in this instance should be conservative, or neutral in terms of the benefit of the intervention.

A challenge faced in the development of any model is in the identification of data to populate the model. As this model is testing a strategy that has not been trialled or tested elsewhere, it was necessary to estimate the treated and untreated risk of stroke. Estimates of the risk of recurrent stroke were based on the results of a high-quality systematic review of clinical studies with longitudinal follow-up. In order to estimate the hyper-acute risk of stroke following TIA a method of extrapolation to points earlier in time using an exponential function was used. It might be that other functional forms better describe the

natural course of risk in TIA, or that other longitudinal follow-up studies of TIA cohorts provide data at more time points to preclude the use of such an assumption.

This model succeeds in providing a simple description of the disease process, but the caveat with this is that this description is not as comprehensive as it might be. The extrapolation of outcomes from the 90 day model used an aggregate life table approach to estimate the life years gained for the general population, and expert opinion/literature to estimate the assumed reduction in expectancy for each of the non-TIA states. This is quite a blunt measure, but not an uncommon one. Several other models reviewed in the critical appraisal used similar techniques (e.g. NICE 2008a).

Finally, while the joint uncertainty of all model inputs using probabilistic sensitivity analysis was tested, this does not negate the chance that the model might be incorrectly structured. For instance, estimation of long-term outcomes follows from a simple extrapolation of the outcomes of the 90 day model. This was a simplifying assumption justified on the basis that the clinically relevant time horizon for the effects of the intervention (which might just involve earlier initiation by a day in some patients) was 90 days. A lifetime time horizon was used to capture the enduring disability of the 90 day outcomes which have important economic consequences beyond the relevant clinical timeframe. The assumption is that post 90 days the treatment of patients would essentially be the same such that the patient risk profiles should be identical. Introducing a probabilistic Markov model for the entire lifetime would introduce random fluctuation into the estimates of intervention effects and would greatly increase the data requirements of the model (for instance, it would also be preferable to consider recurrent stroke) under this

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methodology. Note that it is usual for economic models to restrict their consideration of costs and consequences to those attributable to the intervention, and other models reviewed in Chapter 4 have used similar methods of extrapolation to make projections over a lifetime horizon (e.g. NICE 2008a, the Birmingham TIA model 2008).

Clear guidance on how to perform decision analytic modelling of service delivery interventions is currently lacking, but the selected model structure (Markov) might over-simplify the complex interplay of doctors-patients and treatment decisions.

Furthermore the costing approach within the model used costs reflect average costs associated with current service provision, and it is foreseeable that some of these costs may change post intervention (Coast et al., 2000). It is usual for CEA to assume that resources and costs have a linear and monotonic relationship (such that doubling the quantity doubles the cost) but this assumption has been questioned for service delivery interventions (Godber et al., 1997, Coast et al., 2000). This was a problem also evident from the review of other models (Chapter 4), and is not reflected in good practice guidance for performing economic evaluations.

8.5. Future research

Recommendations to clinical practice

This thesis provides an important de novo health economic analysis of an important clinical question that was not addressed in the NICE (2008a) guidance or elsewhere. It is

hoped that the evidence presented as part of this model should be considered when the guidance for acute stroke and TIA is formally revised. It remains the work of the appropriate Guideline Development Group to consider the merits of the model of service delivery in the light of a lack of evidence relating to the risk of adverse events in patients incorrectly suspected of having a TIA and therefore being inappropriately treated.

Recommendations for research

The cost-effectiveness of GPiT could not be assessed reliably mainly because of the imprecise estimates relating to efficacy. A large scale RCT would be desirable to determine the risk of TIA in the appropriate population, however, a pilot trial similar in nature to the intervention could not recruit, making a future RCT impracticable (Mant, December 2012). This suggests that the intervention might need to be piloted in practice. Prior to this additional research needs to be performed to quantify the risk of haemorrhagic events in incorrectly diagnosed TIA. It may also be appropriate to consider the risk of haemorrhagic events in TIA cases where there are comorbid conditions as the guidance of when, what and who should prescribe needs to be tailored to these different needs. If the efficacy of the intervention can be demonstrated, qualitative research could inform on the acceptability of the intervention to GPs and public.

A logical extension to the existing decision-analytic model presented might consider further application of analytical methods (known as 'Value of Information') for assessing the need for and type of future research. These methods look at the opportunity loss associated with deferring today's decision in the face of uncertainty (Briggs et al., 2006).

At the time of writing, there are also some more general recommendations to research from a commentator within Primary Care. Lasserson (2013) identified that current NICE guidance is based on decision analytic models in service pathways that have typically not considered the subsequent management of false positive TIA patients. This view might question the brief provided by the SDO, that is also the title of this thesis. In other words, shouldn't the question for policy makers be, 'What is the optimal model of service delivery in transient *neurological* attack?' In the model developed here, the approach has begun to consider the downstream outcomes of people with likely differential diagnoses. Nevertheless, this study presents preliminary findings when false positives are treated in error and not by design. More empirical evidence is needed to determine the net benefit of both treatment and assessment in this population, who have also been evidenced as having poor vascular prognosis (Bos et al., 2007).

CHAPTER 9: CONCLUDING THOUGHTS

9.1. Introduction

This chapter draws together the key findings from the thesis. It discusses the contribution made by the thesis overall as well as the limitations. Lastly, there are some concluding thoughts.

9.2. Key findings and contributions

The thesis' overarching contribution is primarily in the development and application of a decision-analytic model to conduct an economic evaluation of GP initiation of treatment versus best practice. It has addressed a number of research questions towards this main aim:

    i.   What informs the decision to develop a decision-analytic model?

   ii.   Subsequent to this, and if modelling is appropriate, what informs the type of model used in a service delivery intervention?

 iii.   What is the effectiveness and cost-effectiveness of initiation of treatments in the hyper-acute phase of TIA?

