Structural neuroimaging in psychosis. Systematic review and economic evaluation.

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1. Definition of terms and list of abbreviations

AQOL	assessment of quality of life
ARIF	Aggressive Research Intelligence Facility
BNF	British National Formulary
BPRS	Brief Psychiatric Rating Scale
CI	confidence interval
CT	computed tomography
CCT	cranial computed tomography
CVA	Stroke
DARE	Database of Abstracts of Reviews of Effects
DSC	dynamic susceptibility contrast
DSM	Diagnostic and Statistical Manual of Mental Disorders
EEG	electroencephalogram
EQ-5D	EuroQoL (quality of life)
FEP	first episode psychosis
HRQoL	health related quality of life
ICD	International Classification of Diseases
ICER	Incremental Cost Effectiveness Ratio
MMSE	Mini Mental State Examination
MRI	magnetic resonance imaging
MTA	medial temporal lobe atrophy
NA	not applicable
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Public Health and Clinical Excellence
NOS	not otherwise specified
NR	not reported
NRR	National Research Register
OHE HEED:	Office of Health Economic Health Economic Evaluation Database
PET	positron emission tomography
QALE	quality adjusted life expectancy
QALY	quality adjusted life year
QoL	quality of life
QUADAS	quality assessment of diagnostic accuracy studies in systematic reviews
RBS	radionucleotide brain scan

rCBV	regional cerebral blood volume
RCT	randomised controlled trial
Rx	treatment
SD	standard deviation
SPECT	single photon emission computed tomography
T	tesla
WM(H)	white matter (hyperintensities)

2. Executive summary

Background

Psychosis is a term used to describe a group of conditions in which severe symptoms of mental illness such as delusions and hallucinations occur, accompanied by the inability to distinguish between subjective experience and reality, and usually there is a lack of insight. Psychosis can be categorised as functional or organic. The prevalence of organic causes of psychosis varies by age, with less in younger than older patients. Patients with psychosis may also have additional pathology such as space occupying brain lesions. The main factors that would lead the clinician to suspect an organic cause of psychosis or additional pathology should be discovered during the initial clinical history and examination. Indication that an organic cause is more likely include an acute onset, features of delirium such as clouding of consciousness, disorientation in time and place, disturbance of memory, impaired attention, fluctuation of conscious awareness and visual hallucinations. A neurological history and examination would look for a recent history of malignancy and/or focal neurological symptoms or signs, but these are not always present. Additional confirmatory tests would be used, depending on the diagnosis hypothesised. However, structural neuroimaging can also be used in all patients presenting with psychosis, irrespective of clinical suspicion, to screen for any additional pathology that would affect the clinical management of the patient. This may include structural MRI or CT scanning but frequently this is not undertaken in the UK.

Objectives

To establish the clinical and cost effectiveness of structural neuroimaging (structural MRI and CT scanning) for all patients with psychosis, particularly a first episode of psychosis, relative to the current UK practice of selective screening only where it is clinically indicated.

Methods

A systematic review of studies (of any study design) reporting the additional diagnostic benefit of structural MRI, CT or combinations of these in patients with psychosis was conducted. The comparator was any current standard practice of diagnostic workup without structural neuroimaging. Only studies reporting clinically relevant outcomes were included. MEDLINE, EMBASE, the Cochrane Library, PsychINFO and CINAHL were searched from inception to November 2006. Inclusion, quality assessment and data extraction were undertaken in duplicate. Studies were assessed qualitatively only. The economic assessment consisted of a systematic review of past economic evaluations and the development of a threshold analysis to predict the QALY gain required to make neuroimaging cost-effective at a threshold of cost per QALY of £20,000 and £30,000. Sensitivity analyses of several parameters including prevalence of psychosis were performed.

Results

Effectiveness

A total of 25 studies were included in this systematic review. There were 24 studies of a diagnostic before-after type design evaluating the clinical benefit of CT, structural MRI or combinations in treatment naïve, first episode or unspecified psychotic patients, including one in schizophrenia patients resistant to treatment. Also included was a review of published case reports of misidentification syndromes. In most

studies, structural neuroimaging identified very little that would influence patient management that was not suspected based on a medical history and/or physical examination and there were more incidental findings. In the four MRI studies, approximately 5% of patients had findings that would influence clinical management whereas in the CT studies, approximately 0.5% of patients had these findings. The review of misidentification syndromes found that 25% of CT scans affected clinical management but this may have been a selected and therefore unrepresentative sample.

Cost effectiveness

The objective of the economic analysis was to measure the difference in costs and benefits of scanning all patients with CT or MRI compared to selective scanning under standard care as any benefit from scanning all patients would only be realised in cases where organic causes were not immediately obvious to the clinician as the treatment pathway would only be altered in these patients.

A decision-analytic model was not possible as it required information on the differential response to treatment by cause and the impact upon quality of life (QoL) from having an early diagnosis as opposed to a late diagnosis of an organic cause, which could not be found in the literature. A threshold analysis with a one-year time horizon was undertaken. This combined the incremental cost of routine scanning with a threshold cost per QALY value of £20,000 and £30,000 to predict the QoL gain required to meet these threshold values.

Routine scanning versus selective scanning appeared to be cost-saving with savings ranging from £228 to £789 with MRI scanning and £346 to £852 with CT scanning with the assumption of a 5% prevalence rate of tumours/cycts or other organic causes amenable to treatment. This meant that for the intervention to be cost-effective, patients would have to suffer a QoL loss of 0.011 to 0.039 with MRI scanning and 0.017 to 0.043 with CT scanning using a £20,000 threshold value. These estimates were subjected to sensitivity analysis on three levels of uncertainty that contributed to the cost of antipsychotic medication. With all of these parameters suitably varied, routine scanning still remained the cost-saving option. However, when the prevalence rate was varied to 0.5%, MRI was no longer cost saving and patients would need a QoL gain. For CT at 0.5% prevalence, all patients and brain tumour patients would have to suffer a QoL loss from CT only in the scenario where 50% of patients were initially treated in hospital.

Discussion and conclusions

The definition of first-episode psychosis is not clearly defined or universally accepted. There is a paucity of good quality evidence on the clinical benefits of structural neuroimaging in psychosis on which to base this health technology assessment. The evidence to date suggests that if screening with structural neuroimaging was implemented in all patients presenting with psychotic symptoms, little would be found to affect clinical management in addition to that suspected by a full clinical history and neurological examination. The strategy of neuroimaging for all may be cost saving, if the prevalence of organic causes is around 5% but not if the prevalence is around 0.5%. The main research priorities are to monitor the current use of structural neuroimaging in psychosis in the NHS to identify clinical triggers to its current use and subsequent outcomes. In addition, well conducted diagnostic before and after studies on representative populations are required to determine the clinical utility of

structural neuroimaging in this patient group. There also needs to be research to determine whether the most appropriate structural imaging modality in psychosis should be CT or MRI.

3. Aim and Background

The aim of this review is to establish the clinical and cost effectiveness of structural neuroimaging (structural CT and MRI scanning) for patients with psychosis, particularly a first episode of psychosis, relative to current UK practice.

3.1 Description of psychosis

Psychosis is a term used to describe a group of conditions in which severe symptoms of mental illness such as delusions and hallucinations occur, accompanied by the inability to distinguish between subjective experience and reality, and usually there is a lack of insight.[1] Psychosis is considered to be a symptom of severe mental illness but not a diagnosis in itself. Psychosis can develop at any age from childhood to late old age.[2,3]

There is no ICD-10 classification of psychosis per se.[4] The most important categories are F20-F29 Schizophrenia, schizotypal and delusional disorders. This includes schizophrenia, as the most important member of the group, schizotypal disorder, persistent delusional disorders, and a larger group of acute and transient psychotic disorders.[4] Other important categories are F30.2 (mania with psychotic symptoms), F31 (bipolar affective disorder) and F32.3 (severe depression with psychotic symptoms).

Within the ICD-10 classification psychosis occurs in:
F03 Unspecified dementia, presenile, psychosis NOS, senile psychosis NOS
F04 Organic amnesic syndrome, not induced by alcohol or other psychoactive substances, including Korsakov's psychosis
F05 Delirium, not induced by alcohol and other psychoactive substances, includes infective psychosis
F06.2 Organic delusional (schizophrenia-like) disorder, schizophrenia-like psychosis in epilepsy
F06.8 Other specified mental disorders due to brain damage and dysfunction and to physical disease, epileptic psychosis NOS
F09 Unspecified organic or symptomatic mental disorder, Psychosis organic NOS, symptomatic NOS
F10.5 to F19.5 psychotic disorder following psychoactive substance abuse
F20-29 Schizophrenia, schizotypal and delusional disorders
F30.2 Mania with psychotic symptoms
F31.2 Bipolar affective disorder, current episode manic with psychotic symptoms
F31.5 Bipolar affective disorder, current episode severe depression with psychotic symptoms
F32.3 Severe depressive episode with psychotic symptoms
F33.3 Recurrent depressive disorder, current episode severe with psychotic symptoms
F44 Associative (conversion) disorders including hysterical psychosis
F53.1 Severe mental and behavioural disorders associated with the puerperium, not elsewhere classified**,** puerperal psychosis
F84.0 Childhood autism, infantile psychosis
F84.1 Atypical childhood autism, atypical childhood psychosis
F84.3 Other childhood disintegrative disorder, disintegrative psychosis, symbiotic psychosis

F84.5 Asperger's syndrome (psychotic episodes occasionally occur in early adult life)

In DSM-IV, psychosis is described principally in the chapter on Schizophrenia and other psychotic disorders (including schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, shared psychotic disorder, psychotic disorder due to a medical condition and substance-induced psychotic disorder (from alcohol, amphetamine, cannabis, cocaine, hallucinogen, inhalant, opioid, phencyclidine, sedative, hypnotic or anxiolytic and other (or unknown) substance)).[5]

First episode psychosis is a term that refers to the first time that a person presents with psychosis. However, there are several issues associated with this term:

- The date of presentation of the first episode does not usually coincide with the onset of the condition because the person could have had psychotic symptoms for years without presenting to a health professional and often psychosis has a gradual onset
- The duration of untreated psychosis is important because it predicts response to treatment[6]
- A first episode could continue for ten years or more without remission, even when the patient is having treatment.[7]

Therefore, in a group of patients in their first episode, some may only have had psychosis for a few weeks and have not yet received treatment whereas some may have had psychosis for years and have been treated for years, constituting very different populations within this group definition. A two year limit for first episode duration has been suggested by a few,[7,8] but this is not generally accepted. Alternatively, others have suggested that a neuroleptic naïve population is more indicative of a population of patients at the start of a psychotic illness.[9].

When a person first presents with a first episode of psychosis, making a definitive diagnosis such as schizophrenia may not immediately be possible. DSM-IV requires that a patient has symptoms for six months before a diagnosis of schizophrenia can be made.[5] but ICD-10 does not have this requirement.[4]

In an Australian case series of 95 young people aged 13-25 presenting with a first episode of psychosis, the diagnosis was schizophrenia (44%), bipolar disorder (14%), substance induced psychosis (14%), schizophreniform (12%), major depression with psychosis (5%), psychosis NOS (5%), brief psychotic disorder (4%), schizoaffective disorder (1%) and non-psychotic disorder (2%).[10] In a UK prevalence study of people aged 25-74 with psychosis living in private households, the diagnosis was schizophrenia (49%), bipolar disorder (42%), both (4%) and no diagnosis (6%).[11]

3.1.1 Aetiology, pathology and prognosis

The actual structural cause of psychosis is unknown, i.e. whether there is a location of a single or multiple lesions in specific parts of the brain that are responsible for this symptom occurring. There is some debate as to whether a specific lesion actually exists and schizophrenia, for example, may be a product of an abnormally functioning cerebral system.[12] There is some evidence for a social contribution to aetiology.[13]

Historically, there have been two main categories of psychosis – organic and

functional. Organic psychoses were those in which an identifiable structural brain lesion is associated with psychotic symptoms such as delusions and hallucinations. Organic psychoses include cerebrovascular accidents, traumatic brain injury, Alzheimer's dementia, Parkinson's disease, Huntington's disease, multiple sclerosis, encephalitis, temporal lobe epilepsy and brain tumours. Functional psychoses include schizophrenia and mood disorders such as mania, bipolar disorder or puerperal psychosis. Atypical psychosis is a term sometimes used to describe psychosis with unusual features including those of organic psychotic disorders. Drug misuse can also precipitate (usually) short-lived psychotic symptoms.

Symptoms that would suggest that an organic cause of psychosis is more likely include an acute onset, features of delirium such as clouding of consciousness, disorientation in time and place, disturbance of memory, impaired attention, fluctuation of conscious awareness and visual hallucinations. Symptoms and signs of a space occupying lesion in the brain (localising signs) include upper motor neurone paralysis, sensory loss, cranial nerve lesions, nystagmus and speech or hearing difficulties.

It is estimated that between 5-10% of psychosis patients have an organic cause.[14] However, the most common causes of psychosis vary by age and gender. For example, young adults who develop psychotic symptoms are mostly diagnosed with a functional psychosis, particularly schizophrenia.[15]Schizophrenia is rare pre-puberty, and in younger age groups males are more commonly affected than females.[16] Most causes of psychosis in the elderly are organic. In one case series of psychogeriatric patients the final diagnosis was dementia (31%), organic psychosis (25%), depressive illness (23%), schizophrenia (11%), affective psychosis (8%) and anxiety (2%).[17] Where functional psychosis does occur in older people, it tends to affect a higher proportion of women than men.[18]

3.1.1.1 Causes of organic psychoses

Psychosis secondary to a brain tumour is rare. The prevalence of brain tumours in psychiatric patients is approximately 1.2% (using CT scan) but this does not distinguish between psychotic patients also with brain tumours and patients with brain tumours causing psychotic symptoms.[19] The classic symptoms of brain tumours causing raised intra-cranial pressure are headache, papilloedema and vomiting but these may not appear until late-stage or at all in a few patients. Other symptoms include mental deterioration and localising signs but again these may be missing in a few patients.[19] Primary brain tumours tend to be gliomas which include astrocytomas (including glioblastoma multiforme), medulloblastomas, ependymomas or oligodendromas. Other primary brain tumours include meningiomas, acoustic tumours and pituitary tumours. Secondary tumours (metastases) also occur, particularly from lung, breast and kidney primary tumours. However, a previous history of primary malignancy is usually present when these occur. Most tumours that cause psychotic symptoms are in the temporal lobe, particularly on the left side but can be caused by tumours in other regions including the frontal and parietal lobes and the corpus callosum. Patients with psychosis secondary to brain tumours tend to have more simple delusions and a tendency to be paranoid and thought disorders are relatively rare.[19] Visual hallucinations are more common and auditory hallucinations tend to be simple such as buzzing or ringing.[19] There may be clouding of consciousness,

confusion or disorientation in time, place or person that may suggest delirium (previously known as an acute organic brain syndrome). Delirium is characterised by disordered orientation, memory, intellect, judgement and affect and caused by diffuse impairment of brain tissue.[20] All of these symptoms are atypical so would lead the clinician to suspect an organic rather than functional cause of psychosis.

It is very rare that patients who have had a stroke will present with psychosis and with no other clinical signs and symptoms of a stroke. With regard to brain injuries, in a large cohort of brain injured servicemen from Finland, approximately 10% developed psychotic symptoms within approximately 5 years.[21] It has been suggested that the incidence of schizophrenia is higher following in-utero exposure to the influenza virus.[18] Limbic encephalitis is associated with psychotic symptoms and can be caused by Epstein-Barr, cytomegalovirus, rubella, herpes simplex, measles and HIV viruses.[21] In patients with Alzheimer's disease, psychosis is often a non-cognitive condition that accompanies dementia whereas in Parkinson's disease patients, treatment with anti-Parkinsonian drugs is the most frequent cause of psychotic symptoms.[22] People with multiple sclerosis rarely develop psychotic symptoms due to their illness.[21] Incidence estimates of schizophrenic symptoms in temporal lobe epilepsy vary widely [21] Psychosis in epilepsy can occur immediately before, during or after a seizure (pre-ictal, ictal and post-ictal) or between seizures (inter-ictal). Pre-ictal events are the classic aura of temporal lobe epilepsy, ictal events include features of psychosis that are regarded as psychic equivalents (classically termed psychomotor fits), post-ictal events present as post-seizure confusion or delirium and inter-ictal psychosis is the so-called schizophrenia-like psychosis of epilepsy. Ordinarily, the psychotic symptoms are described as episodic rather than continuing, with normal functioning between episodes.[23]

The kinds of symptoms and signs that would be checked for to establish whether a patient has an organic cause of psychosis are listed in Table 1

Table 1. Summary of findings looked for in to indicate organic causes of psychosis

Condition	Findings
Temporal lobe epilepsy	Psychosis episodic with normal functioning between episodes
CVA	Very rare to experience psychosis without localising signs and symptoms such as muscle wakness, paralysis, focal neurological signs of rapid onset such as apraxia, dysphasia, hemianopia
Brain injury	History of trauma, skull X-ray indication of trauma
Brain tumours – secondary	Past history of malignancy, usually focal neurological symptoms and signs often of relatively rapid onset
Brain tumours - primary	Usually focal neurological symptoms and signs
Encephalitis	Relatively acute onset, headache and drowsiness
Parkinson's disease	Psychosis usually caused by anti-Parkinsonian drugs
Multiple sclerosis	Upper motor neurone lesions, muscle weakness, patchy sensory loss or tingling, diverse relapsing and remitting course
Alzheimer's dementia	Disorientation in time, place or person, disturbance of memory, impaired attention

3.1.1.2 Prognosis

Because psychosis is a term that refers to a group of disorders or conditions, the prognoses vary depending on the primary disorder. Although all psychotic conditions reduce life expectancy, when considering different conditions such as schizophrenia, schizoaffective disorder and bipolar psychosis, on average, schizophrenia may have a worse prognosis and bipolar psychosis, a better prognosis.[24] Prognosis may also vary by age of onset. In young people, an insidiously developing form of psychosis with personality and developmental abnormalities is at risk of a poorer outcome than a single acute attack in a previously normal adolescent.[16] The prognosis for older people over the age of 40 seems to be better than those with a fist episode under the age of 40.[25]

In schizophrenia, five different patterns of course have been described[24]:

- Single psychotic episode with complete remission
- Single psychotic episode with incomplete remission
- Two or more psychotic episodes with complete remissions between episodes
- Two or more psychotic episodes with incomplete remissions between episodes
- Continuous (unremitting) psychotic illness

In a cohort study of 112 patients presenting with a first episode of psychosis (64% schizophrenia), 10% were dead at the 10 year follow up. Of the 49 who were followed up for lifestyle outcomes, 40 had been living independently for at least five years but 48 had either intermittent or regular neuroleptic medication.[26]

Patients with chronic psychosis (mostly schizophrenia) can be ill for many years. As they get older they can 'graduate' from adult psychiatric services to old-age psychiatry. The physical health of these graduates is often poor and death rates from vascular disorders and other common physical conditions is higher than in the mentally well population,[27] except possibly for cancer.[28] Antipsychotic medication also causes a variety of side effects, including a rare but potentially fatal neuroleptic malignant syndrome.[29]

There is evidence that early intervention in first episode psychosis is effective to promote functional recovery and prevent relapses.[30] In an analysis of 462 participants of an antipsychotic drug trial, the strongest predictors of remission were shorter duration of untreated psychosis and treatment response at six weeks.[31]

3.1.2 Epidemiology of psychosis

3.1.2.1 Incidence of psychosis

There is some UK specific information on physician/research nurse defined incidence of psychosis but there is more research specific to schizophrenia or functional psychoses rather than all psychoses. In a recently published health care needs assessment on severe mental illness, the mean international annual incidence of schizophrenia using a strict definition was estimated to be 0.11 per 1000 (range 0.07-0.17 per 1000) and using a wider definition was 0.24 per 1000 (range 0.07 to 0.52 per 1000).[32] It has been suggested that there is a small but steady decline in the incidence of schizophrenia over the last few years[32] but it is unclear whether this applies to all psychoses. A Nottingham, UK, study examining the incidence of first episode psychotic disorders in two cohorts 1978-80 and 1992-4 found that the age

standardised incidence rates for schizophrenia and related disorders (ICD-10 F20-29) was 0.14 per 1000 per year.[33] They found that the rate for all psychoses rose slightly (but not statistically significantly so) but the rate for schizophrenia only had a significant decline. This suggested that an apparent reduction in schizophrenia incidence over time was likely to be due to the range of other psychosis diagnoses being made in the later cohort.[33]

A study of the annual incidence of schizophrenia and non-affective psychosis in London found a rate of 0.22 per 1000 (95% CI 0.15 to 0.29 per 1000).[34] In a recent Irish study, the annual incidence of all psychoses in people aged over 15 was estimated to be 0.32 per 1000.[35]

In a study of adolescents aged up to 18 years, the 3-year reported incidence of ICD-10 functional psychosis was 5.9 per 100,000,[2] which equates to an annual incidence of 0.017 per 1000 general population and 0.17 per 1000 adolescents at risk.

With regard to the incidence of self-reported psychotic symptoms in the general population, a recent UK study estimated rates to be 3.9% in 18 months (n=2379)[36] (which equates to an annual incidence of psychotic symptoms of 26 per 1000). In this same sample, 7.6% had recovered by follow up from having psychotic symptoms at baseline and 3.3% had persistent psychotic symptoms at both baseline and follow up.

3.1.2.2 Prevalence of psychosis

There have been two recent UK based prevalence studies (see

Table 2). In both of these surveys, a random sample of households was selected and one adult aged between 16-64 or 16-74 interviewed per household. Both surveys found a prevalence of psychosis of approximately 4.5-5 per 1000 population.

The prevalence of psychosis varies by age, gender and ethnic group. Age variation can be seen in Table 3.[11] However, from Hospital Episode Statistics, only 0.2% of episodes are in patients aged 0-14, 83.3% are in patients aged 15-59 and 16.5% in patients aged 60 or over.[37]

In a sample of 200 people with psychosis, 48% were male and 52% were female.[11] In the First National Survey of Psychiatric Morbidity, there was an equal prevalence of psychosis in men and women[38] In the Nottingham cohorts study, in the 1992-4 cohort 58% were men and 42% were women.[33] In the study from London, they found 54% men and 46% women.[34] However, in the study of adolescents, there were 72% men and 28% women.[2] This is an indication that women have a much lower incidence of psychosis than men at age 15-24 but then after this age, the rates in women gradually become similar to those in men.[32] From recent Hospital Episode Statistics, 59% of the finished episodes were in men and 41% in women.[37]

Table 2. UK prevalence of psychosis

Reference	Country	Sample type	Physician/ research nurse defined prevalence
First national survey of psychiatric morbidity[38]	UK	Random sample households, 12,730 adults aged 16-64 interviewed	0.45% (functional psychosis)
Second national survey of psychiatric morbidity[39]	UK	Random sample households, 8,580 adults aged 16-74 interviewed	0.5%

Table 3. Age distribution of psychosis

Age	% of sample (n=200) (O'Brien ONS)
16-24	2
25-34	12
35-44	26
45-54	27
55-64	20
65-74	14

The prevalence of functional psychosis in the UK appears to vary by ethnic group. In one study from London, the incidence rates for broad schizophrenia were estimated to be 0.3 per 1000 for whites, 0.36 per 1000 for Asians and 0.59 per 1000 for African-Caribbean patients.[40] A second study from London found that the incidence ratio in all ethnic minority groups compared with the white population for schizophrenia was 3.6 (95%CI 1.9 to 7.1) and for non-affective psychosis was 3.7 (95%CI 2.2 to 6.2).[34] Results from the First National Survey of Psychiatric Morbidity found a higher rate of functional psychosis in African, African-Caribbean and 'Black-other' participants but a lower rate in South Asians after controlling for socio-demographic and risk factors (employment status, social class, type of housing tenure, age, gender, access to car, stressful life events, perceived social support). However, both of these estimates could have been accounted for by chance alone (see Table 4).[41]

Table 4. Estimates of odd ratios of psychosis in ethnic groups

Ethnic group	Odds ratio	95%CI
White	1.00	
African, African-Caribbean and 'Black other'	2.97	0.66-13.36
South Asian (Indian, Pakistani, Bangladeshi)	0.43	0.05-3.72
Other	2.22	0.46-10.66

3.1.2.3 Mortality from psychosis

UK mortality figures for all psychoses are not available. The mortality rates between 1996 and 2004 for schizophrenia as an underlying cause were 0.7 per million for men and 0.8 per million for women.[42] The mortality rates where the death certificate mentioned schizophrenia were 8.2 per million for men and 7.1 per million for

women.[42]

The suicide rate for psychosis has been estimated at 7.52 per 1000 patient years but this is based on a small number of suicides in the sample only.[43] It is also estimated that there is a 4% lifetime suicide rate in psychotic patients[43] and the lifetime suicide attempt rate is around 22%.[11] A review of the literature between 1939-1998 estimated that the 20-year suicide rate in schizophrenia is between 14-22%.[24]

3.1.3 Significance of psychosis for patients in terms of ill-health (burden of disease).

A patient may suffer one or several episodes of psychosis of varying lengths before they come to the attention of the health services.[44] First point of contact usually comes via a health professional such as a GP but other contacts can be from religious officials or faith healers, or from the criminal justice system.[45]

People with psychosis tend to have poor quality of life. There are widespread problems with social and sexual relationships and in the performance of activities of daily living.[46] A longer duration of untreated psychosis is correlated with a worse quality of life,[47-49] worse treatment outcome[50] and worse prognosis.[6] Quality of life tends to be lower where people with psychosis are single,[51] have psychiatric comorbidity,[51] premorbid adjustment,[49] duration of psychotic symptoms[49] and poor social relations and finances.[52]

From a service user's perspective, being an NHS inpatient has been described as "horrible, scary, surviving the system, institutionalised, feeling strange, labelled, used in experiments, no choice"[53] Patients in this study valued one-to-one contact and personal relationships with carers, active involvement in care, choice and the feeling that their opinions mattered.[53]

3.1.4 Significance of psychosis for NHS

In 2005-6 there were 41,600 NHS finished episodes and 2,617,500 bed days in England due to psychotic illnesses.[37] The mean length of stay for categories of primary psychosis diagnosis (4 character) varied between 33 days (acute and transient psychotic disorder, unspecified) and 329 days (residual schizophrenia).[37]

Because of the finding that early intervention improves symptoms and relapse rates, an international consensus statement on the management of young people with psychosis has been developed on behalf of the World Health Organisation and The International Early Psychosis Association.[54] This lists a number of five-year goals in the care and treatment of young people with psychosis including improving access and engagement, raising community awareness, promoting recovery, family engagement and support and improved practitioner training. In the UK there have been several initiatives aimed at the promotion of specialist early intervention services for psychosis.[55] Another strategy has been to try to educate general practitioners to recognise the signs of early psychosis.[56]

3.2 Current service provision

3.2.1 Diagnostic pathway for psychosis

In the UK, a history is taken from patients and their relatives or friends and a standard

examination is carried out (physical, mental state and neurological examinations) to assess possible causes of first episode psychosis. The neurological history and examination looks for motor, sensory or cognitive deficits. Following this, laboratory investigations (haematological, biochemical, microbiological) and an electroencephalogram (EEG) may be required, depending on possible diagnoses. An EEG is rarely requested for patients with psychosis and it is usually because temporal lobe epilepsy or focal brain lesions are suspected.

The main factors that would lead the clinician to suspect an organic cause of psychosis should be discovered during the initial clinical process. Indication that an organic cause is more likely include an acute onset, features of delirium such as clouding of consciousness, disorientation in time and place, disturbance of memory, impaired attention, fluctuation of conscious awareness and visual hallucinations. A neurological history and examination would look for a recent history of malignancy and/or focal neurological symptoms or signs, but these are not always present. If an organic cause is suspected, an appropriate confirmatory test would be used, depending on the diagnosis hypothesised. This may include MRI or CT scanning but rarely in the UK.[14,57] In the USA it is now increasingly considered good clinical practice to have MRI or CT scans for all patients presenting with first episode psychosis, even where no organic cause is suspected.[14] However, in the American Psychiatric Guidelines, MRI or CT imaging is only indicated for patients where the clinical picture is unclear or where there are abnormal findings from a routine examination.[58]

If no organic cause of psychosis is suspected following the standard clinical process, it is assumed that the patient has a functional psychosis.[59] However, there is a possibility that an organic cause of psychosis may have been missed in this group because, for example, no focal neurological symptoms and signs were present. CT or MRI scanning could possibly be used in this situation to find cases of psychosis with an organic cause missed in the initial clinical process.