Other areas of contribution fit broadly within this thesis' main objective but also stand-alone, these are now considered.

Model methods: Moving from a model developed from operational research purposes to a Markov model

This thesis grew out of a body of work commissioned by the NIHR SDO which culminated in a published report in 2007 (Mant, 2008). The main report (having the same title as this thesis) explored policy questions linked to the provision of services including the scheduling of specialist clinics and the emergency transfer of suspected TIA patients to hospital for rapid assessment. The report documents a simulation model evaluating the cost-effectiveness of various service delivery options. The Birmingham TIA model developed reflects the existence of capacity constraints in the provision of services (for instance, if TIA clinics were only offered once a week, this would result in patients waiting longer for the next available consultation) so the type of model is quite complex (discrete event simulation), with origins in operational research.

While initially this thesis was intended to pursue the research questions arising from the Birmingham TIA model, potentially using a similar simulation based structure, my research training suggested that I could 'pare down' the existing model subject to certain caveats. The major caveat was whether the model needed to consider capacity constraints affecting the provision of services such as waiting lists. At first, this seemed quite important, but as my research questions developed I felt that these could potentially be answered with a simpler decision model (a Markov model). I felt that while I was still concerned with timeliness, waiting lists did not need to be explicitly modelled to determine the cost-effectiveness.

In addition, there could be advantages to developing a simpler model. Compared to simulation models, Markov models might be more transparent and easier to validate; they also typically allow for a more comprehensive treatment of uncertainty (Briggs and Sculpher, 1998). Developing a model from the position of an existing model may also have advantages. Many of the models being developed now are the result of an iterative process of adaptation and change, and it is possible to see that each iteration/model has a role in the evolution of a process towards what might be a more applicable model. In the case of this intervention – and indeed for other complex interventions – understanding the mechanisms which impact on patient outcomes has been important, and it is hoped that this model might lead policy-makers, modelers and clinicians to identifying other potential mechanisms (Grutters et al., 2008).

Policy options: Conceptualising and then modelling a number of alternative

GP management strategies which might be impractable in clinical study settings
Unlike the controlled clinical study setting, modelling can test alternate models of service delivery without prohibitive cost (Buxton et al., 1997, Sculpher et al., 2006). Testing an array of options (for instance in a modelled scenario analysis) can inform which strategies are more effective and cost-effective either for trial in clinical practice or for implementation into policy. A further benefit is that there is no requirement to undergo ethical approval.

In addition to scenario analysis, decision modelling can inform on 'what if' scenarios that can not realistically be tested in the trial setting (sensitivity analysis). In other words, while a clinical trial can really only assess the impact of one (or two) interventions for one

population, in a model one can explore the impact of multiple variants of the intervention in several different populations. For instance, this model can examine the robustness of the ICER to different states of the world. Typically these include varying the model input parameters in isolation or simultaneously. In the context of the GPiT model, an interesting state of the world to test is one in which GPs are better diagnosticians. This leads into the third area in which the PhD has made a contribution.

Addressing uncertainty: re-examining and updating the data on the accuracy of GP diagnosis in TIA to reduce the uncertainty with this model input

The effectiveness of the GPiT strategy is likely to be sensitive to the false positive rate of GPs making the initial diagnosis of suspected TIA, which is why this rate is such an important input for the economic model. More evidence on this input will increase the external validity (generalisability) of the model to clinical practice where regional services have local information on accuracy of GPs making these decisions.

Several studies have compared the false positive rate of GPs in referred TIA with final TIA diagnoses and appear to lend support to a PPV of 50% (Lasserson, 2013). However, regardless of the estimated or assumed PPV, there is an ensuing difficulty in quantifying the risks and benefits of inappropriate treatment in the misdiagnosed. Patients with false positive TIA diagnoses may be a disparate group with a myriad of potential alternative diagnoses. This makes quantification of the benefits and risks of inappropriate treatment difficult without considerable assumptions. In the model, this was made operable by considering the proportion of the cohort who might face an increased risk of haemorrhagic events relative to the base-case assumption.

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9.3. Limitations

Finally, there are limitations in the way this research has been conducted as a process. This thesis reflects a period of experiential learning, and decisions regarding the methods and data sources used to structure and build the model might not reflect the approach that I would use in future.

Since commencing this thesis, there have also been some notable additions to the literature. One challenge I faced was to produce an up-to-date report when the evidence base – which is also experiential – was also shifting. Indeed, over the course of this thesis the definition of TIA itself changed. This results in a potential biases when attempting to compare test-statistics across studies which have used alternative reference standards.

9.4. Concluding Thoughts

Overall, this thesis illustrates the application of a decision model to examine a policy relevant question around treatment urgency in a susceptible group of patients. Results suggest that GP initiation of secondary preventive agents dominates (i.e. is less costly and more beneficial) a comparator which was characterised on the basis of the best performing UK TIA clinics in the UK. It is therefore unsurprising that the direction of these very positive findings (with respect to GPiT) were unchanged and magnified when comparison with a strategy based on nationwide audit of clinical practice.

However, there is considerable uncertainty associated with a number of key inputs of the model, particularly in relation to the accuracy of diagnosis and, related to this, the dangers of inappropriate treatment in those misdiagnosed as TIA by GPs. While the model's results appear to robust to extreme values of these unknowns, there remains a risk of serious events in a few.

Economic evaluation only informs on the efficiency criterion. The acceptability of the intervention to health care providers, professionals and the public remains to be considered.

APPENDIX 1: CRITICAL APPRAISAL OF MODELLING METHODS

Table 46: Embase search strategy for critical appraisal of economic modelling studies

	Citations identified
1. ("prevent$" or service delivery or "health care delivery").mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	1447735
2. 1 and ("decision support techniques decison tree$" or "computer simulation" or "cost benefit analysis" or "cost effective analysis" or "cost utility analysis").mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	12777
3. ("stroke/" or "TIA/").ti.	76076
4. ("Cerebrovascular Accident/" or "Isch$ Attack, Transient/").ti.	696
5. 3 or 4	76755
7. 2 and 5	140
8. 1 and 7	140

APPENDIX 2: MEDLINE/EMBASE SEARCH STRATEGY FOR DIAGNOSTIC ACCURACY REVIEW

1. diagnosis/ or diagnosis.ab.

2. predictive value of tests.sh.

3. primary health care/ or primary health care.mp. or "general prac$"/ or "community care".mp. or "emergency care".mp. or "clinic".mp. or "hospital".mp.

4. ("Isch$ attack, transient/" or "tia" or "stroke").ti.

5. sensitivity.kw.

6. specificity.kw.

7. (diagnostic adj accuracy).kw.

8. (predictive adj value).kw.

9. (general practice or gp$).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, ui]

10. referral/

11. 2 or 5 or 6 or 7 or 8 or 10

12. 3 or 9

13. 11 and 12 and 4

Cochrane, NHS Economic Evaluation Database search

stroke [ti] or tia [ti] and

accuracy [ti] or ppv [ti] or referral [ti] or test [ti] or gp [ti] or diagnosis [ti] or diagnose [ti]

MEDION search

"Signs and symptoms" and "neurological"

APPENDIX 3: RAPID REVIEWS

Cochrane database

Search terms used to identify effectivenss of dipyridamole/clopidogrel

ID	Search	Citations identified
#1	dipyridamole or clopidogrel	2461
#2	systematic review and #1	0
#3	meta-analysis and #2	26
#4	stroke prevention:ti	1551
#5	#1 and (#2 or #3) and #4	12

Search terms used to identify safety associated with dual antiplatelet therapy

safety and (dipyridamole or clopidogrel or dual adj antiplatelet) and secondary prevention and stroke	84
"prevention/" and ("stroke or Tia") AND (haemorrhage or bleed*)	46

APPENDIX 4: DATA EXTRACTED ON DIAGNOSTIC ACCURACY AND

ALTERNATIVE STROKE/TIA DIAGNOSES

Table 47: Extracted data (stratified by referral route) for clinician accuracy[17]

Study	Type	Positive cases	Total, N	PPV, % (95% CI)	Main referral source	Reference diagnosis
Magin et al, 2000	Prospective validation	29	127	0.23 (0.16-0.39)	GP	TIA
Magin et al, 2000	Prospective cohort	9	231	0.04 (0.01-0.06)	GP/ A&E	TIA
Gibbs et al, 2001	Prospective cohort	13	27	0.48 (0.29-0.67)	GP	TIA
Murray et al, 2007	Prospective cohort	217	811	0.27 (0.24-0.30)	GP/ A&E	TIA
Bos et al, 2007	Prospective cohort	282	538	0.52 (0.48-0.57)	Any	TIA
Harbison et al, 2009	Prospective cohort	25	216	0.12 (0.07-0.16)	GP	TIA
Fonseca et al, 2010	Prospective cohort	259	458	0.57 (0.52-0.61)	GP/ A&E	TIA
Kidwell et al,	Prospective cohort	31	36	0.86 (0.75-0.97)	Parame dic	CVA
Magin et al, 2000	Retrospective population-based	50	127	0.39 (0.31-0.48)	GP	CVA

[17] Where there is more than one data entry for a single study this reflects that the study reported outcomes relating to either different reference diagnosis (e.g. TIA, or a composite outcome of all stroke (including TIA).

Study	Type	Positive cases	Total, N	PPV, % (95% CI)	Main referral source	Reference diagnosis
Magin et al, 2000	Retrospective population-based	46	231	0.20 (0.15-0.25)	GP/ A&E	CVA
Gibbs et al, 2001	Prospective cohort	18	27	0.67 (0.49-0.84)	GP	CVA
Mant et al, 2003	Retrspective cohort	376	524	0.72 (0.68-0.76)	Any	CVA
Murray et al, 2007	Retrospective cohort	383	811	0.47 (0.44-0.51)	GP/ A&E	CVA
Fischer et al, 2008	Retrospective cohort	168	558	0.30 (0.26-0.34)	Other	CVA
McNeil et al, 2008	Prospective cohort	22	72	0.31 (0.20-0.41)	GP	CVA
Cameron et al 2011	Prospective cohort	1890	3533	0.53 (0.49-0.58)	Any	TIA

Table 48: Clinical diagnoses recorded by authors in suspected TIA cases identified in Primary Care (frequency by study, pooled totals and percentage of alternative diagnoses attributed)

Clinical diagnosis	Gibbs n=9	Harbison n=64	McNeil n=34	Fonseca n=84	Total n	%
Alcohol/drugs		3			3	2.8
Aneurysm	1					0
Arrhythmia						0
Asymptomatic stenosis carotid artery					1	0.9
Atrial fibrillation			1		3	2.8
Bell's palsy			3		0	0
Brain tumour					2	1.9
Cardiac dysrhythmia	2				5	4.7
Cardiovascular collapse		5			4	3.7
Cervical spondylosis		1	3		7	6.5
Delirium			7	2	0	0
Dementia		6	1		1	0.9
Depression					1	0.9
Epilepsy	1				3	2.8
Hypoglycaemic collapse		1			0	0
Hyponatremia and collapse		3			22	20.6
Iatrogenic				1	3	2.8
Infections/sepsis		9	13		7	6.5
Labyrinthine disorders		3			1	0.9
Malignant tumour		7			2	1.9
Meningitis		1			0	0
Migraine		2		4	0	0