3.2.2 Management of psychosis

Almost all patients with psychosis will be referred to the psychiatric services in the first instance, unless there are symptoms and signs of other pathology, in which case they may be referred to other medical specialties but have a psychiatrist advise on the psychotic aspects of the presenting symptoms. Treatment for psychosis depends on the cause of psychosis. The most common cause of psychosis is schizophrenia. Treatment for this in primary and secondary care should follow the NICE Clinical Guideline[60] and include both psychological and pharmacological treatments. Psychological treatment includes family therapy and cognitive-behavioural therapy. There is a good evidence base that psychological treatments, particularly cognitive-behavioural therapy are effective in patients with psychosis.[61] Pharmacological treatment can include conventional antipsychotics (phenothiazine derivatives or similar) or atypical antipsychotics such as olanzapine or risperidone. The term ‘treatment resistance’ is used to describe patients who have not responded to at least two antipsychotic medications from different classes prescribed at adequate doses for sufficient periods, usually defined as 6-8 weeks. If patients are treatment resistant they can then be offered clozapine.[60] Clozapine is licensed for the treatment of schizophrenia only in patients who are unresponsive to or intolerant of conventional antipsychotic drugs.[29] Clozapine can cause agranulocytosis so patients must be monitored with blood tests. Patients can die from this and from other adverse effects

such as myocarditis or cardiomyopathy.[29]

Between one fifth and one third of patients with schizophrenia have a poor response to treatment despite an adequate treatment trial.[62] For example, 39% of people diagnosed with schizophrenia do not respond after up to eight weeks of chlorpromazine treatment.[63] Patients who are resistant to treatment should be distinguished from those who initially respond to treatment and then deteriorate. CT or MRI scanning may be used in these situations to determine whether an intra-cranial lesion may be a cause of treatment resistance.

In patients with bipolar disorder with psychotic symptoms, antipsychotic medication such as olanzapine or risperidone or the use of ECT if the depressive illness is severe is recommended.[64] Other patients who have psychotic symptoms will mostly be treated with antipsychotic medication in addition to the treatment for the condition that they have.

3.2.3 Variation in services

An audit of early intervention in psychosis services in England in 2005 identified 117 teams, of which 63 were operational with case-managed patients.[65] It found that there were variations in service structure and delivery, treatment and support offered and resources available across teams. Most of the teams appear to offer a service to people under the age of 35. For 23 teams, the estimated duration of untreated psychosis varied between 2-24 months.

3.2.4 National service frameworks

In 2004, the NHS National Plan included the target that all young people who experience a first episode of psychosis will receive early and intensive support. The Planning and Priorities Framework (DH 2003-6) included T16 – to reduce the duration of untreated psychosis to a service median of less than three months (individual maximum less than six months) and provide support for the first three years for all young people who develop first episode psychosis by 2004. The Child and Adolescent Mental Health Services Target and Children's National Service Framework (DH 2003) included the target to provide comprehensive early intervention services by 2006.[66]

In 2006, a National Early Intervention in Psychosis (EIP) programme was started, jointly funded by the National Institute for Mental Health in England, part of the Care Services Improvement Partnership and Rethink.[66] The aim of this programme is the early detection of psychosis, reduced duration of untreated psychosis and to place emphasis on the first 3-5 years following onset for the later biological, psychological and social outcomes. This programme also includes research into the cost effectiveness of early intervention services for psychosis.[66]

There do not appear to be targets for service provision for older people who develop first episode psychosis.

3.3 Description of technology under assessment

Neuroimaging (also called brain imaging) allows the non-invasive visualisation of the anatomical structure and neuropsychological function of the brain. Neuroimaging can

be broadly categorized as either structural (MRI and CT scanning) or functional (functional MRI and PET scanning). In structural neuroimaging the focus is on the anatomical structure in order to assist in the diagnosis of intracranial pathology. Functional neuroimaging investigates brain function and dysfunction, in particular by localising and visualising the metabolic changes of brain neural circuitry underlying mental processes and cognitive functions.

This project investigates the two structural brain imaging techniques that are currently used within the NHS - standard magnetic resonance imaging (MRI) and standard computed (axial) tomography (CT) scanning. Therefore, the techniques not discussed here include functional MRI, diffusion-weighted MRI, diffusion tensor imaging, perfusion MRI, magnetic spectroscopy, photon emission tomography (PET), single photon emission tomography or other research forms of imaging. Also not investigated here are standard ultrasonography, brain angiographic imaging or electroencephalography (EEG).

3.3.1 CT scanning

Computed (axial) tomography (CT or CAT) scanning was introduced in the 1970s and is now widely used as a diagnostic technique in the NHS. A CT scan is a form of X-ray tomographic imaging (ie visualisation by sectioning) where a series of X-rays is used to visualize two-dimensional ‘slices’ through the body.

In standard X-ray imaging a uniform X-ray beam traverses the part of the body to be visualised. As the beam passes through the body tissues, radiation interacts via the phenomena of absorption and scatter to produce a beam of remnant X-rays that varies in intensity according to the tissue characteristics of the anatomical structure passed through. This remnant beam is detected through an intensifying process (ie image intensifying screens, fluoroscopic image intensifier, etc) and is then recorded photographically to produce a two-dimensional image on a film. The film then undergoes automated photochemical processing to produce the final image. Because the X-ray beam travels through a considerable number of tissues, the resulting image can contain indistinct or unclear regions.

X-ray tomography is a radiographic imaging technique where the X-ray beam emitter (X-ray tube) on one side of the body and the film-intensifying screen receiving the image on the other side of the body are moved in opposite directions around a focal point within the body. This enables the focal point to be visualised much more clearly because the structures above and below it do not have as much intensity of beam as the focal point. X-ray tomography enables small areas of the body to be visualised more clearly. With conventional X-ray tomography, the structures above and below the focal point are still seen as blurring on the images.

Computed tomography uses a computer to mathematically reconstruct two-dimensional ‘slices’ through the body, also known as cross-sectional images. A well focused X-ray beam on one side of the patient is passed through the patient, focusing on a very small area and the resulting absorption and scattering is recorded on the other side of the patient by a large array of sensitive detectors. Each element of the array constructs the remnant X-ray projection of the body that the beam focuses on and is recorded as a numerical value of radiation intensity. The X-ray beam emitted through the X-ray tube of the system, together with the array of detectors, is rotated

through a small angle and another projection is recorded. This process is repeated many times (so that the total rotation is 180-360 degrees at least) in order to record sufficient numerical values of the remnant X-ray intensities. These values are combined mathematically in a two-dimensional matrix of picture elements (pixels) to reconstruct a two-dimensional cross-sectional digital image of the part of the body being visualised. Each pixel is assigned a grey scale value, corresponding to the remnant X-ray intensities. Greyscale values range between white (corresponding to structures that fully absorb the original X-ray beam such as bone) and black (corresponding to structures that do not absorb the original X-ray beam, such as air). With multiple projections, a picture is made of pixels of various grey scales representing a cross sectional slice through the part of the body being visualised.

In order to perform a CT scan, the body must not be moving. Where the chest or abdomen is recorded, the patient must hold their breath.

There exists a variety of systematic errors (artifacts) that can affect the quality of the CT images.[67,68]

- Partial-volume effects arise because of slight inconsistencies from measured projections taken along the same path of tissue. This is one reason why it is important to conduct a 360-degree rotation scan so as to compensate for such inconsistencies by combining data from projections in opposite directions
- Volume averaging occurs when the displayed two-dimensional image is reconstructed from data averaged from three-dimensional tissue. Each pixel may misrepresent anatomy and miss small pathological areas so slices above and below the slice being examined should be checked.
- Beam hardening occurs where there is less attenuation and scattering at the end of the beam after it has passed through most of the patient as opposed to the beginning of the beam where it has only just entered the patient. Beam hardening artefacts appear as dark streaks or dark areas just next to areas of high density such as bone
- Motion artefacts occur when patients move during the scan including breathing, heartbeats and peristalsis. Motion artefacts commonly cause blurring or prominent streaks at high to low density tissue interfaces
- Streak artefacts occur from very high density objects such as tooth fillings and orthopaedic hardware as two-dimensional reconstruction algorithms cannot cope with extreme differences in radiation attenuation in the interface between these objects and adjacent soft tissue

Because of these artefacts CT scanning does not have 100% sensitivity and specificity in the diagnosis of lesions in the brain. White matter in the brain is less dense than grey matter so appears darker on a CT scan. CT scans will only detect differences in density so lesions of the same density as surrounding tissue will not be detected.[69] Where this is the case, iodine-based contrast agents injected into a vein may be used to help visualise these lesions.

CT scanning is a painless, non-invasive procedure (unless contrast dye is used) that takes 15-30 minutes. The machine makes a whirring noise as the trolley moves the patient automatically through the ring of the machine. There tend not to be claustrophobic reactions. Contrast dye can occasionally cause relatively mild immediate or delayed allergic reactions in approximately 3% of patients and severe

reactions (such as hypotension, loss of consciousness, cardiac arrest) in 0.04% of patients.[70]

3.3.1.1 Disadvantages of CT scanning

The main disadvantage of CT scanning is the dose of radiation that is absorbed during the process. It is estimated that 40% of all radiation exposure in patients from diagnostic imaging comes from CT scanning.[68] Because of this, there are some radiologists who are reluctant to use CT scanning on patients under the age of 40 yrs. (Personal communication, Dr West, QE Hospital, Birmingham, March 2007)

3.3.2 MRI scanning

Magnetic Resonance Imaging (MRI) is a powerful diagnostic imaging tool that was developed mainly between 1974 and 1985. MRI started to be introduced into clinical practice since the 1980s and is now commonly used in major medical centres.

MRI is also a tomographic imaging technique that exploits the nuclear magnetic resonance (NMR) phenomenon, which originates from the paramagnetic properties of atomic nuclei. The complete description of the complex physics of the NMR phenomenon, which can be given both in terms of classical Newtonian mechanics and quantum mechanics, is beyond the scope of this project. However, a simple and summarised description is necessary for the reader to understand the imaging method. MRI exploits the ability of a small number of hydrogen atoms (protons) within the human body to absorb and emit radio waves (at similar levels of frequency as FM radio) when placed in a strong magnetic field. These protons behave as small dipole magnets, aligning with the strong external magnetic field, where the net effect of this alignment creates a magnetization for the whole body – so the human body can behave like a dipole magnet. Because of the different concentration of protons in different tissue and the inherent paramagnetic characteristics of these protons within their complex biochemical environment, tissue magnetization absorbs and emits radio wave energy in a way that can be differentiated and detected.[68]

When compared with CT, the diagnostic and clinical significance of MRI is from two main physical characteristics. Firstly, image data acquisition in MRI does not require the use of any ionising radiation. Secondly, the magnetic resonance signal is formed from the contribution of four important tissue characteristics:

- The density of hydrogen atoms in the human body (known also as proton density)
- T1 tissue relaxation time (an indication of how quickly a tissue can become magnetised)
- T2 relaxation time (an indication of how quickly a tissue loses its magnetisation)
- The presence of flow or motion within tissue

During an MRI scan, these four characteristics are exploited by the use of combinations of radiofrequency pulses so that a slice can be selected and magnetic resonance signals from this slice can be encoded in two dimensions. These combined radiofrequency pulses are called pulse sequences. In any typical sequence, a radiofrequency gradient is applied in the direction of the main magnetic field while enough data is collected in order to mathematically compute a digital image, where

each pixel intensity corresponds to a magnetic resonance signal from which the proton density, T1, T2 and motion characteristics can be interpreted.

There exist many pulse sequences that have been developed over the years. In broad categories, these include the spin-echo sequences (and their fast equivalents of multiple spin-echo sequences), the inversion recovery sequences, the gradient echo sequences and the echo-planar imaging sequences. Each of these sequences exploits the four tissue characteristics in a different way, in order to provide imaging of different anatomical, morphological and functional information of the body. So for example, in the case of spin-echo brain imaging, T1 weighted images are good for identifying fat, subacute haemorrhage and proteinacious fluids whereas T2 weighted images provide more sensitive detection of oedema and pathological lesions

3.3.2.1 Safety of MRI scanning

Magnetic field is measured in Tesla. (NB 1 Tesla = 10,000 Gauss. The earth's magnetic field is approximately 0.5 Gauss). The MRI scanners commonly used in medical practice are between 0.5-3 Tesla magnetic strength. Research machines for human brain scanning can have up to 7 Tesla. A higher magnetic field improves the signal to noise ratio permitting a higher resolution picture or faster scanning times. However, higher field strengths require more expensive magnets with higher maintenance costs, and have increased safety concerns. In general, MRI is a relatively safe diagnostic technique and few difficulties are encountered in clinical practice. The safety concerns are of five main kinds:

- The high strength magnetic fields will affect all magnetic objects near the MRI scanner. Patients with pacemakers cannot have an MRI because the magnetic field can prevent the pacemaker from working. This also applies to cochlear implants, insulin pumps, neurostimulators etc. Metal objects inside the body such as shotgun fragments or surgical hardware may move under the influence of the magnetic field and cause serious damage to the person. Metallic objects near to the machine can become dangerous projectiles (eg metal buckets, pens, drip poles etc) because they can get sucked into the aperture of the MRI scanner. Also the magnetic strip on bank cards and credit cards can be wiped clean of all details.
- The energy generated inside the body from an MRI scanner can cause body heating. This can result in hyperthermia, particularly in obese persons and those who cannot control their body temperature well. However, this is very rarely a problem in routine use.
- The rapidly alternating electrical field caused by the magnetic field could cause peripheral nerve stimulation resulting in muscle twitching. This could be dangerous if it affected cardiac muscle. Therefore there is now a safety limit to ensure this does not occur.
- The MRI when working is very noisy – up to 130 dB ie similar to the sound of a jet engine at take-off. The higher Tesla machines are slightly noisier than lower Tesla machines but patients must wear ear protection at all times in all machines.
- MRI scanners use helium liquid to cool the magnets. If the helium suddenly boils it can escape into the MRI room (which is relatively well sealed because of the noise) and displace the oxygen, asphyxiating the patient. This is very rare.

A recent European Physical Agents (Electromagnetic Fields) Directive initially set the limit to 2 Tesla but this has now been relaxed.[71] possibly because of the high definition available on brain scans with 3 Tesla machines.

3.3.2.2 Practical considerations of MRI scanning

In order to perform an MRI scan, the body should not be moving. The main types of artefacts that can occur are[72]:

- Distortions due to magnetic objects inside the body which can give a patch of signal void (known as magnetic susceptibility artefacts)
- Motion artefacts which can cause blurring and ghosting (faint duplicate objects) of images
- Interfaces between fat and water which can cause lines of high signal intensity and signal void (known as chemical shift artefacts)
- Truncation errors in the interface between tissues of sharply differing contrast resulting in parallel bands of light and dark signal
- Image wraparound artefacts where one part of the anatomy interferes with another part in the same plane

During a brain MRI scan, the patient lies on a narrow bed in a constricted tunnel-like area and their head is placed in a birdcage-like magnetic coil approximately 5cm wider diameter than the patient's head. The head is prevented from moving to eliminate motion artefacts by using padding inside the coil. The patient stays still in the MRI machine for 30 minutes or more. The MRI scanning procedure is very noisy so patients must be willing to wear earplugs and patients can also get quite hot, particularly in the high Tesla machines and this can make them feel uncomfortable. In a systematic review of anxiety-related reactions in patients undergoing MRI scanning, between 4-30% patients were affected by anxiety in some way. These included panic attacks (1.5% of 3000 patients) and claustrophobia (2.7% of 1160 patients). It was estimated that between 4.3-10% of patients have reactions sufficiently severe to require that the procedure has to be modified, postponed or cancelled.[73]

The size of trolley and aperture of the MRI scanner means that people who weigh over 20 stones (127 kg) will be unlikely to fit inside the machine safely.

A disadvantage of MRI scanning is the number of false positive results. In a retrospective series of 1000 healthy volunteers, 82% of the MRI results were completely normal. Only 1.1% required urgent referral (three arachnoid cysts, two cavernous angiomata, two benign lesions requiring further imaging, one oligodendroglioma, one astrocytoma and one aneurysm).[74] The remaining 16.9% may have been worried by a 'positive MRI finding' of no medical consequence.

3.3.3 Comparison of CT and MRI

MRI scanning provides considerably higher picture resolution than CT so is the preferred option for imaging purposes. MRI scanning is better able to picture the soft tissues of the brain whereas CT scanning is more effective for picturing bone and hard tissues. MRI scanning can be used in pregnant women because there is no known risk to the foetus that has been demonstrated so far whereas CT scanning is contra-indicated because of the X-radiation.

3.3.4 Current use of neuroimaging for psychosis including in the NHS

A CT or MRI image can visualise pathology but can also demonstrate the morphological characteristics of the brain. MRI visualises soft tissues well and has much better resolution than CT so tends to be used for morphological studies. In psychosis there are two main ways that an MRI scan can be assessed for morphological attributes.

1. Region of interest. This is where the radiologist focuses on the main parts of the brain that are thought to be different in schizophrenics compared to healthy people. These are well defined structures and include right and left lateral ventricles, temporal horns, third ventricle, total ventricles, hemispheres, frontal volumes, temporal lobes, hippocampus, amygdala, parahippocampus, superior temporal gyrus, caudate and the whole brain including white matter and grey matter.[75]
2. Voxel-based morphometry. A voxel is a three-dimensional volume element of patient tissue and the tissue composition for each voxel is averaged for display as a pixel. Voxel-based morphometry is an automated whole brain analysis of the patient, specifically to determine the density or concentration of white and grey matter in each part of the whole brain between different groups of patients.[76]

There have been several large systematic reviews of morphological research studies of region of interest[12,77,78] and voxel based morphometry[76] trying to establish whether there are any specific structures or attributes in the brain that are unique to schizophrenia and cause the condition. These systematic reviews have included up to 50 studies or more but to date no unique or specific structures have been found.[78] However, a very recent meta-analysis of voxel-based studies of grey and white matter has identified regions of structural brain changes in first episode schizophrenia. These include structural deficits in the caudate nucleus, thalamus and white matter close to the uncinate fasciculus (I Ellison-Wright and E Bullmore, personal communication, June 2007).

There is very little routinely collected UK information on the use of CT and structural MRI imaging for psychosis. From NHS reference costs, approximately 70,000 CT tests and 57,600 MRI tests are done per year but these are not specifically head scans. UK pathways to care research tends not to mention investigation routinely performed.[79,80]

Discussion with local clinical experts has suggested that routine practice is different in adult psychiatry compared to old age psychiatry (personal communication, Dr Oyebode, QE Psychiatric Hospital, Feb 2007). Within adult psychiatry, people presenting with psychosis tend not to be sent for a CT or MRI scan unless there are additional symptoms or clinical signs such as an acute onset, features of delirium such as clouding of consciousness, disorientation in time and place, disturbance of memory, impaired attention, fluctuation of conscious awareness, recent history of malignancy and/or focal neurological symptoms or signs. There is often a long waiting list for MRI (3-12 months) that reduces the usefulness of this investigation in the acute stages of psychosis. The CT waiting list is usually shorter (2-4 weeks). In old age psychiatry, more patients with psychosis tend to be sent for a CT or MRI scan, possibly because of the greater prevalence of organic psychotic conditions, and this trend is increasing.

3.3.5 Costs of CT and MRI scans

The acquisition cost of a CT machine is large – approximately £500,000 and for an MRI scanner the cost is larger – between £1-2 million. The cost of an MRI also includes the space that the machine and computerised equipment are housed in. Each machine must also have regular maintenance. There are also staff costs for working the machines and staff training to be taken into account.

The cost of MRI and CT scans are available from 2005-6 NHS reference costs (Code RBF1 and RBC5 respectively) and are estimated to be £244 for MRI and £78 for CT scans.[81]

4. Definition of the decision problem

The decision problem for this assessment is to determine whether it is more clinically and cost effective to screen all new psychotic patients with either a CT or structural MRI scan or whether it is more clinically and cost effective to only use structural neuroimaging in those psychotic patients presenting with symptoms and/or signs of additional pathology (i.e. organic cause of psychosis, space occupying lesions in the brain or other conditions that may affect clinical management of the patient). This is not a diagnostic accuracy question per se but a diagnostic or therapeutic yield leading to patient outcomes from improved treatment decisions.

An ideal study design for a standard decision problem, where use of imaging in addition to standard diagnostic workup for a condition is being evaluated, would be a randomised trial. However in this situation, if newly diagnosed psychotic patients were randomised to a strategy of either scan all or scan only when well defined clinical criteria suggested that a scan was warranted and each group was followed up, it would be difficult to determine the appropriate outcomes. This is because multiple conditions are being sought. If health-related quality of life and mortality due to undetected treatable conditions were the outcomes measured, the sample size would need to be massive.

Another type of study design that could answer this type of question is a diagnostic before-after study. In this type of study there would be a baseline clinical assessment of the patient with psychosis, then the patient would undergo structural neuroimaging followed by a second clinical assessment of the patient. The key question would be whether the neuroimaging undergone will affect the subsequent clinical assessment and patient management and ultimately the patient's health. This type of study is easier and quicker to perform than an RCT[82] but is subject to a number of limitations.[83] Some of these can be overcome by careful planning and conduct of the study including the need to carry out the study prospectively, careful specification of eligible participants, consecutive recruitment, independent review of pre-and post test clinical assessment and a strict adherence to a study protocol. However, before and after studies have inherent limitations including a possible discrepancy between stated clinical assessment and actual clinical action and subconscious bias about the benefits of the new technology. If the clinician knows that a test is subsequently going to be performed, they may delay making a definitive diagnosis. Also there can be no comparison of patient outcomes because all have had the new test. In general, it is considered that before-after studies tend to be biased in favour of new interventions so

when no benefit is found, it is unlikely that a stronger study design on the same question, such as an RCT, will find a benefit.[83]

Psychotic patients can develop additional pathology at any time during their life. In some patients this may be hidden, or occult, but in others it may be a cause of treatment resistance or deterioration in a patient who initially responds to antipsychotic treatment. It would be useful to know whether all psychosis patients who are treatment resistant or are deteriorating should be referred for structural neuroimaging, or whether it is more clinically or cost-effective to use structural neuroimaging in those deteriorating or treatment resistant patients presenting with symptoms and/or signs of additional pathology. A well-designed before-after study may be appropriate here, particularly in patients whose condition is deteriorating, because of the speed of completion of such a study and the need to investigate and give appropriate treatment. Also of interest to this evaluation would be an investigation of time to diagnosis or appropriate treatment.

Not included in this assessment is any evaluation of the usefulness of CT and structural MRI to detect brain morphological characteristics as the clinical significance of these are currently unknown.

5. Assessment of clinical effectiveness

5.1 Methods for reviewing effectiveness

5.1.1 Identification of studies

A scoping search based on the ARIF search protocol was undertaken to identify systematic reviews and background material (see Appendix 1).

For the main clinical effectiveness review the following sources were searched:

- Bibliographic databases: Cochrane Library (Wiley) 2006 Issue 4 (CENTRAL); MEDLINE (Ovid) 1966 to November Week 3 2006; MEDLINE (Ovid) In-Process and Other Non-Indexed Citations 4 December 2006; EMBASE (Ovid) 1980 to 2006 Week 48; CINAHL (Ovid) 1982 to November Week 4 2006; PsycINFO (Ovid) 1967 to November Week 4 2006.
- Citations of relevant studies.
- Research registries of ongoing trials included the National Research Register, Current Controlled Trials, and Clinical Trials.gov.
- Relevant internet resources.
- Hand search of appropriate journals-(Magnetic Resonance in Medicine (1985 to 2007), NMR in Biomedicine (1985 to 2007)), American Journal of Psychiatry (1985-2007).
- Further information from contact with relevant experts.

Details of all search strategies may be found in Appendix 2. No language or date restrictions were applied. All citations were exported, or entered by hand, into Reference Manager version 11 (ISI, Carlsband, CA, USA).

Additional searches were carried out on the comparative sensitivity of CT and MRI scanning, which were used to inform part of the economic evaluation (see section 6.2.1.3 on page 90).

5.1.2 Inclusion and exclusion criteria and process

Three reviewers (EA, CM, CD) independently scanned all titles and abstracts identified by the searches for inclusion. The full text was obtained for potentially relevant articles. Publications in foreign languages were assessed using the English abstract where available or a translator was used. Studies were included in the review of effectiveness if they met the following criteria:

Population: adults or children presenting with psychosis, particularly a first episode of psychosis (FEP). Psychosis was considered to be a first episode if the study described psychosis as new, first or of recent onset, a new or first hospital admission for psychosis, first contact with any medical services for psychosis, or antipsychotic treatment naïve. In cases where it was unclear whether the population were presenting with a first episode, the study was included and clearly marked as such.

Judgement on whether a condition was considered to be psychotic was made according to Appendix 3 following clinical input (personal communication, Professor F Oyebode, University of Birmingham, April 2007).

Studies investigating populations of mixed psychiatric patients that had a subgroup of psychotic patients were included if other criteria were met.

In order to capture the subgroup of psychotic patients with a possible psychiatric misdiagnosis, or those who were experiencing a change in their pre-existing psychotic disorder, we also looked for studies evaluating:

- patients who had a prior diagnosis of a psychotic disorder but were failing to respond to treatment
- patients who had a prior diagnosis of a psychotic disorder, had previously responded to antipsychotic treatment but had a recent deterioration in their condition.

Intervention (diagnostic investigation): structural magnetic resonance imaging (MRI) or computed tomography (CT) with or without contrast media.

Comparator: current standard NHS practice without MRI or CT neuroimaging, or before MRI or CT neuroimaging. Current practice was taken to mean medical and psychiatric history, physical and neurological examination, EEG, mental state examination and laboratory investigations, or any combination of these as considered appropriate by the clinician.

Outcomes: any clinically relevant outcomes including number (or percentage) of patients with scans identifying abnormalities; number with pathology that would influence patient care and was not suspected based on history and/or physical examination and the pathology found; incidental pathology found; number (or percentage) of patients with a scan affecting their clinical treatment; and number (or percentage) of patients with a change in diagnosis due to the scan, time to diagnosis, confidence in diagnosis.

Pathology considered to potentially influence patient care included cerebral infarction, cerebral space occupying lesions, subdural haematoma, encephalitis, demyelinating disease and arachnoid cyst. Cerebral structural abnormalities such as white matter lesions, cavum septi pellucidi and atrophy were considered to be incidental unless stated otherwise in the study text. Two reviewers with input from a clinician (FO) judged pathological findings to be either incidental or to influence patient care when details were not provided in the text.

The outcomes above were modified from those listed in the protocol. During piloting of the data extraction form it was found that studies did not report morbidity and mortality, did not report cerebral abnormalities as a cause of psychosis, and employed a number of definitions of “information of clinical value”. Information on severity and progression of first episode psychoses was not available since studies did not report follow up. Subsequent service use (including frequency and duration of hospital admissions), health-related quality of life and adverse effects due to the use of CT/MRI neuroimaging were also not reported.

Study design: Any design that gave diagnostic yield, including prospective or retrospective before and after studies, were included.

Exclusion criteria
Studies employing functional imaging techniques such as magnetic resonance spectroscopy, diffusion weighted MRI, diffusion tensor imaging, perfusion MRI, or PET were excluded.

Studies were excluded where the primary aim of the study was to investigate the cerebral morphometry (such as shape, size or volume measurements) associated with psychosis or a specific psychotic illness.

Individual case reports were excluded

5.1.3 Data extraction strategy
Data extraction from included studies was carried out independently by two reviewers (EA and CM). Study characteristics, outcome results and aspects of study quality were collected using a standardised form (see Appendix 4). Any discrepancies were resolved by discussion, and where necessary, by involvement of a third reviewer.

5.1.4 Quality assessment strategy
There is no validated quality assessment tool for diagnostic before and after studies. Therefore, an evaluation was made of test accuracy quality assessment tools to determine whether any could be tailored to meet the needs of this review. The QUADAS tool[84] (see Appendix 5) was chosen but was modified to more appropriately capture the quality and validity issues apparent in the included studies. The full tool was piloted on a selection of studies prior to full data extraction and subsequently modified (see Appendix 5). However, the modified QUADAS tool did not fully capture all of the quality criteria that needed to be considered. Therefore the quality assessment strategy included four additional questions:

- What was the explanation given for patients who did not receive a scan?
- Were the patients recruited consecutively?
- Was the study and/or collection of clinical variables conducted prospectively?
- Who performed the clinical evaluation and image analysis?

Following tabulation of quality criteria, possible threats to study validity were discussed.