Clinical diagnosis	Gibbs n=9	Harbison n=64	McNeil n=34	Fonseca n=84	Total n	%
Motor neurone disease					0	0
Movement disorder				1	0	0
Multiple sclerosis					0	0
Occluded retinal artery					2	1.9
Pain				3	1	0.9
Parkinson's disease		2			3	2.8
Pentoin toxicity			1		0	0
Peripheral neuropathy		3		2	0	0
Peripheral vertigo					2	1.9
Peripheral vertigo				6	1	0.9
Postural hypotension	2			14	5	4.7
Previous stroke/neurological deficit			1	2	7	6.5
Psychological/Psychiatric	2	3		18	1	0.9
Seizure		6	1	19	5	4.7
Subarachnoid haemorrhage‡		1			0	0
Subdural haemorrhage‡		5			1	0.9
Syncope/pre syncope				8	2	1.9
Temporal arteritis			1		1	0.9
Tension headache		2			2	1.9
Thromboembolism	1				0	0
Transient global amnesia		1	1		0	0
Trigeminal neuralgia						0
Unspecified metabolic disorder				4		0
Wernicke's Encephalophy			1			0

‡ One study (Harbison et al.) considered sub-arachnoid haemorrhage and sub-dural haemorrhage as alternative diagnoses. They were removed from the main analyses because the other studies did not report on stroke sub-types by pathological cause

APPENDIX 5: PARAMETERS USED IN THE MODEL

Table 49: Parameters used within the model and associated candidate distributions for PSA

Rates were converted into daily transition probabilities using the standard formula (Miller and Homan, 1994).
Stroke transitions were determined by survival methods (which are independent not multinomial probabilities) and the beta distribution was therefore used to implement uncertainty into the hazard rates associated with transitions from TIA to (all) stroke. The Dirichlet distribution was used for the remaining multinomial transitions. It should be noted that the implementation of the Dirichlet distribution is challenging in this particular model context where there are several independent sources of evidence informing each set of transitions. Implementation assumed that it was possible to back transform probability data to determine hypothetical transitions in a cohort of 1000 patients.

Transition	Treated		Untreated	
	Daily transition probaility %¥	Distribution (se) *	Daily transition probaility¥	Distribution
TIA - All stroke	Based on time-dependent transitions. Constant hazard rate within discrete intervals. Interval for days 0-7	Beta (0,1106)		Beta (4,536)
	Interval for days 7-90	Beta (0,1107		Beta (0.540)
TIA - Major haemorrhage	0.0067	Dirichlet $\alpha(0.1,2.9,0.2,969.9)$	0.001	Dirichlet $\alpha(0.003,0.2,999.8)$

Transition	Treated		Untreated	
	Daily transition probaility %¥	Distribution (se) *	Daily transition probaility¥	Distribution
TIA - carotid surgery	0.2912	Dirichlet α(2.9,0.1,0.2,969.9)	n/a	
TIA - Other cause death	0.0161	Dirichlet α(0.2,2.9,0.1,969.9)	0.0161	Dirichlet α(0.2,0.003,999.8)
Carotid surgery - Major haemorrhage	0.0067	Dirichlet α(0.1,1.5,3.0,0.3,995.2)	n/a	
Carotid surgery - Ischaemic stroke	0.1205	Dirichlet α(1.5,0.1,3.0,0.3,995.2)	n/a	
Carotid surgery - Haemorrhagic stroke	0.0597	Dirichlet α(3.0,1.5,0.1,0.3,995.2)	n/a	
Carotid surgery - Carotid surgery death	0.3096	Dirichlet α(0.3,0.1,1.5,3.0,995.2)	n/a	
Ischaemic stroke - Fatal iscahemic stroke	0.2993	Normal, (0.001)	As treated	
Haemorrhagic stroke - Fatal haemorrhagic stroke	0.3955	Normal, (0.001)	As treated	

Transition	Treated		Untreated	
	Daily transition probaility %¥	Distribution (se) *	Daily transition probaility¥	Distribution
Major haemorrhage - Fatal major haemorrhage	0.0005	Normal, (0.001)	As treated	
TIA mimic - All stroke	0.0001	Dirichlet α(0.001,0.003,0.2, 999.8)	0.00039	Dirichlet α(0.004,0.2,999.8)
TIA mimic - Major haemorrhage	0.00027	Dirichlet α(0.003,0.001,0.2, 999.8)	0.0000	None (baseline risk assumed nil)
TIA mimic - Other cause death	0.0161	Dirichlet α(0.001,0.003,0.2, 999.8)	0.0161	Dirichlet α(0.2,0.004,999.8)

¥ corresponding to the value used in the model (for the Markov model considered here, transition probabilities are the daily probability of the event occurring).

*used in probabilistic sensitivity analysis and required where the normal distribution was chosen.

Where dirichlet distributions are specified they represent movement to the named health state followed by other possible transitions in order.

For transitions from TIA:
Major haemorrhage, carotid surgery (true TIA only), all stroke (mimic states only), other cause death and a TIA 'sunk' state (used to retain the assumption that the cohort must sum to 1000).
For transitions from carotid surgery:
Major hameorrhage, haemorrhagic stroke, ischaemic stroke, carotid surgery death and a carotid surgery 'sunk' state.