5.1.5 Rationale and details of the QUADAS tool modification
The aim of the QUADAS tool is to assess the quality of studies of diagnostic accuracy, that is, studies designed to evaluate how well an index test (being evaluated by the study) performs compared to a reference standard. In the standard QUADAS tool the reference standard is the best available method to determine the presence or absence of the condition of interest. For the purpose of this review we interpreted the reference standard to be current practice plus CT or MRI, and the index test to be current practice alone. The aim of the review was to investigate the added value of using CT or MRI in addition to current practice in the investigation of patients with psychotic symptoms for additional pathological findings. Current practice was defined as any test(s) or investigation(s), or any combination of tests that would be carried out as part of the initial care of a psychotic patient.

The QUADAS tool was modified for the reasons explained above. The modified version has questions 3 and 7 removed (see in Table 5). Question 3 in the standard tool

is “Is the reference standard likely to classify the target condition correctly?” Unlike most diagnostic yield studies where a single target condition is investigated, this review had several target conditions i.e. any organic disorder with the potential to cause psychosis, including cerebrovascular accident (CVA), various vascular disorders, and brain tumours (see Table 1). The best structural neuroimaging method to determine the presence or absence of these conditions varies depending upon the condition. For example, CT is considered better than MRI for diagnosing calcification, whereas MRI is the gold standard for the diagnosis of space occupying lesions. For the purposes of this review it was necessary to assume that the addition of CT and/or MRI to current practice would increase the accuracy of current practice in diagnosing causes of psychosis.

Item 7 in the standard tool “Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?” was also removed since the index test (current practice) is part of the reference standard (current practice plus CT or MRI). In this case patients would not receive CT or MRI alone.

Table 5. Modified version of the QUADAS quality assessment tool used in the effectiveness review

Qu. No.*	Item	Yes/No/Unclear
1	Was the spectrum of patients representative of patients who will receive the test in practice?	
2	Were the selection criteria clearly described? (Inclusion/ exclusion)	
4	Is the period between neuroimaging and current practice alone short enough to be reasonably sure that the target condition did not change between the two tests?	
5	Did the whole sample (W) or a random selection (R) of the sample receive verification of diagnosis using neuroimaging?	
6	Did the patients receive the same neuroimaging regardless of current practice alone?	
8	Was the execution of current practice described in sufficient detail to permit its replication?	
9	Was the execution of neuroimaging described in sufficient detail to permit its replication?	
10	Were the results from current practice alone interpreted without knowledge of the results of neuroimaging?	
11	Were the neuroimaging results interpreted without knowledge of the current practice?	
12	Were the same clinical results available when test results were interpreted as would be available when the test is used in practice?	
13	Were uninterpretable/intermediate test results reported?	
14	Were reasons for non-scan patients explained?	
* Numbers from the original QUADAS tool have been retained. NB. “Neuroimaging” = neuroimaging in addition to current practice.		

5.1.6 Data synthesis

Study characteristics and results were tabulated. Analysis was qualitative, conclusions being based on patterns revealed in the tables of included studies. It was not possible to pool results for quantitative analysis due to the scarcity of data, the poor quality of included studies and the heterogeneity of study characteristics.

5.2 Clinical effectiveness results

5.2.1 Quantity and quality of research available

The number of potentially relevant studies identified and screened for retrieval was 3526. Of these, 2941 were excluded on the basis of title and abstract. A full copy of the article was retrieved where there was any doubt about its relevance. The full text of 585 articles was retrieved for scrutiny against the inclusion and exclusion criteria. During this process an additional 95 articles were identified through searching of bibliographies of relevant studies, the internet, and hand searching of relevant journals. Thus, a total of 680 articles were obtained in full text. 655 articles were excluded. Of these, 221 articles were excluded purely on the basis of reporting morphometric data (volume, size and shape of the brain) only. The other reasons for exclusion were a lack of relevant data (review article), or that the article addressed a psychiatric condition without associated psychosis.

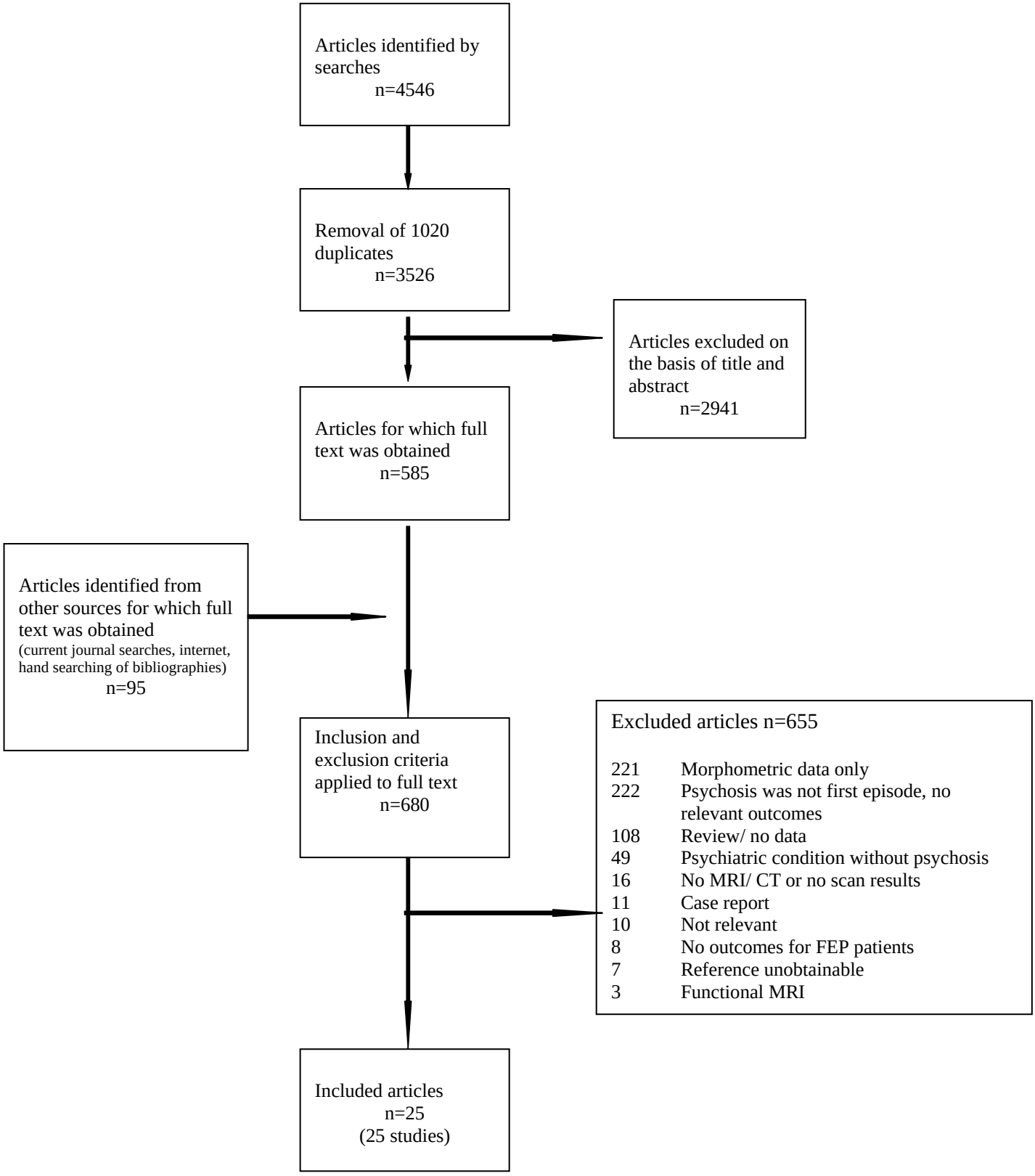
There were no relevant systematic reviews identified by the searches. There were no RCTs evaluating the effectiveness of structural neuroimaging in any psychosis or first episode psychosis identified. There were no cohort or case-control studies looking at the impact of neuroimaging on subsequent management of psychosis. There were no studies investigating structural neuroimaging in psychosis (or subgroups of psychosis) looking at mortality, severity of psychosis, progression of psychosis or subsequent service use. There were no RCTs comparing CT to MRI as a diagnostic strategy in patients with psychosis.

There were 25 articles discussing 25 studies that were included in the review of effectiveness.[57,85-106] This included one study described in a Russian language article [107] and one review of individual case reports of misidentification syndromes[108]. This last review was included because it was the only evidence above a case report that was identified by our searches in these rare disorders. A summary of the search process, reasons for exclusion, and results can be seen in Figure 1.

Twenty four of the included studies could be described as before-after studies,[82] i.e. comparing intended management policies before and after knowledge of neuroimaging test results but many were not explicit about their management policies before structural neuroimaging or about being diagnostic before and after studies. None were diagnostic accuracy studies so did not report sensitivity, specificity, predictive values, likelihood ratios, diagnostic odds ratios or ROC curves.

Some studies included one or more comparator groups (Borgwardt[90], Jeenah[95], Lesser 1991[97], Lubman[99], McKay[101], Miller[102] and Vavilov[107]), which took the form of a healthy control population or patients with another psychiatric diagnosis. The effectiveness of CT or MRI neuroimaging in healthy subjects or non-psychotic patients was not relevant to this review so this information was not extracted. The remaining studies did not formally recruit patients into a comparator group but reported outcomes based on categories of psychiatric diagnosis. These were combined where possible to make one psychosis category.

Figure 1. QUOROM flow diagram



5.2.2 Study characteristics

Ten studies (Ananth 1992[87], Ananth 1993[57], Borgwardt[90], Gewirtz[94], Larson[96], Lesser 1992[98], Lubman[99], Cunningham-Owens[106], Vavilov[107], Wahlund[105])) were designed to determine the prevalence of abnormal scan findings in a psychiatric population and appear to be cross-sectional in nature. The remaining studies sought to evaluate the use or impact of structural neuroimaging in various psychiatric populations (Adams[85], Agzarian[86], Battaglia and Spector[89], Colohan[91], Evans[93], Jeenah[95], Larson[96], McClellan[100], McKay[101], Schemmer[104]), or to examine relationships between scan results and other clinical features (Bain[88], Emsley[92], Lesser 1991[97], Miller[102], Roberts and Lishman[103]).

Eighteen studies employed CT scanning for structural neuroimaging.[57,85-89,91-96,100,103-104,106-108], while four investigated MRI scans(Borgwardt[90], Lesser 1991[97], Lubman[99], Wahlund[105]) and three studies used either CT or MRI to identify cerebral abnormalities in the patient population (Lesser 1992[98], McKay[101], Miller[102]).

In all included studies (except for the review of case reports[108]), it was intended that the patient population received either CT or MRI (or both). None of the studies report any follow-up over time. Eight studies were of a prospective design (Adams.[85], Battaglia and Spector[89], Borgwardt[90], Jeenah[95], Lesser 1991[97], Lesser 1992[98], Miller[102], Cunningham}[106]) while eleven studies were retrospective (Agzarian[86], Bain[88], Emsley[92], Evans[93], Gewirtz[94], Larson[96], McClellan[100], McKay[101], Schemmer[104], Vavilov[107], Wahlund[105]). Five studies employed a retrospective review of medical records in conjunction with additional prospective data collection (Ananth 1992[87], Ananth 1993[57], Colohan[91], Lubman[99], Roberts and Lishman[103]). It was not always clear from the text whether studies were prospectively or retrospectively conducted.

Study design appeared to be of poor quality and was poorly reported. None of the included studies were RCTs or had a high quality diagnostic before-after study design to address the question of whether the routine (or other) use of CT or MRI is of clinical use in first episode psychosis patients.

Publication dates of the CT studies ranged from 1980(Cunningham[106]) to 2007(Jeenah[95]), with eight in the 1980s and nine in the 1990s. MRI studies were published more recently. As expected, none of the included MRI studies were published in the 1980s. Apart from advances in image resolution, the technique of CT scanning has not changed significantly over time so that in this respect, early studies are unlikely to differ significantly from those published more recently. It is possible that the seven studies employing MRI may differ in the range and type of abnormalities detected since the technology of MRI has advanced over time and can be carried out in a number of different ways. One MRI study (Wahlund[105]) employed a low field 0.02T MRI scanner, which is not representative of MRI scanners used in current NHS practice.

Ten studies originated in the USA, four studies in the UK, three studies were conducted in Australia, and two each in Canada and South Africa. For the country of origin for the remaining studies see Table 6.

Nine of the included studies gave a clear indication in the text that some or all of the patient population was in the first episode of psychosis (Adams[85], Bain[88], Battaglia and Spector[89], Borgwardt[90], Gewirtz[94], Jeenah[95], Lubman[99], McKay[101], Schemmer[104]). The patient population recruited in the study by Gewirtz[94] were those with a first hospital admission for psychotic illness. Sample sizes ranged from 30 to 168. The study carried out by Lesser 1992[98] had a high proportion of psychotic patients with illness duration of 2 years or less.

The definition of a first episode was found to vary between studies, and was often not clearly stated. For this reason, thirteen studies, which recruited patients with psychosis without evidence in the text of a first episode were included.
[57,86,87,91,92,93,96,97,100,102,103,105,109] These studies met all other inclusion criteria. Sample sizes ranged from 14 to 244.

Where studies had patients described as fist episode and chronic schizophrenia described in different groups, only the fist episode psychosis patients have been described here

The study conducted by Cunningham-Owens[106] investigated a population of 136 chronic schizophrenic patients. This study was included as the only evidence of unsuspected intracranial disease in a treatment refractory psychotic population identified by the searches. The review of case reports[108] of misidentification syndromes did not report whether these patients were new onset psychotics or not.

Diagnostic tests conducted in addition to structural neuroimaging included medical and psychiatric history, physical and neurological exams, biochemical tests, blood tests, toxicological screens, mental state examinations, EEG, functional neuroimaging and psychiatric rating scales. In general, details of these assessments were poorly reported and it was often not clear what other assessments had been made.

The outcome most frequently reported was the number and type of cerebral abnormalities detected by scanning. These were sometimes presented in categories based on referral status, clinical significance, intracranial location or whether diffuse or focal. Actual pathology was reported by most studies. Included study characteristics are summarised in Table 6.

Table 6. Characteristics of included studies

Reference	Study design	Population	N	Inter-vention	Other assessments (comparator)	Relevant Outcomes*	Aim of study
Adams et al., 1996[85] (Canada)	Prospective diagnostic case series; no control group(s)	**First episode psychosis** adolescents without suspected (or known) medical illness	111 FEP (Full sample)	CT	Medical history; physical examination; endocrine tests; EEG; SPECT	Number and type of scan findings	To determine the diagnostic utility of [endocrine and] neuroimaging tests in first onset adolescent psychosis.
Agzarian et al., 2006[86] (Australia)	Retrospective review of CT scan report	Psychiatric condition without focal neurological signs with referral for scan	241 Psychotic 397 Full sample	CT	Physical examination; serum electrolytes; thyroid function	Number and type of cerebral abnormalities; number of abnormalities considered related to psychiatric condition	To evaluate the clinical use of CT brain scan in patients presenting with a psychiatric condition without focal neurological signs
Ananth etal., 1992[87] (USA)	Prospective diagnostic case series with retrospective use of psychiatric diagnosis	Psychiatric condition with normal physical status based on physical exam	37 +scan** 55 Psychotic 75 Full sample	CT	Medical and psychiatric history; physical and neurological exam; BPRS; toxicological screening; biochemical tests; EEG; EKG	Number and type of previously undetected physical illness; number of disorders changed due to scan	To investigate the prevalence of previously undetected physical illness in psychiatric inpatients

Reference	Study design	Population	N	Inter-vention	Other assessments (comparator)	Relevant Outcomes*	Aim of study
Ananth etal., 1993[57] (USA)	Prospective diagnostic case series with retrospective use of psychiatric diagnosis	Psychiatric condition, random selection from inpatients	27 Psychotic 34 Full sample	CT	Medical and psychiatric history; physical and neurological exam; BPRS; EEG; EKG	Number and diagnosis on study entry and number and diagnosis following scan	To investigate the prevalence of physical illness that was missed during diagnosis in psychiatric inpatients
Bain et al., 1998[88] (USA)	Retrospective review of medical records of patients with CT scan; no control group(s)	**First episode psychosis** without previous CT scan or evaluation for psychosis	127 FEP (Full sample)	CT	Medical history; neurological exam	Number and type of scan findings; number and type of cerebral abnormalities; number and diagnosis at discharge	To examine relationships between CT scan findings and demographic variables, seizure history, neurological abnormalities, and discharge diagnosis. Working hypothesis-psychotic illness alone is not sufficient to warrant a CT scan.
Battaglia & Spector, 1988[89] (USA)	Prospective diagnostic case series; no control group(s)	**First episode psychotic illness** with clear physical exam	45 FEP (Full sample)	CT	Physical and neurological exam; drug use history; BPRS; lab tests in some cases	Number and type of cerebral abnormalities; number and diagnosis at discharge	To examine the utility of the CT scan as a screening instrument for CNS pathology among psychiatric patients presenting with a first-break psychotic illness.

Reference	Study design	Population	N	Inter-vention	Other assessments (comparator)	Relevant Outcomes*	Aim of study
Borgwardt et al., 2006[90] (Switzerland)	Prospective diagnostic case series; included groups of patients with high risk of schizophrenia, FEP, depression, and healthy controls	**First episode psychosis** aged ≥18y	30 FEP 110 Full sample	MRI	For FEP patients: BPRS; other assessments NR	Number and type of scan findings; number and type of cerebral abnormalities	To assess the prevalence of radiological MRI findings in individuals at high risk of schizophrenia.
Colohan et al., 1989[91] (Ireland)	Retrospective review of medical records of patients with CT scan with prospective interview of individual clinicians	Psychiatric condition with referral for CT scan	29 Psychotic 53^ Full sample	CT	Mental status; physical and neurological exam; EEG; other laboratory tests	Number and type of cerebral abnormalities; number and diagnosis following scan; number of diagnoses changed due to scan	To evaluate the impact of CT in relation to psychiatry in Ireland
Emsley et al., 1986[92] (South Africa)	Retrospective review of medical records of patients with CT scan	Psychiatric condition with referral for CT scan	43 Psychotic 100 Full sample	CT	Medical and psychiatric history; EEG in some cases	Number and type of cerebral abnormalities	To determine what clinical features could be useful in identifying those [psychiatric patients] in whom intracranial lesions may coexist
Evans et al., 1982[93] (UK)	Retrospective review of medical records of patients with CT scan	Psychiatric condition with referral for CT scan	19 Psychotic 100 Full sample	CT	Medical history; psychiatric and mental state exam; physical exam	Number and type of cerebral abnormalities	To report experience in the use of CT in clinical psychiatry

Reference	Study design	Population	N	Inter-vention	Other assessments (comparator)	Relevant Outcomes*	Aim of study
Gewirtz et al., 1994[94] (USA)	Retrospective review of medical records of patients with CT scan; no control group(s)	**First admission for psychotic illness** in the absence of an organic disorder	168 FEP (Full sample)	CT	Physical exam; urine toxicology; blood counts; electrolytes; syphilis serology; thyroid status	Number and type of cerebral abnormalities; change in diagnosis following scan; number of abnormalities with implication for patient management	To describe the frequency and types of CT scan findings in patients with diagnosis of psychotic illness.
Jeenah et al., 2007[95] (South Africa)	Prospective diagnostic case series; included non-FEP psychotic patients	**First episode psychosis**, or all psychotic patients with either features of a delirium, some focal physical or neurological signs, and/or abnormal results of special investigations	47 FEP 55 Full sample	CT	Clinical details (physical and mental state); all other special investigations (laboratory, radiological, EEG)	Number and type of cerebral abnormalities	To determine the value of CT in the assessment of mentally ill patients.
Larson et al., 1981[96] (USA)	Retrospective review of medical records of patients with CT scan	Psychiatric illness with or without medical or neurological consultation pre-scan	39 Psychotic 123 Full sample	CT	Medical history; physical exam; other neurodiagnostic studies; treatment and outcomes	Number and type of scan findings; number and type of cerebral abnormalities	To determine the diagnostic yields, the clinical use of CT, and cost of case findings in psychiatric patients referred for CT scanning

Reference	Study design	Population	N	Inter-vention	Other assessments (comparator)	Relevant Outcomes*	Aim of study
Lesser et al., 1991[97] (USA)	Prospective diagnostic case series; included non-psychotic control population	Major depression with psychosis over age 45 without evidence of hemiparesis/ hemisensory deficits	14 Psychotic 86 Full sample	MRI	Medical history; mental state; physical and neurological exam; neuropsychological tests	Number and type of medical and neurological abnormalities	To test the hypothesis that psychotic depression can be the clinical manifestation of subtle brain injury in the elderly
Lesser et al., 1992[98] (USA)	Prospective diagnostic case series	Psychotic disorder NOS over age 45 without localising neurological signs and major medical and neurological problems	8 Psychotic ≤2y duration+scan 16 Full sample	MRI or CT	Neurological and mental state exam; laboratory tests	Number and type of scan findings; number and type of cerebral abnormalities	To evaluate the clinical and neuroimaging results of patients diagnosed with psychotic disorder NOS
Lubman et al., 2002[99] (Australia)	Diagnostic case series including retrospective review of medical records of patients with MRI scan; included patients with FEP, chronic schizophrenia and normal controls	**First episode psychosis**; asymptomatic and without suggestion of underlying organic disease	152 FEP 340 Full sample	MRI	Medical history; physical and mental state exam	Number and type of scan findings; number and type of cerebral abnormalities; number of abnormalities with implication for patient management	To investigate whether patients with first-episode psychosis [or chronic schizophrenia] have an increased incidence of MRI brain abnormalities compared with control subjects.

Reference	Study design	Population	N	Inter-vention	Other assessments (comparator)	Relevant Outcomes*	Aim of study
McClellan et al., 1988[100] (USA)	Retrospective review of medical records of patients with CT scan	Psychiatric illness without focal neurological deficits or other finding suggesting intracranial abnormality	142 Psychotic 261 Full sample	CT	NR	Number and type of cerebral abnormalities; number of scan findings considered related to psychiatric condition	To assess the value of CT of the head as a screening procedure in patients with psychiatric symptoms
McKay et al., 2006[101] (Australia)	Retrospective review of medical records of patients with CT or MRI scan; included FEP, chronic schizophrenics, and normal controls	**First episode psychosis** aged 15-26y	52 +scan 117 Full sample	CT or MRI	Physical exam in some cases; EEG in some cases	Number and type of scan findings	To assess aspects of medical examination, diagnosis [and side-effect monitoring], and to consider the role of routine investigations in this group as recommended by national guidelines.
Miller et al., 1991[102] (USA)	Prospective diagnostic case series; included healthy control group	Late-onset psychosis (over age 45y) without evidence of hemimotor/ hemisensory deficits	24 Psychotic 96 Full sample	MRI or CT	Clinical exam (physical and neurological exam and laboratory tests); psychiatric history; neuropsychological tests	Number and type of cerebral abnormalities	To explore the relationship between structural brain injury and late life psychosis

Reference	Study design	Population	N	Inter-vention	Other assessments (comparator)	Relevant Outcomes*	Aim of study
Roberts & Lishman, 1984[103] (UK)	Retrospective review of medical records of patients with CT scan with prospective interview of individual psychiatrists	Psychiatric condition with referral for CT scan.	244 Psychotic 323 Full sample	CT	Physical, neurological and mental state exams; medical and psychiatric history	Number and type of scan findings.	To look at the relationship between scan results and the expectations of the referring psychiatrist, medical record data and the significance attached to the scan results in relation to diagnosis, management and prognosis
Schemmer et al., 1999[104] (Canada)	Retrospective review of medical records of patients with CT scan	General psychiatric condition including **first episode psychosis** and non-FEP patients	NR FEP 207 Full sample	CT	NR	Number and type of cerebral abnormalities	To evaluate the effect of brain CT on diagnosis and management of general psychiatric patients
Vavilov et al., 1993[107] (Russia)	Retrospective review of medical records of schizophrenic patients with CT scan included mentally normal with suspected organic brain condition and healthy control groups	Schizophrenia	721 Full sample	CT	NR	Number and type of cerebral abnormalities	To analyse the incidence of organic brain lesions in schizophrenics, healthy controls and patients mentally normal with a suspected organic brain condition.

Reference	Study design	Population	N	Inter-vention	Other assessments (comparator)	Relevant Outcomes*	Aim of study
Wahlund et al., 1992[105] (Sweden)	Retrospective review of medical records of psychiatric patients with MRI scan	Psychiatric illness	170 Psychotic 731 Full sample	MRI	Psychiatric history	Number and type of cerebral abnormalities	To investigate the frequency of focal brain damage in psychiatric patients
Cunningham-Owens et al., 1980[106] (UK)	Prospective diagnostic case series	Chronic treatment refractory schizophrenia	136 Full sample	CT	Medical history	Number and type of cerebral abnormalities	To assess the prevalence and degree of clinically unsuspected intracranial disease and cerebral atrophy in relation to history, clinical findings and past treatment in a group of chronic schizophrenic patients.
Forstl et al., 1991[108] (UK)	Review of individual case reports	Misidentification syndromes	80 case reports involving psychosis + scan 260 Individual case reports	CT	Various	Number and type of cerebral abnormalities	To review case reports of misidentification syndromes and to attempt to analyse their relationship to each other and the factors implicated in aetiology
*Scan finding refers to reporting by category e.g. referral status. ** Not clear whether all scanned patients were psychotic. ^ N not clear 54 patients also stated in text							

5.2.3 Critical review and synthesis of information

These sections are reported in five categories – studies in psychotic or first episode psychotic patients where the neuroimaging was by a) CT, b) MRI, or c) both CT and MRI, d) studies in treatment refractory patients and e) review of patients with misidentification syndromes.

5.2.3.1 Patient characteristics

a) CT studies

Of the sixteen studies employing CT alone, six recruited first episode psychotic patients (Adams[85], Bain[88], Battaglia and Spector[89], Gewirtz[94], Jeenah[95], and Schemmer[104]). The study conducted by Gewirtz recruited patients on the basis of a first admission for psychotic illness. The definition of what constituted FEP was not clearly stated in any of the six studies suggesting that there may be variation in the FEP patient population between studies. It is, however, likely that most patients will have had no or very little treatment for a psychotic illness. The duration of illness, a crude measure that may or may not include prodromal illness, was not reported by any of the six studies.

The remaining ten studies. [57,86,87,91,92,93,96,100,103,107] recruited general psychiatric patients with a proportion of these being psychotic. Where the text indicated that a disorder was psychotic, the number of patients with this disorder was included in the total of psychotic patients recorded in Table 7. Where no indication was given, patients with a diagnosis of schizophrenia were assumed to be psychotic and included in the subgroup with psychosis. Depression and bipolar disorders were not considered psychotic unless indicated in the study text. In studies recruiting general psychiatric patients, there was no indication that the psychotic patients were in their first episode. Duration of illness was not reported except by Larson, who had over 50% of the study population with an illness duration of 6 months or less. Therefore, out of 16 CT studies, seven appeared to have patient populations in their first episode or the early stage of a psychotic illness.

All CT studies recruited the study population from hospitalised inpatients, although four studies (Agzarian[86], Evans[93], Larson[96], Roberts and Lishman[103]) also included outpatients.

Six studies (Adams[85], Agzarian[86], Ananth 1992[87], Ananth 1993[57], McClellan[100]) gave some indication that they excluded patients with neurological abnormalities on examination. Four further studies by Bain[88], Battaglia and Spector[89], Evans[93], and Jeenah[95] reported that a small proportion of included patients had neurological symptoms and signs (two patients out of 127 (Bain), 3/45 (Battaglia and Spector[89]), 1/20 (Evans) and 2/47 (Jeenah[95])). The study by Battaglia and Spector[89] state that the three patients with neurological symptoms and signs all had normal CT scans. The study conducted by Colohan[91] had 14/53 psychiatric patients with neurological abnormalities. All patients included in the study by Emsley[92] had suspicion of an intracranial lesion pre-scan, which suggested the presence of neurological symptoms and signs. Similarly, the patients recruited by Roberts and Lishman[103], if referred for clinical reasons (others in this study were research participants), were selected on the basis of a suspicion or needing to eliminate the presence of a cerebral abnormality. Studies by Larson[96] and Vavilov[107] both included psychotic patients with abnormal

neurological examinations but gave no further details. It was not clear whether the psychotic patients in the studies by Gewirtz[94], and Schemmer[104] had any neurological signs and symptoms at the start of the study. It should be noted that although some studies excluded patients with neurological symptoms and signs, the corresponding inclusion criteria included a referral for a CT scan (where scanning was not part of the routine diagnostic work-up). In these patients it may have been necessary to 'rule out' organic pathology.

The setting varied between studies. Most were conducted at general hospitals (Adams[85], Battaglia and Spector[89], Colohan[91], Emsley[92], Evans[93], Jeenah[95], Larson[96], and McClellan[100]) or a tertiary mental health hospital (Agzarian[86], Ananth 1992[87], and 1993[57] and Roberts and Lishman[103]). The study by Roberts and Lishman conducted their study at the Maudsley Hospital, which may have a higher proportion of atypical cases than that seen in a general hospital. The study by Gewirtz[94] was conducted at a community service unit. The study by Bain[88] was based at a military medical centre with a high proportion of young adults. It was not clear what the setting was for the studies by Schemmer[104] and Vavilov[107].

Patient characteristics including those discussed above are summarised in Table 7. Only one study (Adams[85]) investigated CT scanning specifically in an adolescent population. The study by Vavilov[107] recruited patients including those below the age of 10. The studies by Colohan[91], and Larson[96] included patients from 14 years old and McClellan[100] from 16 years old. All other studies recruited patients aged 18 and over. Mean ages were usually reported for the entire study population, which may have included non-psychotic patients as indicated in Table 7. Most studies appeared to have a mean age within the 30 to 40 year range (Agzarian[86], Ananth 1992[87], Ananth 1993[57], Bain[88], Emsley[92], Gewirtz[94], Jeenah[95]). The studies by Colohan[91], Evans[93], Larson[96], McClellan[100], and Roberts and Lishman[103] all had a patient population with a mean of 40 years or above. The study by Battaglia and Spector[89] had a mean age of 26 years whereas the study by Schemmer[104] did not report a mean age.

The proportion of females to males was roughly 50% across most studies except for the study by Bain[88] with only 20% female, and Battaglia and Spector[89] with only 33% female. Proportions were usually reported for entire samples rather than specifically for FEP or psychosis patients alone.

Table 7. Patient characteristics for CT scan studies in (first episode) psychosis patients

Reference	**No. of patients with FEP/** psychosis	**Mean age [range] based on sample size n**	**Proportion female**	**Inpatient/ outpatient**	**Inclusion/ exclusion**	**Mean duration of illness**	**Neurological signs and symptoms at study entry**
Adams et al., 1996[85] (Canada)	**111 FEP**	16.9y [13-19y] n=111	39%	Inpatients	Inclusion: aged 13-19y, unremarkable medical history and normal physical exam. Exclusion: known medical disorders (eg diabetes, epilepsy etc)	Unclear	?No "No suspected medical illness" Normal physical exam but neurological exam not mentioned.
Agzarian et al., 2006[86] (Australia)	241 psychotic	37y [18-86y] n=397	41%	In- and outpatients	Inclusion: psychiatric condition for which a CT was requested. Exclusion: previously documented CT brain abnormalities; focal neurological signs	NR	No No focal neurological signs.
Ananth etal., 1992[87] (USA)	37 with scan mostly psychotic 55	32y [18-57y] n=75	52%	Inpatients	Inclusion: psychiatric admission aged 18-65y Exclusion: possible discharge prior to expected date of test completion, disapproval by ward staff based on whether the patient was likely to elope or become violent.	NR	?No Normal physical status based on a physical exam by a physician in a general hospital.
Ananth etal., 1993[57] (USA)	27 psychotic	36y [24-58y] n=34	47%	Inpatients	Inclusion: psychiatric inpatient Exclusion: possible discharge prior to expected date of test completion, disapproval by ward staff based on whether the patient was likely to elope or become violent.	Average length of hospitalisation 15 days [1-76 days]	?No Normal physical status based on a physical exam by a physician in a general hospital.

Reference	**No. of patients with FEP/** psychosis	**Mean age [range] based on sample size n**	**Proportion female**	**Inpatient/ outpatient**	**Inclusion/ exclusion**	**Mean duration of illness**	**Neurological signs and symptoms at study entry**
Bain et al., 1998[88] (USA)	**127 FEP**	17-30y n=98 31-40y n=23 41y+ n=6	20%	Inpatients	Inclusion: admission/ discharge diagnosis of DSM-III-R psychotic disorder NOS, schizophreniform disorder, schizophrenia, brief reactive psychosis, schizoaffective disorder, delusional disorder, bipolar or major depression. Exclusion: previous evaluation for psychosis, previous CT scan	NR	Yes 2/127 had neurological abnormality on admission. 5/127 had a history of seizure.
Battaglia & Spector, 1988[89] (USA)	**45 FEP**	26y [17-54y] n=45	33%	Inpatients	Inclusion: first psychiatric hospital admission, presence of ≥1 symptom of delusions, hallucinations, markedly disordered thought processes, catatonic, or other grossly disordered behaviour, first presentation of these symptoms, psychotic process incompletely resolved after 48h, medically cleared by ER physician on basis of physical exam.	NR	Yes Neurological exam was abnormal in 3/45 but all had normal CT scan (hyperreflexia in right lower extremity; right sided Babinski reflex with hyperreflexia; diplopia on left gaze).
Colohan et al., 1989[91] (Ireland)	29 psychotic	51y (SD 18y) [14-79y] n=53 or 54	53%	Inpatients	Inclusion: psychiatric patient referral for CT scan.	Average length of hospitalisation 62 days (SD 51) [5-298 days] plus one patient with a stay of 1299 days.	Yes Neurological and physical exam was abnormal in 14/53

Reference	**No. of patients with FEP/** psychosis	**Mean age [range] based on sample size n**	**Proportion female**	**Inpatient/ outpatient**	**Inclusion/ exclusion**	**Mean duration of illness**	**Neurological signs and symptoms at study entry**
Emsley et al., 1986[92] (South Africa)	43 psychotic	34y [18-72y] n=100	49%	Inpatients	Inclusion: psychiatric inpatient with distinct possibility of intracranial lesion.	NR	Yes Details unclear
Evans et al., 1982[93] (UK)	19(+1 with neurological signs) Psychotic part of group with psychological disturbance (32)	49y M: 42y F [NR] n=32	38%	In- and outpatients	Exclusion: patients initially presenting to a psychiatrist but taken over by a neurologist.	NR	Yes 1 with neurological signs (visual field defects and acromegalic features)
Gewirtz et al., 1994[94] (USA)	**168 First hospital admission for psychosis**	35y (SD 12) [18-66y] n=168	53%	Inpatients	Inclusion: first admission for psychotic illness Exclusion: presence of an organic disorder (dementia, AIDS, epilepsy), lack of psychotic illness as final diagnosis	NR	Unclear Absence of organic disorder.
Jeenah et al., 2007[95] (South Africa)	**47 FEP** 55 FEP+non-FEP psychotic	38.6y (SD 16.3) [18-73y] n=55	47%	Inpatients	Inclusion: FEP with or without mood features, psychotic patients with or without mood features with either features of a delirium, some focal physical or neurological signs, and/or abnormal results of special investigations.	NR	Yes 2 with abnormal scan and FEP had focal physical or neurological signs and/or abnormal results of special investigations.

Reference	**No. of patients with FEP/** psychosis	**Mean age [range] based on sample size n**	**Proportion female**	**Inpatient/ outpatient**	**Inclusion/ exclusion**	**Mean duration of illness**	**Neurological signs and symptoms at study entry**
Larson et al., 1981[96] (USA)	39 psychotic	49y (SD 18y) [14-81y] n=123	51%	In- and outpatients	Inclusion: major reason for evaluation and scanning was psychiatric illness	21.1% < 2 wks 33.0% 2 wks- 6m 19.1% 6m- 5 y 26.8% > 5 yrs	Yes Details unclear. With or without neurologic consultation pre-scan.
McClellan et al., 1988[100] (USA)	142 psychotic	Median 41y [16-79y] n=261	59%	Inpatients	Exclusion: previously documented medically or surgically treatable CNS abnormalities; patients with focal neurological deficits or other findings suggestive of intracranial abnormality (eg papilledema, seizures, persistent/ increasing headaches).	NR	No Without focal neurological deficits or other findings suggestive of intracranial abnormality.
Roberts & Lishman, 1984[103] (UK)	244 psychotic	47y [NR] n=323	48% n=323	In- and outpatients	If referred for clinical reasons, patients were selected based on a suspicion of, or needing to eliminate the presence of a cerebral abnormality.	NR	?Yes n NR Needing to eliminate the presence of a cerebral abnormality.
Schemmer et al., 1999[104] (Canada)	**NR FEP**	NR	NR	?Inpatients	NR	NR	Unclear

Reference	**No. of patients with FEP/** psychosis	**Mean age [range] based on sample size n**	**Proportion female**	**Inpatient/ outpatient**	**Inclusion/ exclusion**	**Mean duration of illness**	**Neurological signs and symptoms at study entry**
Vavilov et al., 1993[107] (Russia)	721 psychotic	NR [<10->70y] n=721	54% n=721	Inpatients	Inclusion: schizophrenia	NR	Yes n NR Appearance of atypical symptoms especially neurological.

b) MRI studies

Table 8 summarises patient characteristics for the four studies employing MRI alone (Borgwardt[90], Lesser 1991[97], Lubman[99], Wahlund[105]). Studies by Borgwardt[90] and Lubman[99] stated that they recruited FEP patients, while studies by Lesser 1991[97] and Wahlund[105] included psychotic patients as a subgroup of a more general psychiatric population. As with the CT studies, a clear definition of first episode was not given in either FEP study. The study by Lubman[99] reported duration of illness of less than one year. The mean duration of illness for patients in the Lesser 1991[97] study was 18 months suggesting a sample with a high proportion of psychoses in the early stage of illness. Studies by Borgwardt[90] and Wahlund[105] gave no details of illness duration. Of the four MRI studies, three[90,97,99], appeared to have a study population in their first episode or early stages of psychosis.

The general hospital was the setting for the studies by Lesser 1991[97], Lubman[99] and Wahlund[105]. The study by Borgwardt[90] recruited from an outpatient clinic in a general hospital.

Outpatients were recruited by Borgwardt[90], in- and outpatients by Lesser 1991 [97] and inpatients by Wahlund[105] studies. It was not clear whether the study by Wahlund[105] had also recruited outpatients. The study by Lubman[99] recruited patients already involved in collaborative research studies. Since full inclusion criteria for the research studies was not given, it is hard to ascertain what effect this type of study population may have on generalisability, but it must certainly be treated with caution.

All four studies gave some indication that patients with neurological abnormalities had been excluded from the study population. For example, studies by Borgwardt[90] and Lubman[99] describe this as “without suggestion of organic disease”.

The age range differed between the studies using MRI neuroimaging. The study by Lesser 1991[97] recruited patients over the age of 45, and hence had a mean age of 57 years. The mean age for patients in the Borgwardt[90] study was 30 years old and only 22 years old for the Lubman[99] study. These mean ages were for the FEP or psychotic sample alone. The study by Wahlund[105] gave no details of ages for the study population.

C) CT/ MRI studies

Table 9 summarises patient characteristics for the three studies employing either CT or MRI scanning (Lesser 1992[98], McKay[101], Miller[102]). The study by Lesser 1992[98] did not report the reason for 11 patients receiving an MRI and one receiving a CT scan. The study by McKay[101] neither reports the proportion of patients receiving MRI or CT, nor the reasons. The study by Miller[102] reported that three patients were given a CT scan instead of MRI due to a pacemaker (1) and claustrophobia (2). One patient was too large to be given any scan. The study by McKay[101] recruited patients aged 15-26 years old with FEP. The studies by Lesser 1992[98] and Miller[102] recruited patients over the age of 45 (mean age was over 60 years old in both studies) with psychotic disorder NOS and late-onset psychosis, respectively. The mean duration of illness for the population in the Lesser 1992[98] study was four years but 12 of the 16 patients had illness lasting two years or less, and eight of these received a scan. The study by McKay[101] did not report illness duration. The mean duration of illness for the patients in the Miller[102] study was 20 months. All three studies therefore, suggest

populations either in their first episode of psychosis or in the early stages of the illness.

All three studies recruited in- and outpatients from a general hospital (McKay[101] and Miller[102]) or a veterans affairs medical centre (Lesser 1992[98]). The studies by Lesser 1992[98] and Miller[102] both excluded patients with neurological symptoms and signs on examination. The study by McKay[101] did not give details of neurological examinations.

Table 8. Patient characteristics for MRI scan studies in (first episode) psychosis patients

Reference	**No. of patients with FEP/** psychosis	**Mean Age [range] based on sample size n**	**Proportion female**	**Inpatient/ outpatient?**	**Inclusion/ exclusion**	**Mean duration of illness**	**Neurological signs and symptoms at study entry**
Borgwardt et al., 2006[90] (Switzerland)	**30 FEP**	30.3y (SD 6.9) n=30	27%	Outpatients	Inclusion: ≥18y Exclusion: schizophrenia previously diagnosed and treated with major tranquillisers for more than 3 weeks, substance induced psychosis, psychotic symptomatology secondary to an "organic" disorder or within a diagnosed affective psychosis or borderline personality disorder, IQ ≤70, inadequate knowledge of the German language.	NR	?No "Patients whose symptoms were attributable to organic brain diseases were excluded."
Lesser et al., 1991[97] (USA)	14 psychotic	57y (SD 6y) [NR] n=14	71%	In- and outpatients	Inclusion: major depression with psychotic features; aged >45y. Exclusion: evidence of psychotic or affective disorder prior to age 45; MMSE score less than 24; history of drug or alcohol abuse, stroke, epilepsy, Parkinson's disease, or evidence of hemiparesis or hemisensory deficits.	17.8m [2-48m] n=14	No Without evidence of hemiparesis or hemisensory deficits.
Lubman et al., 2002[99] (Australia)	**152 FEP**	21.6y (SD 3.5) [NR] n=152	32%	NR Patients were involved in collaborative research studies	Inclusion: asymptomatic Exclusion: history of significant head injury, seizures, neurological diseases, impaired thyroid function, steroid use or DSM-III-R criteria for alcohol or substance abuse or dependence.	"Length of illness <1y"	?No "without suggestion of organic disease" Excluded neurological diseases.

Reference	**No. of patients with FEP/** psychosis	**Mean Age [range] based on sample size n**	**Proportion female**	**Inpatient/ outpatient?**	**Inclusion/ exclusion**	**Mean duration of illness**	**Neurological signs and symptoms at study entry**
Wahlund et al., 1992[105] (Sweden)	170 psychotic	NR	NR	Inpatients ?outpatients	Exclusion: obvious neurological signs or symptoms.	NR	No Excluded obvious neurological signs or symptoms.

Table 9. Patient characteristics for the study using CT or MRI scan in (first episode) psychosis patients

Reference	**No. of patients with FEP/** psychosis	**Mean Age [range] based on sample size n**	**Proportion female**	**Inpatient/ outpatient?**	**Inclusion/ exclusion**	**Mean duration of illness**	**Neurological signs and symptoms at study entry**
Lesser et al., 1992[98] (USA)	8 psychotic ≤2y duration+scan	64y (SD 11y) [NR] n=16	56%	In- and outpatients	Inclusion: Free of major medical and neurological problems known to produce behavioural changes; no localising signs on neurological exam; score >24 MMSE; were not acutely ill or delirious; no recent or current drug/ alcohol abuse; no grossly abnormal lab results.	Average length of illness 4y Length of illness ≤2y n=12	No No localising signs on neurological exam.
McKay et al., 2006[101] (Australia)	**52 FEP with scan**	20.2y (SD 2.9) [NR] n=117	36%	In- and outpatients	Inclusion: aged 15-26y	NR	NR
Miller et al., 1991[102] (USA)	24 psychotic	60y (SD 10y) [NR] n=24	58% n=24	In- and outpatients	Excluded: doubt over age of onset; MMSE < 24; history of drug or alcohol abuse, stroke, epilepsy, Parkinson's disease or evidence of hemimotor or hemisensory deficits, not fluent in English.	20m (SD 29m)	No Without evidence of hemimotor or hemisensory deficits.

d) Treatment refractory psychosis

The patient characteristics are shown in Table 10 for the one study in treatment refractory patients[106]. The mean age and proportion that were female was not reported for this chronic schizophrenic population. Average duration of illness was not reported but patients were recruited from both in- and outpatient environments. One patient was recruited with neurological symptoms.

Table 10. Patient characteristics of an included study where the psychosis is treatment refractory

Reference	**No. of patients with FEP/** psychosis	**Mean Age [range] based on sample size n**	**Proportion female**	**Inpatient/ outpatient?**	**Inclusion/ exclusion**	**Mean duration of illness**	**Neurological symptoms and signs at study entry**
Cunningham-Owens et al., 1980[106] (UK)	136 psychotic	NR	NR	In- and outpatients	Inclusion: chronic schizo-phrenia	NR	Yes 1/136 had mild left hemiparesis

e) Misidentification syndromes

Table 11 shows the patient characteristics for the review of case reports of misidentification syndromes[108]. The mean age was given for the whole sample rather than the 80 cases that received a CT scan. There was no evidence to suggest any cases were in their first episode of psychosis.

Table 11. Patient characteristics of a review of case reports of misidentification syndromes

Reference	**No. of patients with FEP/** psychosis	**Mean Age [range] based on sample size n**	**Proportion female**	**Inpatient/ outpatient?**	**Inclusion/ exclusion**	**Mean duration of illness**	**Neurological symptoms and signs at study entry**
Forstl et al., 1991[108] (UK)	80 case reports involving psychosis + scan	42y [NR] n=260	57% 1 NR	NR	Various	NR	NR

5.2.3.2 Details of neuroimaging

a) CT studies

As can be seen from Table 12, six studies (Adams[85], Agzarian[86], Bain[88], Battaglia and Spector[89], Gewirtz[94] and McClellan[100]) report that scanning was given as part of the routine diagnostic work-up on admission. It was not clear whether this was also the case for the study by Schemmer[104]. Patients were scanned following referral in the studies by Evans[93], and Larson[96], and for clinical reasons in the studies by Colohan[91], Emsley[92], Roberts and Lishman[103], and Vavilov[107]. Patients were scanned for the purpose of the study in two studies (Ananth 1993[57], Jeenah[95]). The study by Ananth 1992[87] scanned patients on the basis of random selection from the study population. No further details were given.

Reporting of the machine used, and the scanning process, was generally poor. Emsley[92], Evans[93], Larson[96], Roberts and Lishman[103], and Vavilov[107] report the type of CT scanner used. The remaining CT studies gave no details whatsoever. Agzarian[86] and Vavilov[107] reported that 4% and 1% were contrast scans respectively.

Table 12. Details of neuroimaging - CT studies

Reference (country)	**No. of patients with FEP**/psychosis **who received CT**	**Reason for scan (taken from study text)**	**Details of imaging**
Adams et al., 1996[85] (Canada)	**98 FEP**	Routine on admission	NR
Agzarian et al., 2006[86] (Australia)	241 psychotic	Routine on admission	NR 379/ 397 (96%) non-contrast 18/ 397 (4%) contrast
Ananth etal., 1992[87] (USA)	37 mostly psychotic	Random selection from study population	NR
Ananth etal., 1993[57] (USA)	27 psychotic	Study	NR
Bain et al., 1998[88] (USA)	**127 FEP**	Routine on admission	NR
Battaglia & Spector, 1988[89] (USA)	**45 FEP**	Routine on admission	NR
Colohan et al., 1989[91] (Ireland)	29 psychotic	Clinical	NR
Emsley et al., 1986[92] (South Africa)	43 psychotic	Suspicion of intracranial lesion	NR Siemens Somaton 2 whole-body scanner.
Evans et al., 1982[93] (UK)	19(+1 with neurological signs) psychotic	Referral	NR EMI 1010
Gewirtz et al., 1994[94] (USA)	**168 FEP**	Routine on admission	NR
Jeenah et al., 2007[95] (South Africa)	**47 FEP**	Study	NR
Larson et al., 1981[96] (USA)	39 psychotic	Referral	NR EMI 1010 or AS&E Pfizer 0500 or GE CT/T 8800
McClellan et al., 1988[100] (USA)	142 psychotic	Routine on admission	NR
Roberts & Lishman, 1984[103] (UK)	244 psychotic	Clinical: suspicion of/ needing to eliminate presence of intracranial lesion Research: requirement for various studies	NR 160x160 matrix 1010 head scanner
Schemmer et al., 1999[104] (Canada)	**NR**	?Routine on admission	NR

Vavilov et al., 1993[107] (Russia)	721 psychotic	Psychiatrist request for appearance of atypical symptoms, positive results of other examinations, organic causes of mental ill-health assumed, pre-ECT, resistance to medical treatment	Somaton CR machine in standard mode – 4mm basal slices, 8mm meatal slices. Contrast enhancement using i/v bolus of water soluble dye 0.5ml/kg for 8/721 (1%) in schizophrenia group. Statistical analysis using IBM AT-286

b) MRI studies

Patients received an MRI scan for the purpose of the study in three of the four MRI studies (Borgwardt[90], Lesser 1991[97] and Lubman[99]). MRI scanning was routinely given within three months of the first contact or referral to psychiatric services in the study by Wahlund[105]. Details of the scanner and imaging process were given in full by all four studies. Borgwardt[90], Lesser 1991[97] and Lubman[99] all used 1.5 tesla machines, whereas Wahlund[105] and colleagues used a 0.02 tesla machine, which does not represent that used in current clinical UK practice. This information is shown in Table 13.

Table 13. Details of neuroimaging - MRI studies

Reference	**No. of patients with FEP/** psychosis **who received MRI**	**Reason for scan**	**Details of imaging**
Borgwardt et al., 2006[90] (Switzerland)	**30 FEP**	Study	1.5T clinical scanner system (VISION, Siemens). Dual echo images were acquired parallel to the anterior and posterior commissure (AC-PC) line (first echo time 20ms, second echo time 85ms; repetition time 4300ms, 50 slices of 3mm slice thickness covering the entire brain; matrix size 256x192, field of view 23x17.25cm, respectively).
Lesser et al., 1991[97] (USA)	14 psychotic	Study	Picker MRI 1.5T Multiple plane scans axial scans along cantomeatal line from skull base to vertex in 10mm sections, repetition time 2000 millisecs, echo times 20 and 100 ms to give T1 and T2 weighted scans. Coronal plane through entire brain at 10mm intervals. Sagittal plane inversion recovery images through lateral ventricles with repetition time 2500 ms and inversion time of 600 ms. All scans with two repetitions to maintain image quality.
Lubman et al., 2002[99] (Australia)	**152 FEP**	Study	Signa 1.5T with studies that contained at least a 3D volumetric spoiled gradient recalled echo in steady state (SPGR) sequence which generated 124 contiguous 1.5mm coronal slices.
Wahlund et al., 1992[105] (Sweden)	170 psychotic	Routine within 3m of first contact/ referral	NR Low field MRI 0.02T

c) CT/ MRI studies

Lesser 1992[98] scanned patients either as part of the diagnostic workup, or for the purpose of the study. It is not clear how these two groups of patients may have differed, since patients were excluded if they had neurological symptoms and signs. Miller[102] scanned patients for the study. It was not clear from the text why patients were scanned in the study by McKay[101]. It was likely that the reasons for scanning were clinical, since this was a retrospective review of medical records. The studies by Lesser 1992[98] and Miller[102] both employed 1.5T MRI machines, with full details of the process reported. McKay[101]did not report details of the machine or process used. Details are summarised in Table 14.

Table 14. Details of neuroimaging for CT/MRI studies

Reference	**No. of patients with FEP/** psychosis **who received MRI or CT**	**Reason for scan**	**Details of imaging**
Lesser et al., 1992[98] (USA)	8 ≤ 2 years illness duration MRI 11:CT 1	Study/diagnostic work up.	Picker MRI, 1.5T, scans in multiple planes, axial scans along cantomeatal line from skull base to vertex in 10mm sections, repetition time 2000 ms, echo times 20 and 100 ms to give T1 and T2 weighted scans. Coronal plane through entire brain at 10mm intervals. Sagittal plane inversion recovery images through lateral ventricles with repetition time 2500 ms and inversion time of 600 ms. All scans with two repetitions to maintain image quality.
McKay et al., 2006[101] (Australia)	**52 FEP** proportion MRI:CT NR	Unclear, ?clinical evaluation	NR
Miller et al., 1991[102] (USA)	24 3 given CT instead of MRI- not clear. Suggests these were patients, not controls.	Study	MRI Picker scanner 1.5T superconducting magnet. scans in multiple planes, axial scans along cantomeatal line from skull base to vertex in 10mm sections, repetition time 2000 ms, echo times 20 and 100 ms to give T1 and T2 weighted scans. Coronal plane through entire brain at 10mm intervals. Sagittal plane inversion recovery images through lateral ventricles with repetition time 2500 ms and inversion time of 600 ms. All scans with two repetitions to maintain image quality.

d) Treatment refractory psychosis and e) misidentification syndromes

The study by Cunningham-Owens[106] gave information on the scanner used and the process of imaging. Patients were scanned for the purpose of the study. The review of case reports of misidentification syndromes by Forstl[108] does not report details of CT machine or process used for the 80 individual cases who received a scan. Details of reasons for scanning were not given but were likely to have been for clinical reasons (diagnostic workup), since these case reports were not involved in research studies

Table 15. Details of neuroimaging – treatment refractory psychosis

Reference	**No. of patients with FEP/** psychosis **who**	**Reason for scan**	**Details of imaging**

	received CT		
Cunningham-Owens et al., 1980[106] (UK)	136	Study	EMI CT 5005 whole body scanner at 120 kVP using a 65 second scan time. Scans examined on an EMI Mk II independent viewing console.

5.2.3.3 Quality of included studies

The text below describes the quality issues associated with the five categories of studies. The summary quality tables can be found in Appendix 6.

a) CT studies

External validity

The first question addressed by the modified QUADAS tool (see Table 5 on page 23) is essential to the application of study data to the review question. The population of patients assumed to be seen in practice for the purpose of this review question were those presenting with a first episode, or at the early stage of the illness, antipsychotic treatment naïve, without focal neurological symptoms and signs (since those with overt signs on neurological examination would be likely to be channelled into neurology services). Patients were of any age and gender. Patients could be seen in a psychiatric in- or outpatient setting.

Studies by Adams[85], Bain[88], Battaglia and Spector[89], Gewirtz[94], Jeenah[95] and Schemmer[104]all recruited patients in their first episode of psychosis. Half of the study population recruited by Larson[96] had a duration of illness of less than six months. It is therefore likely that the patient populations in these studies are a better representation of the patients seen in practice for the review question.

The studies that indicated that patients with neurological symptoms and signs were largely, or completely, excluded (Adams[85], Agzarian[86], Ananth 1992[87] and 1993[57], Bain[88], Battaglia and Spector[89], Evans[93], Jeenah[95] and McClellan[100]) might be expected to better represent the patients likely to be seen in practice. It was not clear whether the psychotic patients in the studies by Gewirtz[94], and Schemmer[104] had any neurological symptoms and signs at the start of the study.

The studies with the patient population most closely representing the patients in practice are therefore those of Adams[85], Bain[88], Battaglia and Spector[89], and Jeenah[95]. The remaining studies either recruited general psychiatric patients, with a proportion of these being psychotic and/or included patients with neurological abnormalities.

The population in the study by Adams[85] was restricted to adolescents, and therefore would represent only this population in practice. The populations recruited by the studies by Bain[88] and Battaglia and Spector[89] were largely under 30 years of age so cannot reliably represent an older population in practice. The study by Jeenah[95] recruited patients that were generally older and again using this study to represent patients in practice must take this into consideration.

Internal validity

In all cases, except for the study by Adams[85], it was not clear whether the results of other assessments (usually routine assessments reflecting clinical practice) were interpreted without knowledge of the scan results. It was clear that the scan results

were used in combination with the results of other assessments in making a diagnosis in the Adams[85] study.

Descriptions of study population selection criteria were generally poor, but with some studies giving a little more information than others. Of the studies most likely to represent the patient population in practice, those by Adams[85], Battaglia and Spector[89] and Jeenah[95] provided reasonable details of inclusion and exclusion criteria. The period between the CT scan and other assessments being carried out was not well reported. Studies by Adams[85], Bain[88] and Battaglia and Spector[89] were among those giving an indication of the timing of when assessments were carried out. In all studies, except that by Ananth 1992[87], it was intended that the whole study population receive the scan. The Ananth 1992[87] study only scanned a random selection of the study population. Information on whether all patients received the same CT scan was not given by any studies except for those by Agzarian[86] and Vavilov[107], who reported 4% and 1% of patients respectively, received a contrast scan. The imaging process was well reported by Vavilov[107]. Details of other assessments were not reported by any CT studies.