Table 50: Utilities and Life Expectancy

	deterministic	se†	distribution	alpha	beta
Post TIA	0.880	0.035	Beta	22.10	0.04
Stroke	0.443	0.054	Beta	3.67	0.12
Major haemorrhage	0.310	0.050	Beta	1.93	0.16
Post Surgery	0.710	0.049	Beta	10.30	0.07
TIA Mimic (Minor)	0.880	0.055	Beta	22.10	0.04
TIA Mimic (Serious pathology)	0.443	0.050	Beta	1.93	0.16

†Standard errors estimated using the standard confidence interval for a proportion se$=\sqrt{(p(1-p)}$ where n is known. (Bland, 2000 p.128)

Table 51: Costs and associated candidate distributions

	deterministic	se[18]	distribution	alpha	beta
On treatment (secondary prevention agents)	£0.26	-	Not varied	-	-
Stroke	£7,570.00	375	Gamma	16	93.75
Major haemorrhage	£1,000.00	250	Gamma	16	63
Post surgery	£407.00	102	Gamma	16	25
GP clinic	£43.00	-	Not varied	-	-
Specialist weekly clinic	£246.00	-	Not varied	-	-
Specialist daily clinic	£246.00	-	Not varied	-	-
Carotid endarterectomy	£4,017.00	4,000	Not varied	-	-
Dependent after a stroke within 90 days	£57,378	12,900	Gamma	16	3226
Independent after a stroke within 90 days	£8,415	1,893	Gamma	16	473
Recovered (GP follow-up)	£887	199.50	Gamma	16	49
Recovered (Specialist follow up)	£1475	331.75	Gamma	16	83

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[18] Standard errors estimated using the binomial approximation se=$\sqrt{p(1-p)/n}$ where n is known. (Bland, 2000).

APPENDIX 6: MODEL RESULTS (DETAILED VIEW)

A.6.1. Clinical outcomes

Table 52: Clinical outcomes for all strategies

	No further event	Stroke Ischaemic		stroke Haemorrhagic		Carotid Surgery		haemorrhage Major		Other cause death
		Non-fatal	Fatal	Non-fatal	Fatal	Non-fatal	Fatal	Non-fatal	Fatal	
GPiT	953.59	11.90	2.78	0.08	0.03	14.47	0.05	2.96	0.00	14.14
Best practice	945.65	17.44	4.47	0.11	0.04	15.32	0.06	2.87	0.00	14.04
Current practice	918.73	44.12	12.26	0.29	0.11	8.37	0.03	2.52	0.00	13.56
GPiT refer only high risk	960.85	12.15	2.86	0.08	0.03	6.96	0.03	2.91	0.00	14.14
GPiT no referral	968.04	11.87	2.77	0.08	0.03	0.00	0.00	3.07	0.00	14.14

A.6.2. Scenario analysis for the base-case comparison.

Table 53: Scenario analysis, base-case, 90 day results (deterministic)

	Total QALYs/ patient	Total costs/ patient	Incremental QALYs vs. best practice	Incremental. costs vs. best practice	Net benefit at a £10,000 ceiling ratio	Net benefit at a £20,000 ceiling ratio	Net benefit at a £30,000 ceiling ratio
Current practice	0.2053	£293	-0.0047	£104	-£150	-£197	-£243
Best practice	0.2100	£190					
GPiT	0.2108	£187	0.0009	-£3	£12	£21	£29
GPiT refer only high risk	0.2112	£173	0.0012	-£17	£29	£42	£54
GPiT no referral	0.2115	£159	0.0015	-£31	**£46**	**£61**	**£76**

Note: Figures in bold denote the preferred strategy on the basis of maximum net benefit for each value of the ceiling ratio.

Table 54: Scenario analysis, base-case, lifetime results (deterministic)

	Total QALYs/ patient	Total costs/ patient	Incremental QALYS vs. best practice	Incremental costs vs. best practice	Net benefit at a £10,000 ceiling ratio	Net benefit at a £20,000 ceiling ratio	Net benefit at a £30,000 ceiling ratio
Current practice	7.6607	£2,985	-0.1635	£808	-£2,443	-£4,078	-£5,714
Best practice	7.8243	£2,177					
GPiT	7.8585	£1,160	0.0342	-£1,017	£1,359	£1,702	£2,044
GPiT refer only high risk	7.8600	£1,168	0.0357	-£1,009	£1,366	**£1,723**	**£2,081**
GPiT no referral	7.8594	£1,160	0.0351	-£1,017	**£1,368**	£1,719	£2,069

Note: Figures in bold denote the preferred strategy on the basis of maximum net benefit for each value of the ceiling ratio.

Table 55: Scenario analysis, base-case, 90 day results (probabilistic)

	Total QALYs/ patient	Total costs/ patient	Incremental QALYG vs. best practice	Incremental costs vs. best practice	Net benefit at a £10,000 ceiling ratio	Net benefit at a £20,000 ceiling ratio	Net benefit at a £30,000 ceiling ratio
Current practice	0.2053	£284	-0.0046	£95	-£173	-£187	-£232
Best practice	0.2098	£189	0.0000	£0			
GPiT	0.2107	£185	0.0009	-£4	£19	£21	£30
GPiT refer only high risk	0.2112	£169	0.0013	-£20	£42	£46	£60
GPiT no referral	0.2115	£153	0.0017	-£36	**£65**	**£70**	**£87**

Note: Figures in bold denote the preferred strategy on the basis of maximum net benefit for each value of the ceiling ratio.

Table 56: Scenario analysis, base-case, lifetime results (probabilistic)

	Total / patient	Total costs/ patient	Incremental QALYG vs. best practice	Incremental costs vs. best practice	Net benefit at a £10,000 ceiling ratio	Net benefit at a £20,000 ceiling ratio	Net benefit at a £30,000 ceiling ratio
Current practice	8.8890	£2,083	-0.2573	£560	-£3,132	-£5,705	-£8,278
Best practice	9.1462	£1,523					
GPiT	9.2003	£968	0.0540	-£555	£1,095	£1,635	£2,176
GPiT refer only high risk	9.2008	£974	0.0546	-£549	£1,095	£1,640	£2,186
GPiT no referral	9.2015	£968	0.0553	-£555	**£1,108**	**£1,661**	**£2,213**

Note: Figures in bold denote the preferred strategy on the basis of maximum net benefit for each value of the ceiling ratio.