Studies by Ananth 1993[57], Emsley[92] and Jeenah[95] all appear to have interpreted the scan results without knowledge of the other assessments. The study by Gewirtz[94] stated that a neuroradiologist read the scan blind to the original scan report. It was not clear whether the results of other assessments were available when interpreting the scan. In all other studies except that by Roberts and Lishman[103] it was not clear whether the scan results had been interpreted without knowledge of the results of other assessments. The Roberts and Lishman[103]study had results of other assessments available when interpreting the scan results.

In most cases it was not possible to tell whether the same clinical results were available when test results were interpreted as would be available in practice. The study by Adams[85], however, appeared to represent a similar availability of results as expected in clinical practice.

Uninterpretable or intermediate test results were reported for the studies by Adams[85], Agzarian[86], Jeenah[95], Larson[96], Roberts and Lishman[103] and Schemmer[104] . In all these cases, actual pathology for the FEP or psychosis patients was not reported. The final modified QUADAS question is whether study withdrawals were explained. In twelve studies (Agzarian[86], Ananth 1993[57], Bain[88], Battaglia and Spector[89], Colohan[91], Emsley[92], Jeenah[95], Larson[96], McClellan[100], Roberts and Lishman[103], Schemmer[104] and Vavilov[107]) withdrawals were not reported. In the studies by Adams[85], Ananth 1992[87], and Evans[93], withdrawals were reported but no reasons given. Gewirtz[94] was the only study to report numbers withdrawn and reasons.

Additional quality criteria were collected and tabulated for the CT studies (see Table 46 on page 135). The number of patients who did not receive a scan was only reported by Adams[85], Ananth 1992[87] and Evans[93]. Reasons for non-scans were not stated by any of these three studies. The remaining studies did not give any indication of numbers of patients not receiving a scan. Recruitment was carried out on a consecutive basis by six studies (Adams[85], Agzarian[86], Emsley[92], Evans[93], Gewirtz[94], and Larson[96]). In the remaining studies it was not clear how recruitment had been conducted.

Clinical variables were collected prospectively in the studies by Adams[85], Battaglia and Spector[89], and Jeenah[95]. The studies by Ananth 1992[87] and 1993[57], and Gewirtz[94] relied on retrospective diagnostic data with a prospectively conducted scan (Ananth 1992[87] and 1993[57]) or prospective re-evaluation of scan results (Gewirtz[94]). The remaining CT studies appeared to have relied on retrospective data alone. The reporting of how and when clinical variables were collected was poor.

The person performing clinical evaluation and scan analysis was given in the study text in most of the CT studies. This was not clearly reported in the studies by Agzarian[86], Larson[96], McClellan[100], Schemmer[104] and Vavilov[107].

To summarise, based on the quality criteria above, the studies by Adams[85], Battaglia and Spector[89] and Jeenah[95] are more likely to provide the reliable information relevant to this review question because of external validity. However, it should be remembered that all included studies for this review are of a before and after type design and are very poorly reported so have low internal validity.

b) MRI studies

External validity

The results of the modified QUADAS criteria for the MRI studies are shown in Table 47 on page 137. The studies by Borgwardt[90] and Lubman[99] both recruited patients with a first episode of psychosis. There was very little information on the psychotic patients recruited by the Wahlund[105] study. The study population in the Lesser 1991[97] study had a diagnosis of late onset major depression with psychosis. Although these patients were likely to be in the early stage of the illness (mean duration of illness was 18 months), these patients are likely to differ from patients in the first episode of psychosis with no prior diagnosis or treatment.

Although not well reported, all four MRI studies gave some indication that patients did not have neurological symptoms and signs. As noted in the section for CT studies, it was assumed that patients seen in practice were not likely to have neurological abnormalities on examination. Three studies recruited adult patients (Borgwardt[90], Lesser 1991[97], Lubman[99]). The fourth study (Wahlund[105]) did not give details of the patient age range or mean.

The patients recruited in the study by Lubman[99] had already been involved in collaborative research studies. Details were not provided making it difficult to ascertain how the study population might differ from those likely to be seen in practice. Overall it is likely that the studies with the population most representative of those likely to be seen in practice are those by Borgwardt[90] and Lubman[99].

Internal validity

Descriptions of study population selection criteria were adequate for all MRI studies except that by Wahlund[105]. The period between the MRI scan and other assessments being carried out was not clearly stated in the studies by Lubman[99] and Wahlund[105]. It was possible to identify the timing of assessments in the studies by Borgwardt[90] and Lesser 1991[97]. In all studies it was intended that the whole study population receive the scan.

Whether all patients received the same MRI scan regardless of other assessments was not stated by any of the four studies. The imaging process was well reported in the studies by Borgwardt[90], Lesser 1991[97] and Lubman[99] although these studies gave no details of the other assessments that were performed. Wahlund[105] did not give details of either the imaging process or other assessments.

In all cases it was not clear whether the results of other assessments were interpreted without knowledge of the scan results. The scan results were interpreted without knowledge of the patient's diagnosis in the studies by Borgwardt[90], Lesser 1991[97] and Lubman[99]. It was not clear how scan results had been interpreted by the Wahlund[105] study. It was not possible to tell whether the same clinical results were available when test results were interpreted as would be available in practice in any of the four MRI studies.

Uninterpretable or intermediate test results were reported in the study by Wahlund[105] since actual pathology was not clearly stated. The study by Borgwardt[90] mentioned that six patients did not receive a scan, but did not give reasons. The other three studies (Lesser 1991[97], Lubman[99] and Wahlund[105]) did not report numbers of withdrawals.

The additional quality criteria for the MRI studies are shown in Table 48 on page 137. The only study to comment on the number of patients who did not receive a scan was that by Borgwardt[90], although reasons were not given. It was not clear whether patients had been recruited consecutively in the studies by Borgwardt[90], Lubman[99] and Wahlund[105]. Lesser 1991[97] did not recruit patients consecutively. Clinical variables were collected prospectively by Borgwardt[90] and Lesser 1991[97], and possibly by Lubman[99]. The study by Wahlund[105] appeared to be using retrospective data. Neuroradiologists either read the scans, or were involved alongside a psychiatrist in all four studies.

In summary, the study by Borgwardt[90] is likely to provide better quality evidence of relevance to this review question, but interpretation of the results should be treated with caution due to the very small sample size.

c) CT/ MRI studies

External validity

Table 49 on page 138 shows the modified QUADAS criteria for the three studies using MRI or CT scanning. The study by McKay[101] was the only one to recruit patients in their first episode of psychosis. The study by Lesser 1992[98] recruited patients with psychotic disorder NOS over age 45, some of whom were in the early stage of the illness (under 2 years duration). The study by Miller[102] also recruited patients over age 45, but with late-onset psychosis. The study populations in the Lesser 1992[98] and Miller[102] studies are highly selected groups of patients, which may differ significantly from those patients seen in clinical practice for this review question.

Both the Lesser 1992[98] and Miller[102] studies gave some indication that patients did not have neurological symptoms and signs. Overall it is likely that the study by McKay[101] recruited the population most useful to the review question, despite the lack of information on the presence of neurological symptoms and signs.

Internal validity

Descriptions of study population selection criteria were adequate for all three CT/MRI studies. The period between the CT/ MRI scan and other assessments being carried out was not clearly stated by the Lesser 1992[98] or McKay studies.[101] Only 12 out of the 16 study patients received a scan in the Lesser 1992[98] study, and only 52 out of 117 in the McKay[101] study. It was not clear how these patients had been selected.

For all three studies some patients received an MRI scan, while others received a CT scan. MRI scanning differs from CT scanning in several ways, making it difficult to interpret the group level results. Details of other assessments were not reported by any of the three studies. The imaging process was well reported in the studies by Lesser 1992[98] and Miller[102], but no details were given by McKay. [101]

In all three studies it was not clear whether the results of other assessments were interpreted without knowledge of the scan results. The scan results were interpreted without knowledge of the patient's diagnosis in the studies by Lesser 1992[98] and Miller. [102] It was not clear how scan results had been interpreted by the McKay study.[101] It was not possible to tell whether the same clinical results were available when test results were interpreted as would be available in practice in any of the three studies.

Uninterpretable or intermediate test results were reported in the study by McKay[101] since actual pathology was not clearly stated. The study by Miller[102] reported that one patient was too large for either MRI or CT scanning. The study by Lesser[98] stated that four patients did not receive a scan, but did not give reasons. The McKay[101] study did not report withdrawals.

Table 50 on page 138 reports results of the additional quality criteria. The study by Lesser 1992[98] recruited the study population consecutively. It was not clear how patients had been recruited by the studies by McKay[101] and Miller. [102] The studies by Lesser 1992[98] and Miller[102] both collected clinical variables prospectively and had scans read by neuroradiologists who were blind to subject diagnosis. The study by McKay[101] relied entirely on retrospective data and did not report who performed clinical evaluation or image analysis.

Overall, the studies by Lesser 1992[98] and Miller[102] were of higher quality but the study populations are not likely to be representative of those patients seen in practice.

d) Treatment refractory psychosis

The modified QUADAS criteria and additional quality assessment are reported in Table 51 and Table 52 from page 139 onwards. The study population recruited by Cunningham-Owens[106] were chronic schizophrenics who did not appear to be responding to treatment. This was a highly selected group of patients and the results should only be generalisable to treatment refractory patients. However, the selection criteria were not well reported by this study. Brief details of scanning were given, but in most cases the modified QUADAS criteria were not clearly reported. The numbers of patients withdrawn from the study, or not receiving a scan were not stated, recruitment was not consecutive and it was not entirely clear whether clinical variables had been collected prospectively. Overall, this study was of very poor quality.

e) Misidentification syndromes

The modified QUADAS quality tool was not used as it did not apply to this review of case reports. The number of patients with misidentification syndromes seen in practice is small and it is not clear whether the cases collected in the review by Forstl[108] would be representative of those seen in practice. Data from case reports is generally of low quality and the reports are likely to be specially selected so unrepresentative of a sample of patients with misidentification syndromes.

5.2.3.4 Outcomes

a) CT studies

Table 16 on page 61 shows the results from the CT studies. The psychiatric diagnoses show the numbers and types of diagnosis for each study. Where possible the original, admission or study entry diagnosis was extracted. Unless indicated in the text, we assumed psychiatric diagnoses to be non-psychotic. There was considerable variation between studies in the classification of diagnoses as psychotic or not. It was not clear whether this was due to different criteria used to make diagnoses (eg ICD-10 or DSM-IV-R), difference in the personnel making the diagnosis (e.g. ward physician or psychiatrist) or due to a genuine difference in presentation. This difficulty arose because some diagnoses can be psychotic or non-psychotic and often the text was not explicit.

Generally, depression and bipolar disorders were considered to be non-psychotic but the study by Adams[85] included mania and depression in among the first episode psychosis diagnoses, while that by Agzarian[86] excluded depression and bipolar affective disorder. The studies by Agzarian[86], Jeenah[95] and Schemmer[104] only state the number of patients that were psychotic but give no further breakdown of disorders within this. Some studies included the numbers diagnosed with other disorders such as dementia, personality disorder, anxiety disorder, delirium and conversion disorder, which would not be expected to be psychotic. Other studies did not provide this level of detail.

The proportion of patients with scans identifying abnormalities ranged from 0 to 58%. The studies by Adams[85], Bain[88], Battaglia and Spector[89], Gewirtz[94], McClellan[100] and Vavilov[107] all had 0 to 12% of patients with an abnormal scan. The studies by Ananth 1993[57], Colohan[91], Emsley[92] and Jeenah[95] reported 19 to 33% of patients with abnormalities. There were between 41% and 58% of patients with an abnormal scan in the studies by Roberts and Lishman[103] and Evans[93], respectively. The number of patients with scans identifying abnormalities was not reported for psychotic patients in the studies by Agzarian[86], Ananth 1992[87] and Larson[96]. The text was not clear about the number of abnormalities in psychotic patients in the study by Schemmer[104] .

Incidental findings, i.e. pathology that would not influence patient care, were also extracted from the included studies and are shown in Table 16. Atrophy, calcification, old infarctions, some cysts, cavum septum pellucidum and other morphological variants were all considered incidental unless otherwise indicated in the text.

Pathology identified by scanning that would influence patient care and that was not suspected based on the other assessments included subdural haematoma or effusion, hamartoma, cavernoma, tumours, and infarctions, unless otherwise stated in the text

that no action was taken. This did not include pathology that would influence patient care but could be identified by medical history or a physical/ neurological exam. Where it was not clear from the text, a decision was made based on clinical judgement (Personal communication, Professor F Oyebode, QE Psychiatric Hospital, May 2007). An abnormality that might, or might not, influence patient care was included with the 'pathology influencing patient care' data for the purposes of results presentation in this review. Studies by Adams[85] and Roberts and Lishman[103] did not report the number and details of pathology. The study by Agzarian[86] did not provide details for the psychotic patients. The studies by Ananth 1992[87], Bain[88], Battaglia and Spector[89], Colohan[91], Emsley[92], Evans[93], Larson[96] and McClellan[100] all had no patients with pathology that would influence patient care and that was not suspected based on the other assessments. The study by Ananth 1993[57] had one patient (3.7%), and that by Gewirtz[94] had five patients (3.0%), with pathology that would influence care and was not suspected from other assessments. The study by Jeenah[95] reported that for FEP and non-FEP psychotic patients combined there were six patients (10.9%) with pathology that would influence patient care and that was not suspected based on the other assessments. Data was not given for FEP patients alone. There were 13 (1.8%) of the Vavilov[107] study patients that had pathology that would influence patient care but it was not clear whether other assessments had played a role in their identification. The text was not clear for the study by Schemmer[104] .

Whether a scan result was likely to affect clinical treatment was either reported in the study text or determined using clinical judgement (Personal communication, Professor F Oyebode, QE Psychiatric Hospital, May 2007). The percentage of patients with a scan affecting clinical treatment was zero for the studies by Adams[85], Ananth 1992[87], Battaglia and Spector[89], Emsley[92], Evans[93] and McClellan[100]. In the study by Bain[88] 0.8% of patients had a scan affecting clinical treatment, 1.2% in the study by Gewirtz[94] and 1.8% in the study by Vavilov[107]. The studies by Ananth 1993[57], Jeenah[95] (FEP and non-FEP psychotic patients combined), and Colohan[91] all reported much higher percentages of patients: 7.4%, 10.9% and 13.8% respectively. The studies by Agzarian[86], Larson[96], Roberts and Lishman[103]and Schemmer[104] either did not report this outcome or the text was not clear.

There were no patients with a change in diagnosis due to the scan in the studies by Adams[85], Ananth 1992[87], Colohan[91], Evans[93], McClellan[100] and Schemmer[104] . 3.7% and 0.1% of patients had a change in diagnosis due to the scan in the Ananth 1993[57] and Vavilov[107] studies respectively. Change in diagnosis due to the scan was not reported or was not clear from the text for eight studies (Agzarian[86], Bain[88], Battaglia and Spector[89], Emsley[92], Gewirtz[94], Jeenah[95], Larson[96] and Roberts and Lishman[103]).

Overall, there was very little or no pathology reported by nine studies that would influence patient care that was not suspected from other assessments. Three further studies reported 3%, 4% and 11% of patients with pathology not suspected from other assessments that would influence patient care. The percentage of patients with a scan affecting clinical treatment was zero or very low in nine studies. Three studies showed higher percentages of patients with a scan affecting treatment. There were no changes in diagnosis due to the scan in six studies. There were between 0.1% and 3.7% of patients that had a change in diagnosis due to the scan in two studies.

b) MRI studies

Table 17 on page 69 shows the results from the MRI studies. A breakdown of psychiatric diagnoses was not reported by any of the four studies except for that by Lesser 1991[97], whose psychotic patient subgroup was composed entirely of patients with major depression with psychosis.

The proportion of patients with scans identifying abnormalities was reported by all four studies and ranged from 3.5% to 64.3%. The studies by Borgwardt[90], Lubman[99] and Lesser 1991[97] gave full details of incidental findings. The reporting in the study by Wahlund[105] was poor. Three studies (Borgwardt[90], Lesser 1991[97] and Lubman[99]) provided details of pathology identified by scanning, that would influence patient care and that was not suspected based on the other assessments. The study by Borgwardt[90] had one patient (3.3%), that by Lesser 1991[97] three patients (21.4%) and that by Lubman[99] 13 patients (8.6%) with pathology influencing care and not suspected from other assessments. The percentage of patients with a scan affecting clinical treatment was 3.3%, 8.6% and 21.4% in the studies by Borgwardt[90], Lubman[99] and Lesser 1991[97], respectively. Again, there was not enough information provided in the study by Wahlund.[105] The Borgwardt[90] study reported that no patients had a change in diagnosis due to the scan and there was only one patient with a change in diagnosis due to the scan in the Lubman[99] (0.7%) study. There were 21.4% of patients that had a change in diagnosis due to the scan in the study by Lesser 1991.[97]

Overall, three MRI studies provided information of value to the review question (Borgwardt[90], Lesser 1991[97], Lubman[99]). Pathology that would influence patient care that was not suspected from other assessments and the percentage of patients with a scan affecting clinical treatment was seen in all three studies in approximately 3%, 9% and 21% of patients. A similar range was seen for the percentage of patients with a change in diagnosis due to the scan (0% to 21.4%).

c) CT/ MRI studies

Table 18 on page 71 shows the results from the studies employing a combination of CT or MRI. Psychiatric diagnoses were reported by all three studies. All patients in the Lesser 1992[98] study had a diagnosis of psychotic disorder NOS. The study by McKay[101] gave full details of the breakdown of FEP patient diagnoses but seven patients did not have a diagnosis. The study by Miller[102] gave details of the diagnoses for the psychotic subgroup.

The proportion of patients with scans identifying abnormalities was reported as 7.7% (McKay[101]), 42% (Miller[102]) and 62.5% (Lesser 1992[98] for patients with illness duration 2 years or less). Incidental findings were reported in the studies by Lesser 1992[98] and Miller[102], but full details were not given in that by McKay.[101]

There were no patients with pathology influencing patient care and not suspected from other assessments in the study by McKay.[101] The studies by Lesser 1992[98] and Miller[102] reported 8.3% and 4.2% of patients respectively. The percentage of patients with a scan affecting clinical treatment was 12.5% and 4.2% for the studies by Lesser 1992[98] and Miller[102] respectively. In the study by McKay[101], it was not clear how many patients had a scan affecting clinical treatment. There were only two patients with a change in diagnosis due to the scan in the Miller[102] study (8.3%). No patients had a change in diagnosis due to the scan in the McKay[101] study and this was not reported in the Lesser 1992 study.[98] Overall, percentages of patients with a scan

affecting clinical treatment, with pathology that would influence patient care that was not suspected from other assessments, or with a change in diagnosis due to the scan were low.

d) Treatment refractory psychosis

Table 19 on page 73 shows the outcomes for the study by Cunningham-Owens[106] in chronic schizophrenics. There were 8.8% of patients that had a scan identifying an abnormality. 2.2% of patients had pathology that would influence patient care and that was not suspected from other assessments. These same patients had a scan affecting clinical treatment but the percentage of patients with a change in diagnosis due to the scan was not reported.

e) Misidentification syndromes

The number and type of misidentification syndromes for all cases reviewed by Forstl[108] are shown in Table 20 on page 74. Within these syndromes, the most common diagnosis was schizophrenia (127 cases) and affective disorder (29 cases). No other information was given. A breakdown of syndromes and diagnoses for the 80 cases who received a CT scan was not given. The number of patients with a scan identifying an abnormality was not clearly reported. 39 patients were shown to have cortical atrophy, 9 had a brain infarction and 20 had focal lesions. It was not clear whether some patients may have had an infarction in addition to cortical atrophy. 85% of patients were shown to have cerebral pathology if each patient was counted only once. Incidental pathology of cortical atrophy was seen in 39 patients and old infarctions in 9 patients. Pathology that would influence patient care was seen in 20 patients. It was not clear from the text whether other assessments had resulted in suspicion of a lesion. There were 25% of patients that had a scan affecting treatment. The percentage of patients with a change in diagnosis due to the scan was not reported.

Table 16. Outcomes for CT scan studies in psychosis patients

Reference	**No. patients with FEP/** psychosis **+scan**	**Diagnoses considered psychotic (n) *time point***	**% of patients with scans identifying abnormalities (no. patients)**	**Pathology that would influence patient care and that was not suspected based on history and/or physical exam (no. patients)**	**Incidental pathology (no. patients)**	**% of patients with scan affecting clinical treatment (no. patients)**	**% of patients with change in diagnosis due to scan (no. patients)**
Adams et al., 1996[85] (Canada)	**98 FEP**	*At admission* Schizophrenia (28) Mania (27) Depression (17) Psychosis NOS (12) Schizoaffective (11) Schizophreniform (8) Brief psychotic episode (2) Deferred (2) Other (3) *	12.2% (12)	Details of pathology NR	Details of pathology NR	0	0
Agzarian et al., 2006[86] (Australia)	241 psychotic	*At study entry* Psychosis (241)	NR for psychosis patients	NR for psychosis patients	NR for psychosis patients All abnormalities shown on CT not related to psychiatric condition.	Unclear	Unclear

Reference	**No. patients with FEP/** psychosis **+scan**	**Diagnoses considered psychotic (n) *time point***	**% of patients with scans identifying abnormalities (no. patients)**	**Pathology that would influence patient care and that was not suspected based on history and/or physical exam (no. patients)**	**Incidental pathology (no. patients)**	**% of patients with scan affecting clinical treatment (no. patients)**	**% of patients with change in diagnosis due to scan (no. patients)**
Ananth etal., 1992[87] (USA)	37 mostly psychotic	*At study entry*: Schizophrenia (38) Bipolar disorder (17) Atypical psychosis (12) Organic brain syndrome (4) Adjustment disorder (2) Paranoid disorder (1) Personality disorder (1)	NR	0	NR	0	0
Ananth etal., 1993[57] (USA)	27 psychotic	*At study entry*: Schizophrenia (21) Atypical psychosis (3) Organic delusional syndrome (1) Mixed organic syndrome (2)	33.0% (9)	3.7% Attenuation of post-parietal and occipital area (1) **	Atrophy (4) Asymmetry of Sylvian fissues (1) Prominent sulci (1) Right frontal area of density (1)	7.4% (2)	3.7% Schizophrenia changed to organic mental disorder (1) **

Reference	**No. patients with FEP/** psychosis **+scan**	**Diagnoses considered psychotic (n) *time point***	**% of patients with scans identifying abnormalities (no. patients)**	**Pathology that would influence patient care and that was not suspected based on history and/or physical exam (no. patients)**	**Incidental pathology (no. patients)**	**% of patients with scan affecting clinical treatment (no. patients)**	**% of patients with change in diagnosis due to scan (no. patients)**
Bain et al., 1998[88] (USA)	**127 FEP**	*At discharge* Schizophrenia/ schizophreniform (41) Bipolar (21) Major depression (15) Psychosis NOS (13) Schizoaffective (8) Delusional (6) Brief reactive psychosis (4) Other (19)	0	0 2 had neurological abnormality on admission	Calcification (1) Arachnoid cyst (2) Suspected pineal tumour (1) but normal on MRI All classed as incidental by text.	0.8% (1)	NR

Reference	**No. patients with FEP/** psychosis **+scan**	**Diagnoses considered psychotic (n) *time point***	**% of patients with scans identifying abnormalities (no. patients)**	**Pathology that would influence patient care and that was not suspected based on history and/or physical exam (no. patients)**	**Incidental pathology (no. patients)**	**% of patients with scan affecting clinical treatment (no. patients)**	**% of patients with change in diagnosis due to scan (no. patients)**
Battaglia & Spector, 1988[89] (USA)	**45 FEP**	*At discharge* Schizophreniform (20) Atypical psychosis (14) Brief reactive psychosis (4) Schizoaffective (2) Organic brain syndrome (2) Borderline personality disorder (1) Bipolar (1) Major depression with psychotic features (1)	6.7% (3)	0	Mild cortical atrophy (1) Central atrophy and possible infarct (1) Possible basal ganglia infarct (1)	0	NR

Reference	**No. patients with FEP/** psychosis **+scan**	**Diagnoses considered psychotic (n) *time point***	**% of patients with scans identifying abnormalities (no. patients)**	**Pathology that would influence patient care and that was not suspected based on history and/or physical exam (no. patients)**	**Incidental pathology (no. patients)**	**% of patients with scan affecting clinical treatment (no. patients)**	**% of patients with change in diagnosis due to scan (no. patients)**
Colohan et al., 1989[91] (Ireland)	29 psychotic	*At study entry* Organic psychotic condition (11) Schizophrenia (10) Affective psychosis (3) Paranoid state (2) Neurosyphilis (1) Schizoaffective (1) Korsakoff's psychosis (1)	31% (9 plus 2 inconclusive)	0	Old infarction secondary to cerebral atrophy (1) Cerebral atophy (2) Inconclusive (2).	13.8% (4) Brain tumour (3), brain tumour post-hypophysectomy (1)	0
Emsley et al., 1986[92] (South Africa)	43 psychotic	*At admission* Schizophrenia (9) Affective disorder (17) Other psychosis (including depression) (15) Hallucinosis (2)	18.6% (8)	0	Calcification (4) (1 with atrophy) Infarct (3) (2 with atrophy) Porencephalic cyst and atrophy (1)	0	NR ?6 or less (2 had neurological signs)
Evans et al., 1982[93] (UK)	19(+1 with neurological signs) psychotic	*At study entry* Schizophrenia (including atypical, paranoid, non-affective) (19)	57.8% (11)	0	Atrophy (11)	0	0

Reference	**No. patients with FEP/** psychosis **+scan**	**Diagnoses considered psychotic (n) *time point***	**% of patients with scans identifying abnormalities (no. patients)**	**Pathology that would influence patient care and that was not suspected based on history and/or physical exam (no. patients)**	**Incidental pathology (no. patients)**	**% of patients with scan affecting clinical treatment (no. patients)**	**% of patients with change in diagnosis due to scan (no. patients)**
Gewirtz et al., 1994 [94] (USA)	**168 FEP**	*At admission* Schizophrenia (82) Schizoaffective (22) Bipolar with psychosis (23) Depression with psychosis (16) Schizophreniform (11) Psychosis NOS (9) Delusional disorder (3) Brief reactive psychosis (2)	6.0% (10)	3.0% Arachnoid cyst (2), Arachnoid cyst with mild cortical atrophy (1), Venous angioma (1), Colloid cyst with obstruction of foramen of Munro (1)	Old infarction and diffuse cortical atrophy (1) Old infarction and cavum vellum interpositum (1) Diffuse ischaemic changes and mild cortical atrophy (2) Cavum septum pellucidum (1)	1.2% "2 patients had implications for patient management."	NR
Jeenah et al., 2007 [95] (South Africa)	**47 FEP** 55 FEP+non-FEP psychotic	NR	FEP 31.9% (15) FEP+psychosis 36.4% (20)	FEP NR FEP+psychosis 10.9% Mass lesion (6) (pituitary adenoma, TB granuloma, neurocysticercosis)	FEP NR FEP+psychosis Trauma Blow out fracture of orbits (1) Old infarct with/ without calcification (6) Global cerebral atrophy (7)	FEP NR FEP+psychosis 10.9% (6)	NR

Reference	**No. patients with FEP/** psychosis **+scan**	**Diagnoses considered psychotic (n) *time point***	**% of patients with scans identifying abnormalities (no. patients)**	**Pathology that would influence patient care and that was not suspected based on history and/or physical exam (no. patients)**	**Incidental pathology (no. patients)**	**% of patients with scan affecting clinical treatment (no. patients)**	**% of patients with change in diagnosis due to scan (no. patients)**
Larson et al., 1981[96] (USA)	39 psychotic	*At study entry* Schizophrenia (19) Unspecified psychosis (20)	NR	0	NR	NR	NR
McClellan et al., 1988[100] (USA)	142 psychotic	*At admission* Schizophrenia (103) Paranoid disorders (39)	7.7% (11)	0	Atrophy (8) Other (3) (could be non-specific basal ganglia calcification, old lacunar infarction or osteoma)	0	0
Roberts & Lishman, 1984[103] (UK)	244 psychotic	*At study entry* Schizophrenia (57) Affective psychosis (59) Other psychosis (13) Organic psychosis (115)	40.6% (99)	NR	NR	NR	NR
Schemmer et al., 1999 [104] (Canada)	NR	NR	Unclear	Unclear	Including cortical atrophy, ventriculomegaly, asymmetric lateral ventricles (7)	Unclear	0

Reference	**No. patients with FEP/** psychosis **+scan**	**Diagnoses considered psychotic (n) *time point***	**% of patients with scans identifying abnormalities (no. patients)**	**Pathology that would influence patient care and that was not suspected based on history and/or physical exam (no. patients)**	**Incidental pathology (no. patients)**	**% of patients with scan affecting clinical treatment (no. patients)**	**% of patients with change in diagnosis due to scan (no. patients)**
Vavilov et al., 1993[107] (Russia)	721 psychotic	Schizophrenia (721)	8% (58)	1.8% Meningioma (4) Glioma (1) Metastases (2) Hypophyseal tumour (4) Arachnoid cyst/porencephalic cyst (2) It was not clear how many were not suspected on the basis of other assessments.	Genetic malformations (3) Secondary dysplasia (4) Multiple sclerosis (1) Post traumatic changes (3) Vascular damage (34)	1.8% (13)	0.1% Schizophrenia changed to multiple sclerosis (1)
Incidental pathology: pathology that would not influence patient care (management and/or treatment) with/ without suspicion prior to scan *adds to 110 ** 1 patient with mild bifrontal atrophy had change in care due to scan plus history							

Table 17. Outcomes for MRI scan studies in psychosis patients

Reference	**No. patients with FEP/** psychosis **+scan**	**Diagnoses considered psychotic (n)** ***time point***	**% of patients with scans identifying abnormalities (no. patients)**	**Pathology that would influence patient care and that was not suspected based on history and/or physical exam (no. patients)**	**Incidental pathology (no. patients)**	**% of patients with scan affecting clinical treatment (no. patients)**	**% of patients with change in diagnosis due to scan (no. patients)**
Borgwardt et al., 2006[90] (Switzerland)	**30 FEP**	NR	40.0% (12)	3.3% Subdural effusion (1)	Single hyperintense lesion (2) Neuroepithelial cyst (3) Arachnoid cyst (1) Cavum septum pellucidum (1) All classed as incidental by text. Generalised atrophy (3) Hamartoma (1) Frontal atrophy (2)	3.3% (1)	0
Lesser et al., 1991[97] (USA)	14 psychotic	DSM-III-R major depression with psychotic features (14)	64.3% (9)	21.4% Mass (3) (arteriovenous malformation, arachnoid or cysticercal cyst, pituitary adenoma)	White matter lesions (3) Infarct (2)	21.4% (3)	21.4% Post traumatic injury changed to encephalomacia (1) Post traumatic injury changedto dementia (2) (Pick's Disease, vascular)

Reference	**No. patients with FEP/** psychosis **+scan**	**Diagnoses considered psychotic (n)** ***time point***	**% of patients with scans identifying abnormalities (no. patients)**	**Pathology that would influence patient care and that was not suspected based on history and/or physical exam (no. patients)**	**Incidental pathology (no. patients)**	**% of patients with scan affecting clinical treatment (no. patients)**	**% of patients with change in diagnosis due to scan (no. patients)**
Lubman et al., 2002[99] (Australia)	**152 FEP**	NR	22.4% (34)	8.6% Urgent referral: possible Huntington's disease (1) Vascular lesion (sulcal AVM) (1) Arachnoid cyst (1) Routine referral: Pineal cyst (3) Possible demyelinating disease (2) Cortical displasia? (1) Vascular infarction (1) Minimal communicating hydrocephalus (1) Periventricular leukomalacia (1) Pituitary enlargement (1)	No referral: Hippocampal asymmetry (4) WMH (5) Cerebellar ectopia (1) Prominent ventricles/ sulci for age (7) Craniosynostosis (1) Chari I malformation (1) Cavum septum pellucidum (1) Cavum velum interpositum (1)	8.6% (13) "needing subsequent referral i.e. of clinical importance affecting prognosis, diagnosis or management"	0.7% Demyelination to multiple sclerosis (1)
Wahlund et al., 1992[105] (Sweden)	170	NR	6 (3.5%)	Unclear	Enlarged ventricles or infarctions (6)	Unclear	NR

Table 18. Outcomes for the studies using CT/ MRIscan in psychosis patients

Reference	**No. patients with FEP/** psychosis **+scan**	**Diagnoses considered psychotic (n) *time point***	**% of patients with scans identifying abnormalities (no. patients)**	**Pathology that would influence patient care and that was not suspected based on history and/or physical exam (no. patients)**	**Incidental pathology (no. patients)**	**% of patients with scan affecting clinical treatment**	**% of patients with change in diagnosis due to scan (no. patients)**
Lesser et al., 1992[98] (USA)	**8 FEP** 12 FEP+psychotic	*At study entry* DSM-III-R for psychotic disorder NOS (12) Illness ≤2y (8)	62.5% (5) Illness ≤2y 75% (9)	8.3% Arachnoid cyst (1) (Illness ≤2y)	Atrophy (4) (1 with infarct) (1 Illness ≤2y) White matter lesion (4) (3 Illness ≤2y)	8.3% (1) 12.5%(1)(Illness ≤2y)	NR
McKay et al., 2006[101] (Australia)	**52 FEP** **Proportions of CT: MRI NR**	*At time of prescribing first antipsychotic medication* FEP (43%) Schizophrenia (16%) Drug-induced psychosis (12%) Affective psychosis (13% made up of bipolar 8%, psychotic depression 5%) Brief reactive psychosis (2%) No diagnosis (14%)	7.7% (4)	0	Small lesion (1) Referred for MRI (2) MRI normal (1)	0	0

Reference	**No. patients with FEP/** psychosis **+scan**	**Diagnoses considered psychotic (n) *time point***	**% of patients with scans identifying abnormalities (no. patients)**	**Pathology that would influence patient care and that was not suspected based on history and/or physical exam (no. patients)**	**Incidental pathology (no. patients)**	**% of patients with scan affecting clinical treatment**	**% of patients with change in diagnosis due to scan (no. patients)**
Miller et al., 1991[102] (USA)	24 psychotic	*At study entry* Schizophrenic disorder (10) Delusional disorder (7) Schizophreniform disorder (2) Psychosis NOS (5)	42% (10)	4.2% Tumour (1)	Vascular lesions (cortical or subcortical WM infarctions) (6) Post traumatic brain injury (1)	4.2% (1)	8.3% Early primary degenerative dementia (DSM-III-R) with psychosis as presenting clinical feature (2)

Table 19. Outcomes for treatment refractory psychosis

Reference	**No. patients with FEP/** psychosis **+scan**	**Diagnoses considered psychotic (n)** ***time point***	**% of patients with scans identifying abnormalities (no. patients)**	**Pathology that would influence patient care and that was not suspected based on history and/or physical exam (no. patients)**	**Incidental pathology (no. patients)**	**% of patients with scan affecting clinical treatment**	**% of patients with change in diagnosis due to scan (no. patients)**
Cunningham-Owens et al., 1980[106] (UK)	136	Chronic schizophrenia (136)	8.8% (12)	2.2% Meningioma (1) Subdural haematoma (2)	Cerebral infarction (7) Large pineal body (1) Porencephalic cyst (1)	2.2% (3)	NR

Table 20. Outcomes for misidentification syndromes

Reference	**No. patients with FEP/** psychosis **+scan**	**Diagnoses considered psychotic (n)** ***time point***	**% of patients with scans identifying abnormalities (no. patients)**	**Pathology that would influence patient care and that was not suspected based on history and/or physical exam (no. patients)**	**Incidental pathology (no. patients)**	**% of patients with scan affecting clinical treatment**	**% of patients with change in diagnosis due to scan (no. patients)**
Forstl et al., 1991[108] (UK)	80 case reports involving psychosis + scan	*NR* Capgras (174) Fregoli (18) Intermetamorphosis (11) Reduplicative paramnesia (17) Other forms of mistaken identity (40)	?85%* ?68/80 *	25% Focal lesions (infarcts/ tumours) (20)	Cortical atrophy (39) Brain infarction (9)	25% (20)	NR
* Not clear whether some patients had more than one abnormality and were therefore counted more than once.							

5.2.3.5 Sub-group outcomes

Two studies reported a breakdown of abnormalities by age and/ or gender. The study by Jeenah[95] reported data for FEP and non-FEP patients combined (see Table 21). Also in this study 9/20 patients with an abnormal scan were male and 11 were female. The study by Gewirtz[94] reported the frequency of cortical atrophy by age (not reported here because cortical atrophy is not considered to affect clinical management of the patient). The study by Vavilov[107] reported the numbers of tumours, cerebral pathology and vascular damage by age group (see Table 22).

Table 21. Subgroup results – abnormal scan by age group

Age group (y)	Number of patients with abnormal scan
18-30	6/25 (24%)
31-45	1/12 (8.3%)
46-60	6/10 (60%)
Over 60	7/8 (87.5%)

Table 22. Subgroup results – pathology by age group

Age group (y) (number in study)	Tumours	Cerebral pathology	Vascular damage
10 or less n=37	3 (8.1%)	3 (8.1%)	0 (0%)
11-20 n=119	2 (1.7%)	2 (1.7%)	0 (0%)
21-30 n=148	3 (2.0%)	3 (2.0%)	1 (0.7%)
31-40 n=120	2 (1.7%)	2 (1.7%)	1 (0.8%)
41-50 n=78	0 (0%)	0 (0%)	3 (3.8%)
51-60 n=99	1 (1.0%)	1 (1.0%)	6 (6.1%)
61-70 n=69	2 (2.9%)	2 (2.9%)	13 (18.8%)
over 70 n=53	0 (0%)	0 (0%)	10 (18.9%)

5.2.4 Discussion of clinical effectiveness results

Quantitative analysis of the results of the included studies was not possible due to the high level of methodological heterogeneity between studies and the poor reporting of relevant outcomes.

Only six CT studies, two MRI studies and one MRI/CT study were identified that recruited first episode psychosis patient populations. The remaining ten CT, two MRI and two MRI/CT studies recruited psychotic patients in various stages of the illness. These studies were included since very little relevant data was identified in FEP patients and the definition of first episode was found to vary between studies.

The methodological quality of included studies was poor. Classifying the study design was difficult since the studies did not conform to conventional trial designs but were mostly similar to a before-after type of study design. Studies were often designed to

assess prevalence of intracranial abnormalities, which suggested a cross-sectional design, but results were presented in the form of a case series. Sixteen studies relied on retrospective data from medical records, which is a source of information bias. The QUADAS checklist not only revealed that studies were likely to be poorly conducted, but also poor reporting of patient selection, the neuroimaging process, other assessments that were carried out, and blinding of image analysis and clinical evaluation. It should be noted that the QUADAS tool was applied even though the studies were not designed to compare a reference standard with an index test but were more of a before-after design. Sample sizes were generally not large, varying from 8 to 721 patients (median 52 patients). Sample sizes ranged from 8-168 patients in the studies of FEP patients. Sampling bias is likely to be a factor affecting the results of all the included studies. Individual patient data was provided by a number of studies. Overall, the internal validity of the included studies is questionable.

The included studies were highly heterogeneous with respect to the patient population. Two studies specifically recruited adolescent, or adolescent and young adult patients. Two studies recruited only patients over 45 years old. Four studies included children or adolescents within an adult population. The remaining studies recruited adult populations. As discussed in the background section, the causes of psychosis change with age (see section 3.1.1 on page 2). It might be expected that a greater number of patients with scans affecting clinical treatment would be seen in studies with an older population.

Studies that stated included patients were in their first episode of psychosis did not generally explain how this was defined. Even within the FEP studies, it was not clear whether individual patients had entered the study at a similar point in their illness progression. Patients with a chronic psychotic disorder may differ from those in the early stages of the illness for several reasons. There is evidence that in schizophrenia, chronicity causes changes in brain structure. There may also be an effect on brain structure from the long-term use of antipsychotic medication. In addition, FEP patients are likely to have untreated symptoms that may cause practical difficulties for neuroimaging. Finally, the definition of “current practice” is likely to differ in FEP patients to those with long-term illness in terms of investigations and review of diagnosis.

The presence or absence of neurological symptoms and signs in the study population is likely to greatly affect the number of cerebral abnormalities identified since they are an indicator of possible structural organic disease. In the context of current NHS practice most psychiatric patients presenting with overt neurological signs and symptoms will be seen and managed by the Department of Neurology and will not, therefore, be seen by mental health services in the first instance (personal communication, Professor F Oyebode, University of Birmingham, April 2007). Studies assessing patients presenting with psychosis in the absence of neurological signs and symptoms are of particular relevance to the review question. This patient group are more likely to be seen by psychiatric services and may have an occult organic cause of psychosis.

There were no FEP studies where it was clearly stated that patients did not have neurological abnormalities. Three studies (Adams[85], Borgwardt[90], Lubman[99]) recruited FEP patients who probably did not have neurological symptoms and signs.

Bain[88], Battaglia and Spector[89], and Jeenah[95] included FEP patients with neurological symptoms and signs but numbers were very small.

The reason for neuroimaging varied between studies but could be roughly grouped into referral/ clinical reasons, routine on admission and for the purpose of the study. Studies recruiting patients for neuroimaging based on referral or for clinical reasons might be expected to have a higher number of patients with abnormalities. However, this was not seen in practice.

All studies had varying proportions of psychotic diagnoses making it difficult to compare results between studies. Different proportions of psychotic diagnoses within a study could have an effect on how well the study population represents that seen in practice. Whether cerebral structural abnormalities, such as infarction and tumours, are more likely to be identified in certain psychotic disorders than others is a matter for continued debate.

The setting of the included studies also varied. Those studies conducted in general hospitals might recruit a different severity of psychotic illness to those set in tertiary psychiatric hospitals. The clinician carrying out the clinical assessment or the radiographic interpretation is also important to the external validity of the studies. It was often not reported who did the clinical assessment or whether it was a single person or a consensus from more than one person. It would be useful to know whether it was a neurologist or a psychiatrist performing the neurological examination and whether they were fully trained or during a training placement. Similarly, it would have been useful to know if a psychiatrist or neuroradiologist was interpreting the neuroimaging report. Also, assessments conducted in a research setting are likely tobe different to those conducted in a busy psychiatric assessment unit. Lastly, only two CT studies, and no MRI studies were conducted in the UK. The above factors may affect the external validity, or generalisability, of the study results to routine clinical practice.

It was not possible to do formal meta-analysis of the results due to the study design and quality of the studies. However, looking across the spread of results it was estimated that MRI may demonstrate lesions requiring a change in clinical management of approximately 5% (approximate range 0-10%). For CT the corresponding figures are approximately 0.5% (approximate range 0-5%) With only one poor quality study upon which to comment on the use of structural neuroimaging in treatment refractory psychosis, it is not possible to draw reliable conclusions. However, chronic schizophrenia patients with a poor response to treatment are an important population seen in clinical practice. The study showed that 2.2% of patients may benefit from a scan.

Discussion of results by subgroup (age, gender) was not possible due to lack of reporting.

The review of case reports of misidentification syndromes did not provide clear data for any of the outcomes considered for this review. It is possible that 25% of study patients had a scan that affected their clinical treatment. The most common diagnosis within misidentification syndromes was schizophrenia. Whether it would be justified to extrapolate the results seen for studies in which a large number of patients were

diagnosed with schizophrenia, to the patients with misidentification syndromes cannot be reliably concluded by this review.

The results discussed above suggest that using structural neuroimaging in first episode psychosis as a tool to be used in addition to current standard practice is not an effective method to detect organic causes of psychosis, however the results were based on a small number of poorly conducted and poorly reported studies.

Given the lack of benefit of structural neuroimaging found in patients with psychosis and no additional symptoms and signs, it has been suggested that structural neuroimaging should only be used where there is an uncertain or poor medical history available, symptoms and/or signs of an organic cause of psychosis, or a space occupying brain lesion, or where there is a positive past medical history.[85]

6. Assessment of cost-effectiveness

This chapter is organised into the following sections: (1) an overview of previous literature on the cost and cost-effectiveness of structural neuroimaging in first episode psychosis; (2) an overview of previous literature reporting the utility-based quality of life of patients with first episode psychosis; (3) a threshold analysis to explore the cost effectiveness of structural neuroimaging in first episode psychosis.

6.1 Systematic review of existing cost-effectiveness evidence

6.1.1 Search strategy and numbers of papers found

A comprehensive search for literature on the cost and cost-effectiveness of structural neuroimaging in first episode psychosis was carried out. The strategies in full may be found in Appendix 2.

Studies on costs, quality of life, cost effectiveness and modelling were identified from the following sources:

- Bibliographic databases: MEDLINE (Ovid) 1966 to November Week 3 2006, EMBASE (Ovid) 1980 to 2006 Week 47, Cochrane Library (Wiley) 2006 Issue 4 (CENTRAL) DARE and NHS EED and the Office of Health Economics HEED database November 2006 issue.
- Industry submissions
- Internet sites of national economic units

Searches were not be limited by date and there were no language restrictions

A total of 967 abstracts were identified. Of these, 46 were regarded as potentially relevant and full papers were requested. It was found that no papers reported directly on the cost-effectiveness of neuroimaging in patients with first-episode psychosis. As a consequence, the inclusion criteria were broadened to encompass papers that reported use of neuroimaging within the mental health clinical area more generally as it was felt that this would still provide useful information to inform the overall economic evaluation. For the quality of life papers, all papers reporting utility-based QoL values within the mental health clinical field were also included.

In summary, seven papers were classified as economic evaluations. There were also two cost papers, eleven quality of life papers and 24 papers were regarded as non-relevant.

The following section contains a summary of the seven papers classified as economic evaluations.

6.1.2 Review of previous literature on the cost effectiveness of neuroimaging within mental health

Appendix 7 contains full details of the review of the economic evaluation papers. No economic evaluation reporting the cost-effectiveness of neuroimaging in first-episode psychosis was identified. It was found that five papers explored the cost-effectiveness of neuroimaging within mental health more generally and these results are summarised in Table 23.

Because of the inconsistency in the measurement and objective of the economic evaluations it was not possible to synthesise the results in the form of a pooled analysis. As such, the review of the economic papers comprises a qualitative description of the main study findings and not data that can be used directly to populate the economic model.

Table 23. Summary of review of economic evaluation papers

Author	Intervention	Results
Mooney et al, 1990[110]	Routine v selective MRI for detection of MS	ICER: $4,877/QALY
Simon and Lubin, 1986[111]	Use of CT to diagnose surgically treatable causes of dementia	ICER: Selective scanning versus routine scanning with CT: <$50,000/QALY. Comparing MRI with CT incremental cost ranges from $46k for 60 yr olds to $144k for 80 yr olds.
McMahon and Araki et al, 2000[112]	Explore the cost-effectiveness of standard diagnostic strategy versus functional neuroimaging in Alzheimer disease centre.	MRI plus DSC MRI versus standard strategy = ICER $479,500/QALY.
Evens and Jost, 1977[113]	Cost effectiveness of CCT versus RBS in patients with suspected intracranial pathology	$141 per correct diagnosis using CCT. $51 per correct diagnosis using RBS.
Szczepura, Fletcher and Fitz-Patrick, 1991[114]	Is MRI in routine neuroscience worth its cost?	Average cost of scanning patient = £176.40. Marginal cost per diagnostic change = £626.

6.1.3 Review of utility-based QoL papers in first episode psychosis

This section provides an overview of the utility-based QoL information reported in the 10 studies (11 papers) identified in the literature search. As mentioned previously, the literature search was broadened to encompass papers that report QoL within the mental health clinical field more generally to inform further economic analysis. Only one paper was identified that measured QoL in a sample of patients that had been classified using the ICD-9 criteria (diagnosis of psychotic disorder). This paper will be reviewed in full. The remaining ten papers reported QoL within a population of patients that had been diagnosed with schizophrenia (ICD-10). It is generally accepted that the symptom profile and severity of symptoms are very similar for patients with established schizophrenia and first-episode psychosis.[115] These QoL values are therefore potentially useful for the economic evaluation and are reviewed and reported in Appendix 8. As Voruganti et al. (2000)[116] reports later results from the same study as Awad et al. (1997)[52] only Voruganti et al. (2000)[116]is summarised in Appendix 8.

Herrman H et al., 2002[117]

This study sets out to assess the validity of the World Health Organisation's short Quality of Life instrument (WHOQOL-Brèf) and the Assessment of Quality of Life (AQoL) for measuring health-related quality of life (HRQoL) in people receiving long-term community treatment for psychosis.

The WHOQOL-Brèf has 26 items and provides unweighted measurement on 4 domains: physical, psychological, social and the environment. The best possible QoL score is 100. The AQoL is a multi-attribute utility instrument and contains 15 questions covering five dimensions of HRQoL: illness, independent living, social relationships, physical senses and psychological wellbeing. Prior to this study, neither of these instruments had previously been used in patients with psychosis. There were 173 patients that took part in the study who were aged 18-64 years and had a diagnosis of a psychotic disorder (ICD-9). The study took place in the State of Victoria, Australia. During interviews, patients were administered with a series of self-completed questionnaires that contained the Short-Form 36 (SF-36) instrument – a health status profile instrument that can be used to derive utility information.

All patients were receiving treatment for a persistent psychotic disorder. Overall, the SF-36 instrument produced scores of 48.1 and 42.2 for the physical and mental categories respectively. The AQoL produced a mean utility value of 0.50 for the patients. When the care managers completed the AQoL instrument as a proxy, an overall utility value of 0.45 was produced. The authors compared these scores with those for the general population and found patient scores to be significantly lower on all WHOQOL-Brèf domains, AQoL domains and utility scale (ANOVAs, F-range: 15.14-193.07; $p<0.01$ for all comparisons). On average, utility scores were 37% lower than population norms.

The authors report that patients had little difficulty in completing these instruments and that psychotic patient's self-reported HRQoL should be included in outcome evaluation.

Table 24. QoL values for patients with psychosis

Instrument	Psychosis	Source
	Treated	
SF-36: Physical (PCS) (mean +-SD) Mental (MCS) (mean +-SD)	 48.1 (+-9.1) 42.2 (+-11.2)	Herrman et al, 2002[117] (age: 18-64 yrs)
AQoL utility: Patients: mean (SD) Case managers (proxy): mean (SD)	 0.50 (0.31) 0.45 (0.24)	Herrman et al, 2002[117] (age: 18-64 yrs)

Appendix 8 provides a summary of the nine papers that report QoL in patients with schizophrenia. These values provide potential to be used as a proxy for the QoL experienced by patients with psychosis. Utility scores can only be derived from SF-36/12 scores when fully disaggregated scores are reported so five of the nine papers are not useful as only aggregated SF-36/12 scores are provided. Four papers report utility values for patients with schizophrenia (Chouinard and Albright, 1997[118]; Lenert et al, 2005[119]; Montes J et al, 2003[120]; Voruganti et al, 2003[116]) and two of these report values for a treated and untreated state (Montes[120]; Lenert[119]). Three of the four papers report patient-rated values whilst Chouinard and Albright[118] used psychiatric nurses to rate preferences. Table 25 reports the patient-rated values along with average utility scores calculated across the three papers. In summary, the average utility scores for a schizophrenia patient are estimated as 0.5 for untreated and 0.75 for treated.

Table 25. Utility scores reported for patients diagnosed with schizophrenia

	Before treatment	After treatment	Duration of treatment	Age range of patients	Source
	0.729	0.775	1 year after treatment	18-85 years	Lenert et al,2005[119]
	0.538	0.596			Lenert et al,2005
	0.5	0.85	6 mths after treatment	< 40 years	Montes et al, 2003[120]
	0.5	0.86			Montes et al, 2003
	0.4	0.65			Montes et al, 2003
	0.473	0.73			Montes et al, 2003
	0.396	0.67			Montes et al, 2003
	0.467	0.64			Montes et al, 2003
		0.77	'stabilised'	Mean:34 yrs	Voruganti et al, 2000[116]
		0.85			Voruganti et al, 2000
		0.81			Voruganti et al, 2000
Average	**0.5**	**0.75**			
These utility values have been elicited using different methods,as detailed in Appendix 8					

6.2 Independent economic assessment

This section provides details of a threshold analysis developed by the assessment team to evaluate the cost-effectiveness of the routine use of structural neuroimaging (CT or MRI) in the diagnosis of various conditions associated with a first episode of psychosis compared to the standard diagnostic strategy. The objective was to estimate the difference in costs and the difference in outcomes of routine use of MRI or CT compared to the standard diagnostic strategy within the UK, which is typically scanning only when medical history or physical findings have suggested an increased likelihood of an organic cause of psychosis. The details of the economic analysis are described in the following sections.

6.2.1 Methods

To estimate the benefits as well as the economic costs of using alternative screening strategies, the framework of a threshold analysis that follows patients for one year was used. A one-year time horizon was adapted for pragmatic reasons due to paucity of data. Ideally, a longer time frame would have been used in the analysis, however there was no information reporting these effects. All costs were calculated from the perspective of the NHS and PSS and were estimated in 2005-6 UK£ (inflation indices: Netten and Curtis, 2006[121]). Where appropriate, costs were converted to UK£ (FT.com exchange rates, June 2007). Costs and benefits were not discounted due to the model assessing one year only.

6.2.1.1 Description of the models

In the UK, a patient who is experiencing first-episode psychosis will initially receive a standard examination (history, physical, mental state and neurological examinations, blood and urine tests) to determine possible causes. Indication of an organic cause of psychosis from mental state examination includes an acute onset, features of delirium such as clouding of consciousness and fluctuation in conscious awareness, disorientation in time and place, disturbance of memory, impaired attention, and visual hallucinations. Where no organic cause of psychosis is suspected, it is assumed that the patient has a functional psychosis.[59] Under standard practice if an organic cause is suspected, then an appropriate confirmatory test would be used. This may include CT or MRI scanning but frequently not in the UK.[14,57] There are many organic causes of psychosis such as temporal lobe epilepsy, stroke, brain injury, encephalitis, dementia, Parkinson's disease, multiple sclerosis and brain tumours. Some of these organic causes will have associated signs and symptoms that are immediately obvious to the clinician leading to a rapid diagnosis and referral to the appropriate speciality. These causes are detailed in Table 1 on page 4.

The primary objective of the economic analysis was to measure the difference in costs and benefits of scanning all patients with MRI or CT compared to selective scanning under standard care. Any benefit from scanning all patients will only be realised in cases where the organic causes are not immediately obvious to the clinician as the treatment pathway will only be altered in these patients (under standard care patients with obvious symptoms will receive an automatic referral to a consultant who specialises in that organic cause). For this reason, the Birmingham economic model sought to consider only the organic causes of psychosis that were likely to benefit from routine neuroimaging, i.e. causes with signs/symptoms that may not be

immediately obvious to the clinician (personal communication, Professor F Oyebode, QE Psychiatric Hospital, April 2007) . These are listed below:

- Epilepsy
- Brain Tumour
- Dementia

The most common causes of psychosis vary significantly by age. It is more common to find epilepsy causing psychosis among young adults whereas dementia is more common in an older age group. To address this distinction, the economic analysis was originally set up to model the cost-effectiveness of neuroimaging in two age groups: less than 65 years; 65 years and older. It was assumed that possible organic causes of psychosis in the younger age group (<65 years) were either epilepsy or brain cyst or tumour and in the older age group, either dementia or brain cyst or tumour. The two models therefore had the following possible outcomes following an initial clinical assessment of a patient with first-episode psychosis:

< 65 years	65 years and over
Functional psychosis	Functional psychosis
Organic cause: epilepsy	Organic cause: dementia
Organic cause: brain cyst or tumour	Organic cause: brain cyst or tumour

6.2.1.2 Model structure

To explore the cost effectiveness of neuroimaging using a conventional decision-analytic model, data on the differential response to antipsychotic drug therapy by type of cause (organic and functional) was required. This type of model structure is outlined in Figure 2 and Figure 3 for each of the age groups considered.

There are four possible diagnostic strategies within the model:

1. Scan all patients.
2. Scan all patients who do not respond to 1st choice antipsychotic therapy (olanzipine)
3. Scan all patients who do not respond to 2nd choice antipsychotic therapy (risperidone)
4. Scan all patients who do not respond to 3rd choice antipsychotic therapy (clozapine)

This model structure provided an estimate of the incremental cost effectiveness of scanning patients at various stages within the diagnostic pathway. Thus in addition to producing an estimate of the difference in cost and benefit from routine scanning versus no routine scanning, it also gives results for different selective scanning strategies (defined as only scanning patients who failed on either 1st, 2nd or 3rd choice antipsychotic therapy).