A.6.3. Scenario analysis results for the secondary comparison

Table 57: Scenario analysis, secondary comparison, 90 day results (deterministic)

	Total QALYs/ patient	Total costs/ patient	Inc. QALYS vs. current practice	Inc. costs vs. current practice	Net benefit at a £10,000 ceiling ratio	Net benefit at a £20,000 ceiling ratio	Net benefit at a £30,000 ceiling ratio
Current practice	0.2053	£293					
Best practice	0.2100	£190	0.0047	-£104	£104	£197	£243
GPiT	0.2108	£187	0.0055	-£107	£162	£217	£273
GPiT refer only high risk	0.2112	£173	0.0059	-£120	£179	£238	£297
GPiT no referral	0.2115	£159	0.0062	-£134	**£196**	**£257**	**£319**

Note: Figures in bold denote the preferred strategy on the basis of maximum net benefit for each value of the ceiling ratio.

Table 58: Scenario analysis, secondary comparison, lifetime results (deterministic)

	Total QALYs/ patient	Total costs/ patient	Inc. QALYS vs. current practice	Inc. costs vs. current practice	Net benefit at a £10,000 ceiling ratio	Net benefit at a £20,000 ceiling ratio	Net benefit at a £30,000 ceiling ratio
Current practice	8.8870	£2,055					
Best practice	9.1439	£1,477	0.2569	-£578	£3,147	£5,717	£8,286
GPiT	9.1977	£926	0.3107	-£1,129	£4,236	£7,343	£10,450
GPiT refer only high risk	9.1979	£932	0.3109	-£1,123	£4,232	£7,341	£10,450
GPiT no referral	9.1982	£925	0.3112	-£1,130	**£4,242**	**£7,354**	**£10,467**

Note: Figures in bold denote the preferred strategy on the basis of maximum net benefit for each value of the ceiling ratio.

Table 59: Scenario analysis, secondary analysis, 90 day results (probabilistic)

	Total QALYs/ patient	Total costs/ patient	Inc. QALYS vs. current practice	Inc. costs vs. current practice	Net benefit at a £10,000 ceiling ratio	Net benefit at a £20,000 ceiling ratio	Net benefit at a £30,000 ceiling ratio
Current practice	0.2053	£284					
Best practice	0.2098	£189	0.0046	-£95	£173	£187	£232
GPiT	0.2107	£185	0.0055	-£99	£192	£208	£263
GPiT refer only high risk	0.2112	£169	0.0059	-£115	£215	£233	£292
GPiT no referral	0.2115	£153	0.0063	-£131	**£238**	**£257**	**£319**

Note: Figures in bold denote the preferred strategy on the basis of maximum net benefit for each value of the ceiling ratio.

Table 60: Scenario analysis, secondary comparison, lifetime results (probabilistic)

	Total QALYs/ patient	Total costs/ patient	Inc. QALYS vs. current practice	Inc. costs vs. current practice	Net benefit at a £10,000 ceiling ratio	Net benefit at a £20,000 ceiling ratio	Net benefit at a £30,000 ceiling ratio
Current practice	8.8890	£2,083					
Best practice	9.1462	£1,523	0.257	-£560	£3,132	£5,705	£8,278
GPiT	9.2003	£968	0.311	-£1,115	£4,228	£7,341	£10,454
GPiT refer only high risk	9.2008	£974	0.312	-£1,109	£4,227	£7,345	£10,464
GPiT no referral	9.2015	£968	0.313	-£1,115	**£4,240**	**£7,366**	**£10,491**

Note: Figures in bold denote the preferred strategy on the basis of maximum net benefit for each value of the ceiling ratio.

A.6.4. Sensitivity analysis results across all strategies

Results presented are deterministic.

Table 61: Results for alternative assumption regarding accuracy of GP diagnosis (PPV=75%), 90 days

	Total QALYs/ patient	Total costs/ patient	Inc. QALYS vs. current practice	Inc. costs vs. current practice	Net benefit at a £10,000 ceiling ratio	Net benefit at a £20,000 ceiling ratio	Net benefit at a £30,000 ceiling ratio
Current practice	0.2014	£303					
Best practice	0.2084	£147	0.0070	-£155	£155	£295	£365
GPiT	0.2097	£143	0.0083	-£160	£243	£326	£409
GPiT refer only high risk	0.2102	£122	0.0088	-£181	£269	£357	£445
GPiT no referral	0.2107	£101	0.0093	-£202	**£294**	**£387**	**£479**

Note: Figures in bold denote the preferred strategy on the basis of maximum net benefit for each value of the ceiling ratio.

Table 62: Results for alternative assumption regarding accuracy of GP diagnosis (PPV=75%), lifetime horizon

	Total QALYs/ patient	Total costs/ patient	Inc. QALYS vs. current practice	Inc. costs vs. current practice	Net benefit at a £10,000 ceiling ratio	Net benefit at a £20,000 ceiling ratio	Net benefit at a £30,000 ceiling ratio
Current practice	8.6703	£2,531					
Best practice	9.0557	£1,664	0.3854	-£867	£4,721	£8,575	£12,429
GPiT	9.1364	£1,057	0.4661	-£1,474	£6,135	£10,796	£15,457
GPiT refer only high risk	9.1362	£1,059	0.4659	-£1,471	£6,131	£10,790	£15,449
GPiT no referral	9.1377	£1,056	0.4674	-£1,475	**£6,149**	**£10,823**	**£15,498**

Note: Figures in bold denote the preferred strategy on the basis of maximum net benefit for each value of the ceiling ratio.