Despite the rationale of the original economic model structure, the clinical effectiveness review of neuroimaging identified no papers reporting detection of dementia with psychosis following either a CT or a MRI scan (see section 5.2, starting on page 24) and epilepsy cannot be diagnosed by CT or MRI. Therefore there were

no results to populate these treatment pathway arms within the economic model. As a consequence, the model structure had to be redesigned to allow for only one organic cause to be detected from either a CT or MRI scan: brain cyst or tumour. The two distinct model structures defined previously by age groups (<65 years and 65 years and over) were no longer necessary, as the detection of brain cyst/tumour was common to both model structures. The re-designed model structure therefore covered both age groups and is outlined in Figure 4.

Figure 2. Model structure for < 65 year olds

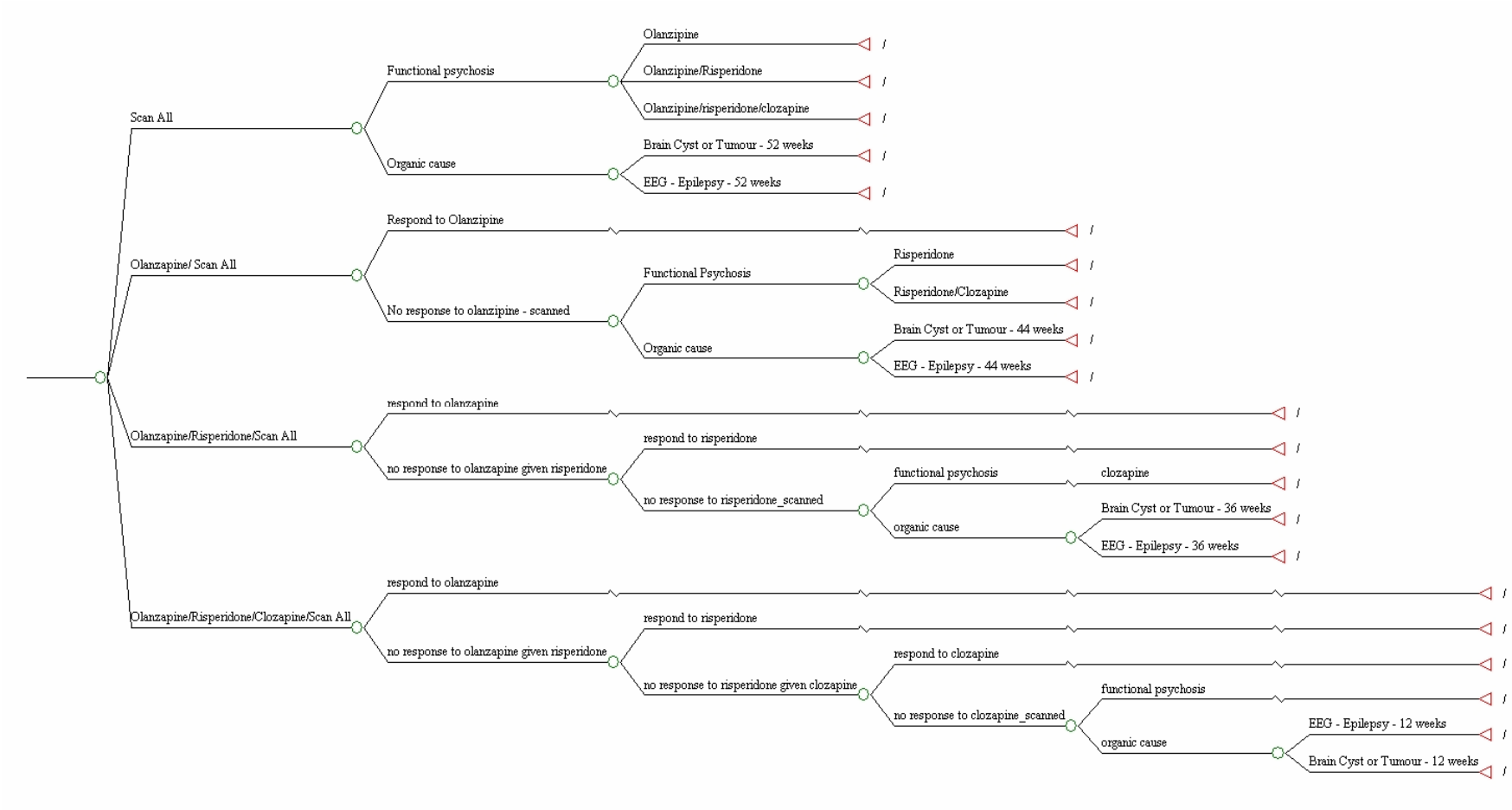


Figure 3. Model structure for 65 years and over

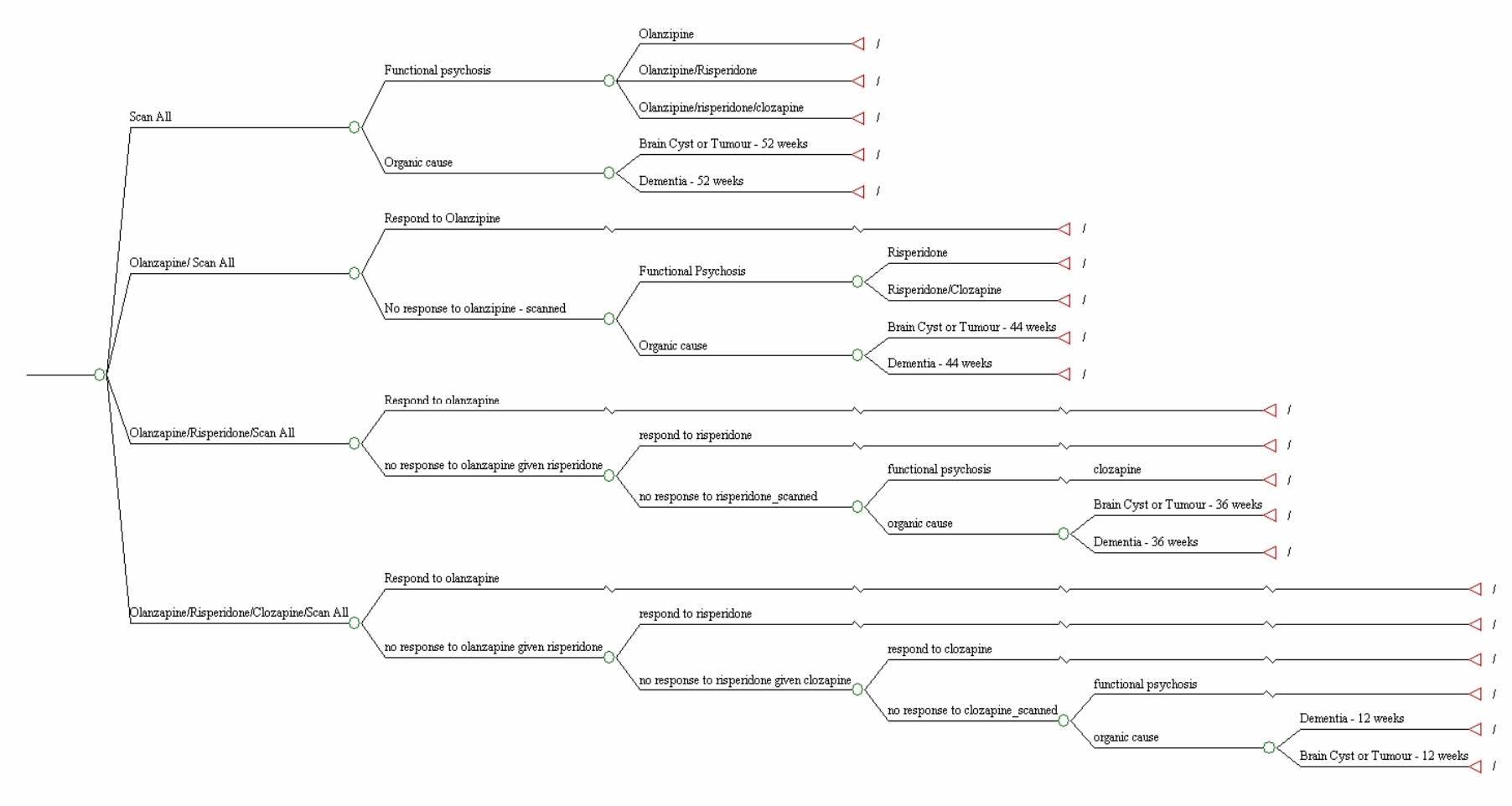
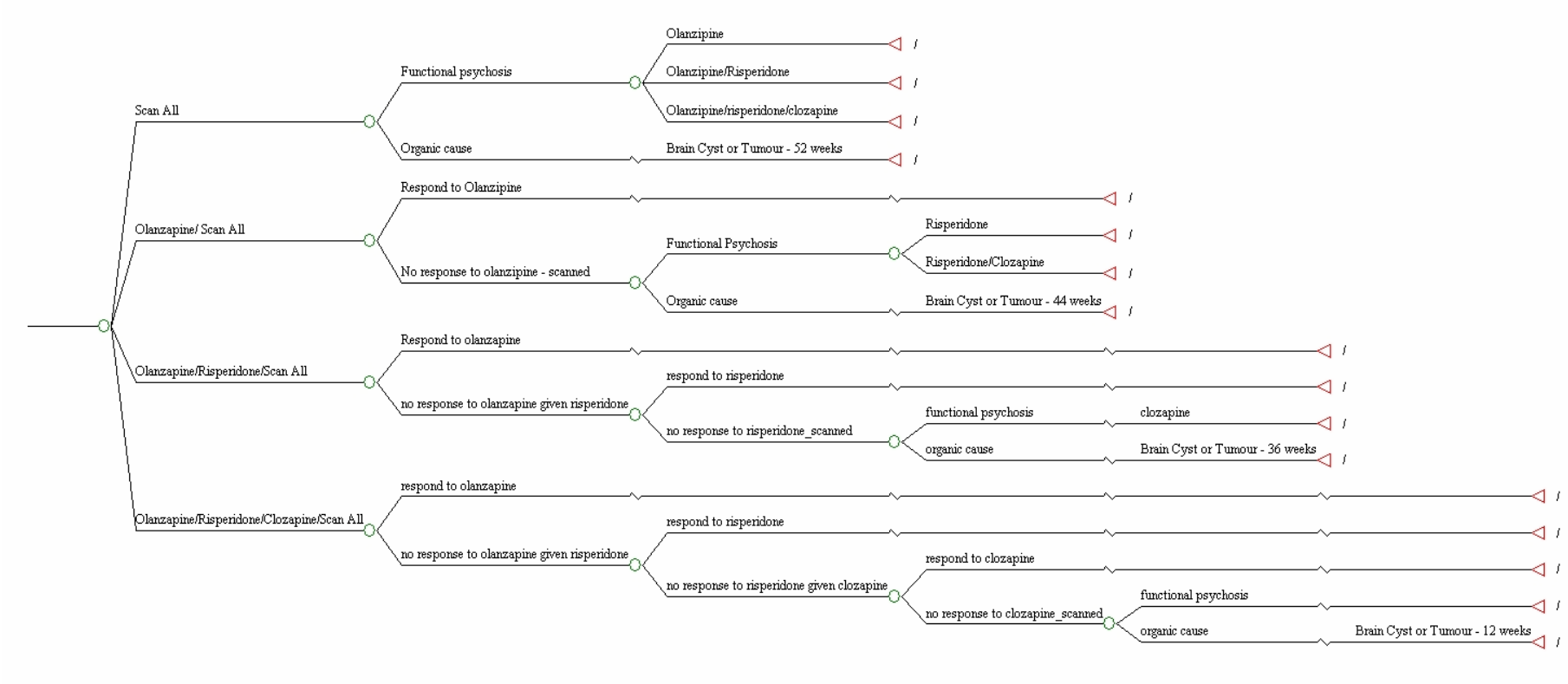


Figure 4. Re-designed model structure for all age groups



This model structure assumed that patients who have an organic cause of psychosis will not respond to antipsychotic treatment. However discussions with clinical experts revealed that this assumption does not hold in practice as it is possible that patients who have an organic cause of psychosis would respond to antipsychotic treatment.

The decision-analytic model described above had to be reconsidered as not only did it require information on the differential response to treatment by cause but also information on the impact upon QoL from having an early diagnosis as opposed to a late diagnosis of an organic cause. Such QoL data was not found in our literature review. Due to these complexities inherent within the various causes (and treatment) of psychosis (and quality of life effects) it was decided that the appropriate form of analysis under these circumstances would be to undertake a threshold analysis. A threshold analysis predicts the QALY gain required for the programme to be regarded as cost effective. By combining the incremental cost of routine scanning with a threshold cost per QALY value of £20,000 and £30,000, the QoL gain required to meet these threshold values was estimated. It is recognised that this form of analysis is limited because of its inability to consider detailed progress of patients through treatment pathways and the impact routine scanning would have on this process. However without the data to populate such a model, it is our view that a threshold analysis provided the best alternative.

To enable this analysis a list of all cost-incurring events of the two strategies (routine versus selective scanning) was listed (see Table 26). For the same reasons as before, only patients with a brain tumour/cyst were considered as the organic cause.

Table 26. Cost-incurring events for cohort of patients with first episode psychosis

Condition	Routine scanning	Selective scanning (usual care)	Cost Difference (£)
Functional psychosis	Cost of Physical Examination Cost of Neurological Examination Cost of baseline blood tests Cost of neuroimaging Cost of Rx*	Cost of Physical Examination Cost of Neurological Examination Cost of baseline blood tests Cost of Rx*	 Cost of neuroimaging
Organic cause: Brain tumour/cyst	Cost of Physical Examination Cost of Neurological Examination Cost of baseline blood tests Cost of neuroimaging Cost of Surgery	Cost of Physical Examination Cost of Neurological Examination Cost of baseline blood tests Cost of neuroimaging Cost of Rx* Cost of Surgery	 Cost of Rx*

* Rx: treatment with atypical antipsychotic drugs (average patient)

Table 26 outlines the aspects of patient management that determine the difference in cost between the two strategies (routine and selective scanning). The focus was on the cost difference between the two strategies and therefore costs common to both strategies automatically cancel out. Table 26 categorises the cost by type of patient (functional and organic). For the functional psychosis patients, the difference in cost was determined by the extra cost of scanning all patients under the routine strategy so

is the cost of either MRI or CT, all other costs remain as before. For the brain tumour/cyst patients, the cost difference was determined by the period of time that antipsychotic medication was provided before a later diagnosis within the selective screening strategy (cost of Rx). Obtaining information on the exact period of time that patients were left undiagnosed under the selective screening strategy proved to be a challenge for this review so to explore this uncertainty, we assumed a variable time period of 6 and 12 months. This was varied in a sensitivity analysis to 3 months. Cost of treatment for brain tumour/cyst is common to both strategies as it was assumed that even in the selective screening strategy, a diagnosis (and subsequent treatment) of a brain tumour/cyst would be achieved within the 12-month period. Together these costs (for both functional and organic patients) determined the incremental cost of performing routine versus selective scanning which was then combined with a threshold cost per QALY value of £20,000 and £30,000 to determine the QALY gain required to make routine scanning cost-effective.

6.2.1.3 Estimation of model parameters for the threshold analysis

Costs

All patients within the analysis were assumed to receive an initial standard examination comprising history, physical, mental state and neurological examinations, and blood and urine tests regardless of the diagnostic strategy. These costs were assumed to be equivalent for both diagnostic strategies within the analysis and were thus excluded from further analysis.

The cost of MRI and CT scanning were drawn from 2005-6 NHS reference costs (Code RBF1 and RBC5 respectively)[81] and set at £244 for MRI and £78 for CT scanning.

Costs of Drug therapy and Monitoring

Patients with functional psychosis receive antipsychotic medication provided as a predefined sequence of drugs. The sequence of drugs chosen for the model was based on an audit of atypical antipsychotic drug use within the West Midlands (Department of Medicine, University of Keele) alongside clinical expert advice. It was assumed that following diagnosis of first-episode psychosis a patient will receive olanzapine as the first choice drug, if this drug failed then risperidone is the next choice drug. If the patient failed to respond to or was intolerant to both olanzapine and risperidone, then clozapine was assumed to be the third-choice drug. Annual cost of drug therapy was derived from the BNF 53, March 2007[122] and estimated assuming two levels of dosage that were varied within the analysis. A detailed breakdown of how these costs were derived is available in Appendix 10.

Patient response to each drug was assumed to be monitored over an eight-week period comprising two weeks of a titration dose followed by six weeks of a maintenance dose. The costs associated with this monitoring phase were determined by a proportional split of patients receiving either hospital or home care. The proportional split between hospital and home care was varied within the analysis from 0/100 to 50/50 hospital/home split to explore the effect of this assumption. The values of 20/80 and 50/50 split between home and hospital were chosen following consultation with a clinical expert (Personal communication, R Upthegrove, QE Psychiatric Hospital, Feb

2007). The unit cost for an inpatient stay was derived from NHS reference costs 2005-6 (£243) and for a home visit (£73) from PSSRU, 2006.[121]

Annual costs associated with drug therapy and monitoring are summarised in Table 27.

Table 27. Drug therapy and monitoring costs for antipsychotic medication

Drug Name and Duration of Treatment	Drug Cost Lower- Higher Dose	Monitoring costs Hospital/Home Split		
		0/100	20/80	50/50
Olanzapine for 52 weeks	£1250-£2383	£4105	£6005	£8856
Olanzapine for 8 weeks Risperidone for 44 weeks	£990-£1468	£8210	£12010	£17713
Olanzapine for 8 weeks Risperidone for 8 weeks Clozapine for 36 weeks	£1178-£1726	£1231	£18105	£26569

To determine the average cost of antipsychotic treatment, information on response to drug therapy was extracted from a Health Technology Assessment report reviewing the cost-effectiveness of atypical antipsychotic drugs in schizophrenia.[123] These response rates were then used as statistical weights (Table 28) to apply to the drug and monitoring cost to determine the average patient cost of antipsychotic treatment (Table 29).

Table 28. Response to Drug Therapy

Drug	Probability of response	Weights
Olanzapine	0.54	0.2523
Risperidone	0.84	0.3925
Clozapine	0.76	0.3551
Sum	2.14	1
*Assumption: response to a drug is independent to response to another drug		

Table 29. Cost of treatment for an average patient with psychosis

Drug Cost	3 months†	6 months*	12 months
Lower Dose	£173	£556	£1,122
Higher Dose	£301	£908	£1,791
*Olanzapine/Risperidone/Clozapine for 6 months is an approximate estimate since Clozapine should be given for a minimum of 6 months † Cost items for the 3-month scenarios considered in the sensitivity analysis were simply calculated by dividing the 6 month items by 2, excluding clozapine			
Monitoring Cost	**0/100**	**20/80**	**50/50**
Hospital/Home Split	£8,632	£12,628	£18,623

The economic analysis assumed that the treatment for brain cyst/tumour was not altered following an earlier detection with CT or MRI. The analysis therefore assumed no deterioration in the disease state from being detected at a later stage with standard practice compared to early stage detection under routine scanning. It is

acknowledged that this is a large assumption but for pragmatic reasons was unavoidable.

Costs of treatment for a brain tumour were extracted from Blomqvist et al (1996)[124] and are reported in Table 30. The authors reported direct and indirect costs of brain tumour. Direct costs included diagnosis of brain tumour (CT or MRI), major surgery, radiation therapy and cytostatics (drugs used in the treatment of malign tumours). Indirect costs were 75% of the total cost of brain tumour and included costs due to sickness leave episodes, early retirements and mortality. Indirect costs were excluded here because the analysis was done from an NHS perspective.

Note that the cost of treating and/or managing a tumour (including cost of surgery) is not affecting the analysis because it would the same for both routine and selective scanning.

Table 30. Cost of brain tumour treatment

Year	Diagnosis	Therapy	Total
1996 (US dollars)	$925.44	$13,535	$14,460
2006 (US dollars)*	$1,308.96	$19,143.55	$20,452.51
2006 (UK pounds)**	£659.44	£9,644.33	£10,303.77
*Inflated using Unit Costs of Social Care, 2006 Pay and Prices Index. ** Converted using ft.com exchange rate.			

Probability of detection with MRI/CT

The extra systematic review estimated the test accuracy rates for detecting brain tumours/cysts to be 100% for MRI and above 90% for a CT scan (see Appendix 9). The probability of a brain tumour/cyst being detected following an MRI scan was extracted from the clinical effectiveness review and estimated to be 5%. Since MRI was estimated to have a sensitivity rate at or close to 100% it was assumed that the prevalence of brain tumour/cysts among a psychotic patient population was 5% and thus the probability of detecting brain tumours in a cohort of patients was 5% with an MRI and 4.5% with a CT (assuming that 0.5% with CT were false negatives).

6.2.1.4 Quality of life

One of the principal difficulties in this analysis was that there was no access to utility-based quality of life data to give information on the utility gain from an earlier/accurate diagnosis compared to a 'late' diagnosis for the group of patients who have a brain tumour/cyst. It was assumed that a utility gain will be achieved (and indeed an improvement in prognosis) from providing a patient with a correct diagnosis earlier in their treatment pathway but estimation of this gain would be purely arbitrary. As a consequence it was thought to be more informative to explore what QoL (and QALY gain) was required to make routine scanning cost effective for a full cohort of patients diagnosed with first episode psychosis.

6.2.2 Results

6.2.2.1 Routine scanning using MRI

Table 31 outlines the cost events that determine the difference in cost between the selective and routine screening strategy when using a MRI.

Table 31. Costs of two strategies when scanning with MRI

Condition	Proportion	Routine scanning	Selective scanning (usual care)	Cost Difference (£)
Functional psychosis	95%	Cost of initial tests Cost of MRI Cost of Rx	Cost of initial tests Cost of Rx	 Cost of MRI
Organic cause: Brain tumour/cyst	5%	Cost of initial tests Cost of MRI Cost of Surgery	Cost of initial tests Cost of Rx (6 /12 months) Cost of MRI Cost of Surgery	 Cost of Rx (6/12 months)

The incremental cost of routine versus selective scanning was directly affected by three aspects of uncertainty within the analysis:

1. Time period of treatment for brain tumour under selective scanning (6 or 12 months)
2. Antipsychotic drug dosage (higher or lower dose)
3. Hospital and home split within the monitoring phase (0/100, 20/80 or 50/50 hospital/home).

To explore the effect of this uncertainty, Table 32 presents the incremental cost for routine versus selective screening for each of the possible scenarios.

Table 32. Incremental cost of routine versus selective scanning

Scenarios	Duration (months)	Hospital/Home split	Dose	Incremental cost
1	6	0-100	Lower	-228
2	6	0-100	Higher	-245
3	12	0-100	Lower	-256
4	12	0-100	Higher	-289
5	6	20-80	Lower	-427
6	6	20-80	Higher	-445
7	12	20-80	Lower	-456
8	12	20-80	Higher	-489
9	6	50-50	Lower	-727
10	6	50-50	Higher	-745
11	12	50-50	Lower	-755
12	12	50-50	Higher	-789

The scenarios have been ordered by incremental cost and all show routine scanning using MRI to be cost-saving compared to selective scanning. The greatest cost saving was apparent when the largest proportion of patients were hospitalised during the monitoring phase (50/50 split) so it was this assumption that was having the biggest impact upon the incremental cost. Even with the conservative assumption, however, that there were no patients hospitalised (0/100 split), routine versus selective scanning was still cost saving.

Threshold analysis for MRI

Where an intervention is more costly than its alternative, a threshold analysis predicts the QALY gain necessary to meet the threshold value of £20,000 and £30,000 per QALY. Each of the scenarios presented in Table 32 however are cost-saving and so instead of the threshold analysis predicting the QALY gain, it will predict the QALY loss at which the decision on cost-effectiveness grounds changes. If the QALY loss is greater than the threshold, then the QALY loss is not justified by the cost saving. Any QALY loss less than the threshold (and any QALY gain) would result in routine scanning being viewed as cost-effective. These results are presented for the cohort of patients overall and for the brain tumour patients in Table 33.

Table 33. Threshold analysis for routine MRI scanning

Scenarios	Duration (months)	Hosptial/ Home Split	Dose	Incremental cost (£)	QALY loss (all patients)		QALY loss (brain tumour patients)	
					£20k	£30k	£20k	£30k
1	6	0-100	Lower	-228	0.011	0.008	0.228	0.152
2	6	0-100	Higher	-245	0.012	0.008	0.245	0.163
3	12	0-100	Lower	-256	0.013	0.009	0.256	0.171
4	12	0-100	Higher	-289	0.014	0.01	0.289	0.193
5	6	20-80	Lower	-427	0.021	0.014	0.427	0.285
6	6	20-80	Higher	-445	0.022	0.015	0.445	0.297
7	12	20-80	Lower	-456	0.023	0.015	0.456	0.304
8	12	20-80	Higher	-489	0.024	0.016	0.489	0.326
9	6	50-50	Lower	-727	0.036	0.024	0.727	0.485
10	6	50-50	Higher	-745	0.037	0.025	0.745	0.497
11	12	50-50	Lower	-755	0.038	0.025	0.755	0.504
12	12	50-50	Higher	-789	0.039	0.026	0.789	0.526

This table predicts that as the cost saving from having routine scanning in place gets greater, so too does the loss in QALYs that can be tolerated for routine scanning to be still regarded as cost-effective at acceptable threshold levels. As logic would predict when focusing just on the QoL of brain tumour patients the QALY loss from having an early detection needs to be even greater (Scenario 1: Threshold value of £20,000: QALY loss 0.011 for full cohort versus 0.228 for brain tumour patients only). Such losses in QoL could seem implausible and so the routine use of MRI could appear to be a cost effective policy option.

6.2.2.2 Routine scanning using CT

Table 34 outlines the cost events that determine the difference in cost between the selective and routine screening strategy when using a CT. CT has a 90% sensitivity of detecting brain tumours/cysts so using the prevalence of 5%, it was estimated that 0.5% of patients would have a false negative result.

Table 34. Costs of two strategies when scanning with CT

Condition	Proportion		Routine scanning	Selective scanning (usual care)	Cost Difference (£)
Functional psychosis	95%		Cost of initial tests Cost of CT Cost of Rx	Cost of initial tests Cost of Rx	 Cost of CT
Organic cause: Brain tumour/ cyst	5%	True positive 4.5%	Cost of initial tests Cost of CT Cost of Surgery	Cost of initial tests Cost of Rx (6 /12 mths) Cost of MRI Cost of Surgery	 Cost of CT – Cost of MRI - cost of Rx (6/12 months)
		False negative 0.5%	Cost of initial tests Cost of CT Cost of Rx (6/12 mths) Cost of MRI Cost of surgery	Cost of initial tests Cost of Rx (6/12 mths) Cost of MRI Cost of surgery	Cost of CT

For those patients who had a false negative result under routine scanning, it was assumed (as in selective scanning) that after a period of treatment, they would receive an MRI which would correctly diagnose the brain tumour. It was also assumed that under routine scanning, this treatment would be the same as under selective scanning. Again as in the MRI case, to explore the uncertainty around the duration, dosage and monitoring costs, Table 35 presents the incremental cost for routine versus selective screening for each of the possible scenarios using CT.

Table 35. Incremental cost of routine versus selective scanning

Scenarios	Duration (months)	Hospital/ Home Split	Dose	Incremental cost (£)
1	6	0-100	Lower	-346
2	6	0-100	Higher	-362
3	12	0-100	Lower	-372
4	12	0-100	Higher	-402
5	6	20-80	Lower	-526
6	6	20-80	Higher	-542
7	12	20-80	Lower	-552
8	12	20-80	Higher	-582
9	6	50-50	Lower	-796
10	6	50-50	Higher	-812
11	12	50-50	Lower	-822
12	12	50-50	Higher	-852

The scenarios have been ordered by incremental cost and (similar to MRI) all show routine scanning using CT to be cost-saving compared to selective scanning. As in the MRI scenario, the greatest cost-saving (£852) was within the scenario where the highest proportion of patients were being hospitalised during the monitoring phase. Again as in the MRI case, even when the proportion of patients being hospitalised was zero, the dosage was low and the duration of treatment was six months, the intervention was still cost-saving.

Threshold analysis for CT

The results of the threshold analysis for CT for each of the scenarios are presented in Table 36.