Table 63: Results for alternative assumption regarding accuracy of GP diagnosis (PPV=25%), 90 days

	Total QALYs/ patient	Total costs/ patient	Inc. QALYS vs. current practice	Inc. costs vs. current practice	Net benefit at a £10,000 ceiling ratio	Net benefit at a £20,000 ceiling ratio	Net benefit at a £30,000 ceiling ratio
Current practice	0.2092	£284					
Best practice	0.2115	£232	0.0023	-£52	£52	£98	£122
GPiT	0.2119	£231	0.0028	-£53	£81	£109	£136
GPiT refer only high risk	0.2122	£224	0.0030	-£60	£90	£120	£149
GPiT no referral	0.2122	£217	0.0031	-£67	**£98**	**£128**	**£159**

Note: Figures in bold denote the preferred strategy on the basis of maximum net benefit for each value of the ceiling ratio.

Table 64: Results for alternative assumption regarding accuracy of GP diagnosis (PPV=25%), lifetime horizon

	Total QALYs/ patient	Total costs/ patient	Inc. QALYS vs. current practice	Inc. costs vs. current practice	Net benefit at a £10,000 ceiling ratio	Net benefit at a £20,000 ceiling ratio	Net benefit at a £30,000 ceiling ratio
Current practice	9.1036	£1,579					
Best practice	9.2321	£1,290	0.1285	-£289	£1,574	£2,858	£4,143
GPiT	9.2590	£795	0.1553	-£784	£2,337	£3,890	£5,443
GPiT refer only high risk	9.2595	£804	0.1558	-£775	£2,333	**£3,892**	**£5,450**
GPiT no referral	9.2587	£795	0.1550	-£784	**£2,335**	£3,885	£5,436

Note: Figures in bold denote the preferred strategy on the basis of maximum net benefit for each value of the ceiling ratio.

Table 65: Results for alternative assumption about prognosis of non true TIA on adverse events (major haemorrhage) [two fold increase in both events in mimic population], 90 days

	Total QALYs/ patient	Total costs/ patient	Inc. QALYS vs. current practice	Inc. costs vs. current practice	Net benefit at a £10,000 ceiling ratio	Net benefit at a £20,000 ceiling ratio	Net benefit at a £30,000 ceiling ratio
Current practice	0.2053	£293					
Best practice	0.2100	£190	0.0047	-£104	£104	£197	£243
GPiT	0.2108	£187	0.0055	-£107	£162	£217	£273
GPiT refer only high risk	0.2112	£173	0.0059	-£120	£179	£238	£297
GPiT no referral	0.2115	£159	0.0062	-£134	**£196**	**£257**	**£319**

Note: Figures in bold denote the preferred strategy on the basis of maximum net benefit for each value of the ceiling ratio.

Table 66: Results for alternative assumption about prognosis of non true TIA on adverse events (major haemorrhage) [two fold increase in events in mimic population], lifetime horizon

	Total QALYs/ patient	Total costs/ patient	Inc. QALYS vs. current practice	Inc. costs vs. current practice	Net benefit at a £10,000 ceiling ratio	Net benefit at a £20,000 ceiling ratio	Net benefit at a £30,000 ceiling ratio
Current practice	8.8870	£2,055					
Best practice	9.1439	£1,477	0.2569	-£578	£3,147	£5,717	£8,286
GPiT	9.1976	£926	0.3106	-£1,129	£4,236	£7,342	£10,449
GPiT refer only high risk	9.1976	£932	0.3106	-£1,123	£4,229	£7,335	£10,441
GPiT no referral	9.1976	£925	0.3106	-£1,130	**£4,236**	**£7,343**	**£10,449**

Note: Figures in bold denote the preferred strategy on the basis of maximum net benefit for each value of the ceiling ratio.

Table 67: Adjustment for poor outcomes following carotid surgeries not performed in Current practice and GPiT alternative 2 (no referral to a specialist), 90 days

	Total QALYs/ patient	Total costs/ patient	Inc. QALYS vs. current practice	Inc. costs vs. current practice	Net benefit at a £10,000 ceiling ratio	Net benefit at a £20,000 ceiling ratio	Net benefit at a £30,000 ceiling ratio
Current practice	0.2053	£293					
Best practice	0.2100	£190	0.0047	-£104	£104	£197	£243
GPiT	0.2108	£187	0.0055	-£107	£162	£217	£273
GPiT refer only high risk	0.2112	£173	0.0059	-£120	£179	£238	£297
GPiT no referral	0.2115	£159	0.0062	-£134	**£196**	**£258**	**£319**

Note: Figures in bold denote the preferred strategy on the basis of maximum net benefit for each value of the ceiling ratio.

Table 68: Adjustment for poor outcomes following carotid surgeries not performed in Current practice and GPiT alternative 2 (no referral to a specialist), lifetime horizon

	Total QALYs/ patient	Total costs/ patient	Inc. QALYS vs. current practice	Inc. costs vs. current practice	Net benefit at a £10,000 ceiling ratio	Net benefit at a £20,000 ceiling ratio	Net benefit at a £30,000 ceiling ratio
Current practice	8.8870	£2,055					
Best practice	9.1439	£1,477	0.2569	-£578	£3,147	£5,717	£8,286
GPiT	9.1977	£926	0.3107	-£1,129	£4,236	£7,343	£10,450
GPiT refer only high risk	9.2002	£955	0.3132	-£1,100	£4,232	£7,365	£10,497
GPiT no referral	9.2098	£1,040	0.3228	-£1,015	**£4,244**	**£7,472**	**£10,701**

Note: Figures in bold denote the preferred strategy on the basis of maximum net benefit for each value of the ceiling ratio.

Table 69: Adjustment for variation in utility values used (van Exel et al., 2004)), 90 days

	Total QALYs/ patient	Total costs/ patient	Inc. QALYS vs. current practice	Inc. costs vs. current practice	Net benefit at a £10,000 ceiling ratio	Net benefit at a £20,000 ceiling ratio	Net benefit at a £30,000 ceiling ratio
Current practice	0.1779	£293					
Best practice	0.1801	£190	0.0022	-£104	£104	£148	£171
GPiT	0.1805	£187	0.0026	-£107	£133	£159	£185
GPiT refer only high risk	0.1807	£173	0.0029	-£120	£149	£178	£207
GPiT no referral	0.1809	£159	0.0030	-£134	**£165**	**£195**	**£225**

Note: Figures in bold denote the preferred strategy on the basis of maximum net benefit for each value of the ceiling ratio.

Table 70: Adjustment for variation in utility values used (van Exel et al., 2004), lifetime horizon

	Total QALYs/ patient	Total costs/ patient	Inc. QALYS vs. current practice	Inc. costs vs. current practice	Net benefit at a £10,000 ceiling ratio	Net benefit at a £20,000 ceiling ratio	Net benefit at a £30,000 ceiling ratio
Current practice	7.6358	£2,055					
Best practice	7.8175	£1,477	0.1817	-£578	£2,395	£4,212	£6,029
GPiT	7.8555	£926	0.2197	-£1,129	£3,326	£5,524	£7,721
GPiT refer only high risk	7.8565	£932	0.2207	-£1,123	**£3,330**	**£5,537**	**£7,744**
GPiT no referral	7.8559	£925	0.2201	-£1,130	**£3,330**	£5,531	£7,731

Note: Figures in bold denote the preferred strategy on the basis of maximum net benefit for each value of the ceiling ratio.

Table 71: Variation in lifetime cost of stroke (50% increase in all long-term care costs), 90 days

	Total QALYs/ patient	Total costs/ patient	Inc. QALYS vs. current practice	Inc. costs vs. current practice	Net benefit at a £10,000 ceiling ratio	Net benefit at a £20,000 ceiling ratio	Net benefit at a £30,000 ceiling ratio
Current practice	8.8870	£4,109					
Best practice	9.1439	£2,953	0.2569	-£1,156	£3,725	£6,295	£8,864
GPiT	9.1977	£1,851	0.3107	-£2,258	£5,365	£8,472	£11,579
GPiT refer only high risk	9.1979	£1,863	0.3109	-£2,246	£5,355	£8,464	£11,573
GPiT no referral	9.1982	£1,850	0.3112	-£2,260	**£5,372**	**£8,484**	**£11,596**

Note: Figures in bold denote the preferred strategy on the basis of maximum net benefit for each value of the ceiling ratio.

Table 72: Varying the discount rate (Undiscounted costs and benefits), lifetime horizon

	Total QALYs/ patient	Total costs/ patient	Inc. QALYS vs. current practice	Inc. costs vs. current practice	Net benefit at a £10,000 ceiling ratio	Net benefit at a £20,000 ceiling ratio	Net benefit at a £30,000 ceiling ratio
Current practice	10.6198	£2,441					
Best practice	10.9268	£1,754	0.3070	-£686	£3,757	£6,827	£9,897
GPiT	10.9911	£1,100	0.3713	-£1,341	£5,054	£8,766	£12,479
GPiT refer only high risk	10.9913	£1,107	0.3715	-£1,334	£5,049	£8,764	£12,479
GPiT no referral	10.9917	£1,099	0.3719	-£1,342	**£5,061**	**£8,780**	**£12,499**

Note: Figures in bold denote the preferred strategy on the basis of maximum net benefit for each value of the ceiling ratio.

Table 73: Varying the discount rate (6% costs and benefits), lifetime horizon

	Total QALYs/ patient	Total costs/ patient	Inc. QALYS vs. current practice	Inc. costs vs. current practice	Net benefit at a £10,000 ceiling ratio	Net benefit at a £20,000 ceiling ratio	Net benefit at a £30,000 ceiling ratio
Current practice	6.6409	£1,824					
Best practice	6.8329	£1,311	0.1920	-£513	£2,433	£4,353	£6,273
GPiT	6.8730	£822	0.2322	-£1,002	£3,324	£5,645	£7,967
GPiT refer only high risk	6.8732	£827	0.2323	-£997	£3,320	£5,643	£7,966
GPiT no referral	6.8734	£821	0.2326	-£1,003	**£3,328**	**£5,654**	**£7,980**

Note: Figures in bold denote the preferred strategy on the basis of maximum net benefit for each value of the ceiling ratio.

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Appendix 7: Application of the CHEERS checklist to the GPiT model. CHEERS checklist reproduced from Husereau (2013).

Section/item	Item No	Recommendation	Reported on page No
		Title and abstract	
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	p.80
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base-case and uncertainty analyses), and conclusions.	Abstract
		Introduction	
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	pp.80-82
		Methods	
Target population and subgroups	4	Describe characteristics of the base-case population and subgroups analysed, including why they were chosen.	pp. 85-7
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	pp. 85-7
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	pp.89-90
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	p.90
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	p.90
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	p.96
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	n/a
	11b	*Synthesis-based estimates:* Describe fully	pp.102-122

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Section/item	Item No	Recommendation	Reported on page No
		the methods used for identification of included studies and synthesis of clinical effectiveness data.	
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	pp.122-3
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	p.125
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	pp.125-8
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	p.88; p.91-3
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	p.90-6
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half	pp.105-135; pp.135-152

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Section/item	Item No	Recommendation	Reported on page No
		cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	
		Results	
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	pp.215-9
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	pp.167-9; p.176
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	n/a
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	pp.178-189
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	n/a
		Discussion	
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Discussion chapter pp. 192-207
		Other	
Source of funding	23	Describe how the study was funded and the role of the funder in the identification,	Preface

Section/item	Item No	Recommendation	Reported on page No
		design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Preface

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