Table 36. Threshold analysis for routine CT scanning

Scenarios	Duration (months)	Hosptial/ Home Split	Dose	Incremental cost (£)	QALY loss (all patients)		QALY loss (brain tumour patients)	
					£20k	£30k	£20k	£30k
1	6	0-100	Lower	-346	0.017	0.012	0.346	0.231
2	6	0-100	Higher	-362	0.018	0.012	0.362	0.242
3	12	0-100	Lower	-372	0.019	0.012	0.372	0.248
4	12	0-100	Higher	-402	0.020	0.013	0.402	0.268
5	6	20-80	Lower	-526	0.026	0.018	0.526	0.351
6	6	20-80	Higher	-542	0.027	0.018	0.542	0.361
7	12	20-80	Lower	-552	0.028	0.018	0.552	0.368
8	12	20-80	Higher	-582	0.029	0.019	0.582	0.388
9	6	50-50	Lower	-796	0.040	0.027	0.796	0.531
10	6	50-50	Higher	-812	0.041	0.027	0.812	0.541
11	12	50-50	Lower	-822	0.041	0.027	0.822	0.548
12	12	50-50	Higher	-852	0.043	0.028	0.852	0.568

This table predicts the same with CT scanning as with MRI scanning – as the cost saving became greater, so too does the loss in QALYs that can be tolerated for routine scaaning to be regarded as cost effective at acceptable threshold levels. The QALY loss is at its greatest in 'scenario 12' (proportion of patients being hospitalised 50%, 12 months of treatment under selective screening, 12 months of treatment for patients with false negatives and dose of antipsychotic treatment being high).

6.2.2.3 Sensitivity analysis

The threshold analysis for both MRI and CT showed that routine scanning versus selective scanning was cost-saving. This result was consistent across all possible scenarios in both cases. By ranking the scenarios by incremental cost, it can be deduced that the hospital/home proportional split had the greatest impact upon the result. Within this category, the most conservative assumption of no patients being hospitalised and all patients being monitored at home cannot be altered any further to 'reduce' this monitoring cost as the only alternative was to assume that patients incurred no monitoring cost whatsoever and this seemed somewhat unrealistic.

Time period

A major area of uncertainty within the analysis centres on the time period of inaccurate diagnosis under the selective screening strategy. There was no information on the average length of time that a brain tumour/cyst patient would go undetected under usual care. In this analysis it was assumed that a variable length of time of six and 12 months that treatment for psychosis is administered. For the sensitivity analysis this time period was altered to three months to determine the impact upon the overall results. The results are presented in Table 37.

Table 37. Sensitivity analysis: 3-month 'time delay'

Scanning using MRI								
Scenarios	**Duration (months)**	**Hosptial/ Home Split**	**Dose**	**Incremental cost (£)**	**QALY loss (all patients)**		**QALY loss (brain tumour patients)**	
					£20k	£30k	£20k	£30k
1	3	0-100	lower	-208	0.010	0.007	0.208	0.139
2	3	0-100	higher	-215	0.011	0.007	0.215	0.143
3	3	20-80	lower	-408	0.020	0.014	0.408	0.272
4	3	20-80	higher	-415	0.021	0.014	0.415	0.276
5	3	50-50	lower	-708	0.035	0.024	0.708	0.472
6	3	50-50	higher	-714	0.036	0.024	0.714	0.476
Scanning using CT								
1	3	0-100	lower	-329	0.016	0.011	0.329	0.219
2	3	0-100	higher	-334	0.017	0.011	0.335	0.223
3	3	20-80	lower	-509	0.025	0.017	0.509	0.339
4	3	20-80	higher	-514	0.026	0.017	0.515	0.343
5	3	50-50	lower	-778	0.039	0.026	0.779	0.519
6	3	50-50	higher	-784	0.039	0.026	0.785	0.523

With a time delay of three months before accurate diagnosis is achieved under the selective screening strategy, routine scanning with both MRI and CT is still cost saving.

Sensitivity rate

It was assumed in the basecase analysis that CT had a 90% sensitivity rate for detecting brain tumours/cysts. This allowed for a 0.5% rate of false negatives (10% of the prevalence rate). To explore the affect of this assumption, this sensitivity rate was altered to 50% thus allowing for a 2.5% rate of false negatives. These results are presented in Table 38.

Table 38. Sensitivity analysis: 50% sensitivity rate for CT

Scenarios	**Duration (months)**	**Hosptial/ Home Split**	**Dose**	**Incremental cost (£)**	**QALY loss (all patients)**		**QALY loss (brain tumour patients)**	
					£20k	£30k	£20k	£30k
1	6	0-100	Lower	-158	0.008	0.005	0.158	0.105
2	6	0-100	Higher	-166	0.008	0.006	0.167	0.111
3	12	0-100	Lower	-171	0.009	0.006	0.172	0.115
4	12	0-100	Higher	-188	0.009	0.006	0.189	0.126
5	6	20-80	Lower	-257	0.013	0.009	0.258	0.172
6	6	20-80	Higher	-266	0.013	0.009	0.267	0.178
7	12	20-80	Lower	-271	0.014	0.009	0.272	0.181
8	12	20-80	Higher	-288	0.014	0.01	0.289	0.192
9	6	50-50	Lower	-407	0.02	0.014	0.408	0.272
10	6	50-50	Higher	-416	0.021	0.014	0.416	0.278
11	12	50-50	Lower	-421	0.021	0.014	0.422	0.281
12	12	50-50	Higher	-438	0.022	0.015	0.438	0.292

With the sensitivity rate of 50%, routine scanning using CT versus selective scanning was still producing a result that is cost-saving.

Prevalence rate

On the basis of the clinical effectiveness systematic review (assuming a 100% sensitivity rate for MRI), it was estimated that the prevalence of a brain tumour/cyst among the study population was 5%. To explore the effect of this assumption, the prevalence of a brain tumour/cyst was altered to 0.5% and 1%. These results are presented in Table 39 and Table 40 for MRI and in

Table 41 and Table 42 for CT.

Table 39. Prevalence of Brain Tumour in study population: 0.5% - Results for MRI

Scenarios	Duration (months)	Hospital/ Home Split	Dose	Incremental cost (£)	QALY gain (all patients)		QALY gain (brain tumour patients)	
					£20k	£30k	£20k	£30k
1	6	0-100	Lower	196.84	0.010	0.007	1.968	1.312
2	6	0-100	Higher	195.08	0.010	0.007	1.951	1.301
3	12	0-100	Lower	194.01	0.010	0.006	1.940	1.293
4	12	0-100	Higher	190.67	0.010	0.006	1.907	1.271
5	6	20-80	Lower	176.86	0.009	0.006	1.769	1.179
6	6	20-80	Higher	175.10	0.009	0.006	1.751	1.167
7	12	20-80	Lower	174.03	0.009	0.006	1.740	1.160
8	12	20-80	Higher	170.69	0.009	0.006	1.707	1.138
9	6	50-50	Lower	146.89	0.007	0.005	1.469	0.979
10	6	50-50	Higher	145.13	0.007	0.005	1.451	0.968
11	12	50-50	Lower	144.06	0.007	0.005	1.441	0.960
12	12	50-50	Higher	140.71	0.007	0.005	1.407	0.938

Table 40. Prevalence of Brain Tumour in study population: 1% - Results for MRI

Scenarios	Duration (months)	Hospital/ Home Split	Dose	Incremental cost (£)	QALY gain (all patients)		QALY gain (brain tumour patients)	
					£20k	£30k	£20k	£30k
1	6	0-100	Lower	149.68	0.007	0.005	0.748	0.499
2	6	0-100	Higher	146.16	0.007	0.005	0.731	0.487
3	12	0-100	Lower	144.02	0.007	0.005	0.720	0.480
4	12	0-100	Higher	137.33	0.007	0.005	0.687	0.458
5	6	20-80	Lower	109.72	0.005	0.004	0.549	0.366
6	6	20-80	Higher	106.20	0.005	0.004	0.531	0.354
7	12	20-80	Lower	104.06	0.005	0.003	0.520	0.347
8	12	20-80	Higher	97.37	0.005	0.003	0.487	0.325
9	6	50-50	Lower	49.77	0.002	0.002	0.249	0.166
10	6	50-50	Higher	46.25	0.002	0.002	0.231	0.154
11	12	50-50	Lower	44.11	0.002	0.001	0.221	0.147
12	12	50-50	Higher	37.42	0.002	0.001	0.187	0.125

Table 41. Prevalence of Brain Tumour in study population: 0.5% - Results for CT

Scenarios	Duration (months)	Hospital/ Home Split	Dose	Incremental cost (£)	QALY gain/loss (all patients)		QALY gain/loss (brain tumour patients)	
					£20k	£30k	£20k	£30k
1	6	0-100	Lower	35.56	0.0018	0.0012	0.0356	0.0237
2	6	0-100	Higher	33.97	0.0017	0.0011	0.0340	0.0226
3	12	0-100	Lower	33.01	0.0017	0.0011	0.0330	0.0220
4	12	0-100	Higher	30.00	0.0015	0.0010	0.0300	0.0200
5	6	20-80	Lower	17.57	0.0009	0.0006	0.0176	0.0117
6	6	20-80	Higher	15.99	0.0008	0.0005	0.0160	0.0107
7	12	20-80	Lower	15.03	0.0008	0.0005	0.0150	0.0100
8	12	20-80	Higher	12.02	0.0006	0.0004	0.0120	0.0080
9	6	50-50	Lower	-9.40	-0.0005	-0.0003	-0.0094	-0.0063
10	6	50-50	Higher	-10.99	-0.0005	-0.0004	-0.0110	-0.0073
11	12	50-50	Lower	-11.95	-0.0006	-0.0004	-0.0120	-0.0080
12	12	50-50	Higher	-14.96	-0.0007	-0.0005	-0.0150	-0.0100

Table 42. Prevalence of Brain Tumour in study population: 1% - Results for CT

Scenarios	Duration (months)	Hospital/ Home Split	Dose	Incremental cost (£)	QALY gain (all patients)		QALY gain (brain tumour patients)	
					£20k	£30k	£20k	£30k
1	6	0-100	Lower	-6.89	-0.0003	-0.0002	-0.0069	-0.0046
2	6	0-100	Higher	-10.06	-0.0005	-0.0003	-0.0101	-0.0067
3	12	0-100	Lower	-11.98	-0.0006	-0.0004	-0.0120	-0.0080
4	12	0-100	Higher	-18.00	-0.0009	-0.0006	-0.0180	-0.0120
5	6	20-80	Lower	-42.85	-0.0021	-0.0014	-0.0429	-0.0286
6	6	20-80	Higher	-46.02	-0.0023	-0.0015	-0.0460	-0.0307
7	12	20-80	Lower	-47.95	-0.0024	-0.0016	-0.0479	-0.0320
8	12	20-80	Higher	-53.97	-0.0027	-0.0018	-0.0540	-0.0360
9	6	50-50	Lower	-96.81	-0.0048	-0.0032	-0.0968	-0.0645
10	6	50-50	Higher	-99.98	-0.0050	-0.0033	-0.1000	-0.0667
11	12	50-50	Lower	-101.90	-0.0051	-0.0034	-0.1019	-0.0679
12	12	50-50	Higher	-107.92	-0.0054	-0.0036	-0.1079	-0.0719

For MRI with both values of prevalence there was no longer a cost saving, therefore a QALY gain was necessary to meet the threshold value of £20,000 and £30,000 per QALY. The lower the incremental cost, the lower the QALY gain required to make the intervention cost-effective. For all of the scenarios, when focusing on all patients, the necessary QALY gain to make early scan cost-effective was relatively small (Scenario 8: Threshold value of £30,000: QALY gain required 0.006 for full cohort for the 0.5% prevalence and 0.003 for the 1% prevalence).

Table 41 and Table 42 present the results for CT. The effects of altering the prevalence of brain cyst/tumour was explored among the study population by keeping the sensitivity of a CT detecting a brain tumour/cyst constant to 90% (estimate provided by the test accuracy systematic review (see Appendix 9)).

When the prevalence is set at 0.5% (

Table 41) there was no longer a cost saving and therefore a QoL gain was necessary to meet the threshold value of £20,000 and £30,000 per QALY. However there was a cost saving for scenarios 9 to 12 where the hospital/home split was 50-50. This can be explained by the fact that the monitoring cost was higher under those scenarios and hence the 10% of the cases missed by scanning selectively with a CT (sensitivity 90%) were more costly than scanning all patients routinely.

When the value of prevalence was set to 1%, routine scanning using CT versus selective scanning produced a result that was cost-saving for all patients.

6.2.3 Discussion of the economic evaluation

The benefits of routine scanning will be experienced by the group of patients who have an organic cause of psychosis with signs and symptoms that are not immediately obvious to the clinician. This is because with routine scanning, an earlier diagnosis can be achieved avoiding the use of antipsychotic medication and potentially improving the prognosis of the patient. Apart from receiving an early scan following the initial diagnosis of psychosis, the treatment pathway of all other patients will remain the same.

The organic causes that are likely to benefit from routine scanning were identified as brain tumour/cyst and possibly dementia. Epilepsy would not be diagnosed with CT or MRI scanning. No evidence was found from the clinical effectiveness review on the identification of epilepsy or dementia with psychosis being identified by either a CT or MRI scan. The analysis thus reduced to consideration of just brain tumour/cysts.

The original economic model structure was based on the proposition that patients with an organic cause will fail to response to antipsychotic medication. This proposition was however unfounded and together with the lack of information on QoL effects meant that the appropriate form of economic analysis was to undertake a threshold analysis. From this analysis it appears that routine scanning versus selective scanning is cost-saving with savings ranging from £228 to £789 with MRI scanning and £346 to £852 with CT scanning with the assumption of a 5% prevalence rate of tumours/cycts or other organic causes amenable to treatment. This means that for the intervention to be viewed as cost-effective, the maximum acceptable QALY loss would be between 0.011 to 0.039 with MRI scanning and 0.017 to 0.043 with CT scanning using a £20,000 threshold value. These estimates were subjected to sensitivity analysis given the three levels of uncertainty that contributed to the cost of antipsychotic medication. With all of these parameters suitably varied, routine scanning still remained the cost-saving option. Not surprisingly, when the prevalence rates were reduced to 0.5% and 1%, the results altered with patients (in some scenarios) requiring a QALY gain for the intervention to be cost-effective.

Discussion therefore needs to focus on the QoL effects of scanning all patients. One might argue that there is a disutility associated with a MRI scan with respect to the noise and the claustrophobic nature of the procedure. Using the figures from the threshold analysis, for this to affect the cost-effectiveness of routine scanning this disutility would have to amount to a decrement of at least 0.01. This needs to be offset against the QoL impact for all the patients with a brain tumour/cyst that receive

an early diagnosis under routine scanning and thus potentially a better prognosis. It is considered here that this would result in a QoL gain for these patients.

A weakness in the analysis is that it only considers the affect of scanning all patients over 12-months. This is largely due to data limitations as we have no information on the impact of early scanning upon the prognosis of a brain tumour/cyst patient. However it is likely that the QoL gain from an early diagnosis goes beyond 12 months and this has been ignored in the analysis but further supports the implementation of routine scanning. Another limitation of the analysis is that the assumption that no mortality effects within the cohort will occur.

If it is agreed that the affects of routine scanning would not cause a QoL loss overall, and the prevalence of organic causes is approximately 5%, then our analysis has shown the intervention to be cost-saving. This result is apparent due to the expense of antipsychotic medication and the associated cost of treatment following a delayed diagnosis. As all other costs remain the same between the two strategies the cost of scanning all patients is more than offset by the cost saving from avoiding treating patients, even if this time-period is as short as 3-months.

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

Recent NHS policy with respect to first episode psychosis has focused on ensuring early access to assessment and intervention (DoH 2003-6) and includes the development of the National Early Intervention in Psychosis programme.[66] This initiative is in response to the evidence base linking the length of untreated psychosis with reduced quality of life and a worse prognosis (e.g. Melle 2005[47]; Garety 2006[50]; Marshall 2005[6]) and providing intensive, integrated, sustained outreach-based care during a critical period in the course of illness.[65] Despite reported problems with funding and inequities in access, the number of individuals served by early intervention teams increased from ~1000 to 12000 between 2002 and 2007.[125]

It is not clear precisely how neuroimaging in first episode psychosis would contribute to the aims of early intervention in psychosis programme. Neuroimaging is not an investigation that would be a pre-requisite to commencing anti-psychotic treatment. Psychosis is a symptom requiring treatment and identification of underlying pathology that may change a diagnosis or alter clinical management but would not include withholding treatment for psychosis per se.

Potential benefits of neuroimaging in psychosis include the utility for patients and carers of an early and more accurate diagnosis including identification of reversible causes of psychosis or co-morbidity. This in turn may shorten the time over which anti-psychotics are needed, reduce stigma associated with certain psychiatric diagnoses and promote timely intervention. However, the clinical effectiveness review suggests that a policy of screening all first episode psychosis would result in small numbers of clinically significant findings - (0.5% (0%-5%) when CT is used and 5% (0-10%) when MRI is used. On the basis of one study concerned with treatment refractory psychosis (Cunningham-Owens et al., 1980[106]) the number of clinically significant findings appears to increase in patients with chronic psychosis (point estimate 2% with CT). However the yield of findings that impact on diagnosis or management must be balanced against the proportion of findings of unknown clinical significance or incidental findings (10% for MRI and 5% for CT). These incidental findings may lead to further investigation with associated costs and associated anxiety on behalf of patients and carers. A further consideration is the anxiety associated with undergoing neuroimaging investigations themselves. MRI in particular is associated with anxiety reactions in a considerable number of patients (4-30%).[73] Only one study in the clinical effectiveness review provided any information on patients in whom scanning was not possible[102] and only a minority of studies in the review of test accuracy (see Appendix 9) gave this information. It is likely that in practice these types of reactions will be more common in psychotic patients. The issue of consent under such circumstances must also be considered. Finally, CT delivers a dose of radiation to the head. Given that those presenting with a first episode of psychosis are likely to include considerable numbers of young patients, the ethics of screening this patient group with CT, given the low yield of abnormalities, is questionable.

Any potential benefit of neuroimaging in psychosis has to be interpreted in the light of the poor quality of included studies. In addition it has been demonstrated likely that different imaging techniques have different test accuracies (see Appendix 9) and that

test accuracy will be dependent on the underlying pathology. Apart from cost considerations, it has not been possible, given the existing evidence base, to recommend one mode of imaging over another in a heterogeneous group of patients with psychosis. No direct comparisons of the relative performance of CT and MRI were identified in the clinical effectiveness review and indirect comparisons are complicated by the multiplicity of target disorders that may be revealed by neuroimaging. Evidence therefore does not allow investigation of more targeted use of imaging.

New developments in CT and MRI technology, including interventional neuroradiology, and government guidelines for the investigation and treatment of acute stroke and cancer have added to workload pressure by increasing patient throughput and the complexity of examination. A recent report by the British Society of Neuroradiologists[126] further identified that referrals from non-neurological specialities (including psychiatry) have contributed to the pressure on consultant workload. The report cites barriers to local service development including the substantial costs associated with the technology, facilities to house the technology and staff capacity. Although the development of 'hub and spoke' arrangements, with consultant neuroradiologists providing visiting support to radiologists working in district general hospitals, may increase capacity, it is unclear whether this will be sufficient to manage increases in demand. Current, typical waiting times are in the order of 2-4 weeks for CT investigation and 3-12 months for MRI .

Based on recent UK epidemiological studies and population statistics[33,127] the number of cases of first episode psychosis occurring per year in England and Wales can be estimated as approximately 7476. Neuroimaging all cases of first episode psychosis would cost between £583,128 and £1,824,144 (£1.8 million) (NHS reference cost 2005-6[81]) depending on whether CT or MRI is used. This is likely to be an underestimate of the true cost as abnormalities detected on CT may require additional imaging with MRI to determine their precise clinical significance; a diagnostic work-up pattern that can be observed in three of the included studies in the review of clinical effectiveness (Agzarian [86], Bain[88] McKay[101]) and one in the review of relative test accuracy of CT and MRI (see Appendix 9). In addition the cost of modifying or rescheduling imaging in this patient group may not be insignificant as refusal rates are likely to be in excess of the 5-10% quoted in the literature.[73]

Mental health expenditure is reported to be 8-9% of NHS expenditure.[125] The opportunity costs associated with a decision to undertake routine neuroimaging in this patient group need to be considered; in particular the continued need to ensure equitable access to effective treatments and good quality care in patients with psychosis.[32,65,125] In addition, the opportunity cost of routine neuroimaging in first episode psychosis compared to the broader work profiles of diagnostic and interventional neuroradiology require consideration.

8. Discussion

8.1 Statement of principal findings

8.1.1 Clinical effectiveness

- High quality evidence of the benefit of CT or MRI in patients with psychosis was not found. All of the included studies most resembled before-after studies. There were no studies found on time to correct diagnosis or certainty of diagnosis
- There were 16 CT studies, six of which were in FEP patients, plus one CT study in treatment refractory psychosis (schizophrenia) and one review of case reports of misidentification syndromes.
- There were four MRI studies, two of which were in FEP patients.
- There were three CT/ MRI studies, one of which was in FEP patients.
- Almost all of the studies were small so probably underpowered to find a significant additional benefit of structural neuroimaging. The only large study[109] (n=721) included an unspecified proportion of patients with neurological symptoms and signs so cannot address the question whether structural neuroimaging is of benefit in patients with psychosis and no clinical suspicion of additional pathology. It was not considered viable to contact the authors for information on the proportion of patients in this study with no neurological symptoms and signs of additional pathology.
- No studies were found in which patients had specifically experienced deterioration in psychotic symptoms.
- In the CT studies, the percentage of patients with a scan affecting treatment was zero or less than 1.8% in nine studies, four of which were in FEP patients. Three studies in non-FEP patients reported up to 14% of patients with a scan affecting treatment. There were no patients with a change in diagnosis due to the scan in six studies (two of these studies were in FEP patients). In two non-FEP studies, 0.1% and 4% of patients were given a new diagnosis due to the scan. This information was not reported by the remaining studies.
- For MRI studies, two FEP studies reported that only 3% and 9% of FEP patients had a scan affecting treatment. A third non-FEP study reported that 21% of patients had a scan affecting treatment. There were 1% (FEP), 3% (FEP) and 21% (non-FEP) of patients that had a change in diagnosis due to the scan. The fourth study did not provide any useful information.
- For studies using CT or MRI, 4% and 13% of non-FEP patients had a scan affecting treatment. It was not clear how many patients had a scan affecting treatment in the single FEP study. No FEP patients had a change in diagnosis due to the scan (one study) but 8% of non-FEP patients had a change in diagnosis due to the scan (one study).
- In the single study of treatment refractory schizophrenic patients, 2% of patients had a scan affecting clinical treatment but the percentage of patients with a change in diagnosis due to the scan was not reported.
- In a review of case reports of misidentification syndromes, 25% of patients had a scan affecting treatment. The percentage of patients with a change in diagnosis due to the scan was not reported.

- The studies where the patient group was not specified to be first episode or treatment naïve possibly had more clinically significant findings but the accuracy of this is difficult to determine
- The included studies were of a design similar to a before-after study and most used retrospective data. All studies were low in the hierarchy of evidence, with poor levels of reporting. The internal and external validity of the included study was questionable.

8.1.2 Cost effectiveness

- There were no industry submissions for this technology appraisal
- No articles were found that reported directly on the cos-effectiveness of structural neuroimaging (or any form of neuroimaging) in patients with psychosis
- There were five papers, including one based in the UK (1991) that explored the cost-effectiveness of neuroimaging within mental health and neurology (including multiple sclerosis, dementia, neurological diagnosis and intracranial pathology).
- The UK study measured the diagnostic certainty and impact on patient management of MRI in neurosciences. This large cost/outcome descriptive study (n=782) was based on a diagnostic before-after study. It found overall cost savings of procedures rplaced by MRI of £81 per patient and the marginal cost per diagnostic change of £626
- One Australian paper reported the quality of life in a sample of 173 patients with psychosis using two questionnaire measures including SF-36. The physical symptoms mean (SD) scores were 48.1 (9.1) and for mental symptoms was 42.2 (11.2)
- Nine papers reporte quality of life in patients with schizophrenia, using SF-36, SF-12, standard gamble, time trade off or EQ-5D. Putting these results together suggested an average utility for a person with schizophrenia before treatment of 0.5 and after treatment of 0.75

8.1.3 Economic model

- A decision-analytic model was not possible as it required information on the differential response to treatment by cause and the impact upon QoL from having an early diagnosis as opposed to a late diagnosis of an organic cause, which was not found in the literature review
- A threshold analysis with a one-year time horizon was undertaken. This combined the incremental cost of routine scanning with a threshold cost per QALY value of £20,000 and £30,000 to predict the QoL gain required to meet these threshold values
- Routine scanning versus selective scanning appeared to be cost-saving with savings ranging from £228 to £789 with MRI scanning and £346 to £852 with CT scanning with the assumption of a 5% prevalence rate of tumours/cycts or other organic causes amenable to treatment. This meant that for the intervention to be cost-effective, patients would have to suffer a QoL loss of 0.011 to 0.039 with MRI scanning and 0.017 to 0.043 with CT scanning using a £20,000 threshold value.
- These estimates were subjected to sensitivity analysis on three levels of uncertainty that contributed to the cost of antipsychotic medication. With all of

these parameters suitably varied, routine scanning still remained the cost-saving option

- However, when the prevalence rate was varied to 0.5%, MRI was no longer cost saving and patients would need a QoL gain. For CT at 0.5% prevalence, all patients and brain tumour patients would have to suffer a QoL loss from CT only in the scenario where 50% of patients were initially treated in hospital

8.2 Strengths and limitations of the assessment

8.2.1 Strengths of the assessment

- The definition of FEP is not clearly defined or universally accepted. Studies with treatment-naïve psychotic patients could have been included only but the few studies found in new onset psychotic patients did not clearly state whether all included patients had no anti-psychotic treatment before they had a brain scan. Therefore in order to increase the usefulness of the clinical effectiveness review, the inclusion criteria were broadened so that more studies in psychotic patients could be reviewed. This was done because it became obvious during the course of the review that it would be difficult to establish whether first episode psychosis patients were any more or less likely to have unsuspected brain lesions than a more general group of psychotic patients. Also it was difficult to determine how accurately having a first episode was measured and whether the first episode studies were comparable to each other because first episode was not clearly defined.
- Well established systematic review techniques were used. A very wide search looking at a large number of full papers was considered necessary in order to ensure that no relevant studies were missed. This was particularly important for studies including manic, depressed and bipolar patients where the condition may or may not have beeen psychotic in the patients described.
- It is possible that a form of publication bias may have affected the research base available for this systematic review. Where there is a new technology available, there tends to be great enthusiasm for its uptake. If a study does not find a benefit of the new technology there may be reluctance to publish. However, it is noticeable that in the case of the studies evaluating CT, most did not find beneficial effects of the additional use of CT scans in diagnostic workups in psychotic patients with no additional symptoms and signs. It cannot be proven that the reason for such a small number of studies found evaluating structural MRI was because of this type of publication bias. It is highly likely that any study demonstrating the usefulness of a new imaging modality would have been published, so more unpublished studies may exist but they are more likely to demonstrate a lack of effect rather than a benefit.
- No economic evaluation reporting the cost-effectiveness of neuroimaging in first episode psychosis was identified. Therefore our economic evaluation is probably the first to be attempted in this area. A decision-analytic model was attempted but there was insufficient information to populate this so rather than using estimates which could have been relatively inaccurate, a more basic threshold analysis was completed instead.
- The assessment of the clinical benefits of structural neuroimaging would normally be the next step after having assessed the diagnostic accuracy of CT and structural MRI. However, there was no information on sensitivity and specificity of structural neuroimaging in psychosis found. Therefore, one of the

strengths of this report is the incorporation of a systematic review of the test accuracy of CT and MRI in patients with Alzheimer's disease, epilepsy and primary and secondary brain tumours.

8.2.2 Limitations of the assessment

- There is a paucity of good quality evidence on the clinical benefits of structural neuroimaging on which to base this health technology assessment. There were no RCTs, cohort or case-control studies of the benefits of CT or MRI neuroimaging in psychosis. Also, there were no studies found reporting clinical outcomes of structural neuroimaging where patients had a mean age of over 65 years.
- Although there are large numbers of CT and structural MRI studies in treatment naïve or first episode psychosis patients, only morphological outcomes were reported in most of these studies and so they were excluded from this systematic review. The brain morphology in psychotic patients was mostly compared to brain morphology in healthy volunteers or other psychiatric patients. To date, no systematic reviews of either region of interest or voxel-based morphology have demonstrated morphological changes of clinical use for the care of psychotic patients. Therefore this systematic review could not make use of the information from these reviews.
- The included studies did not conform to the traditional model of a diagnostic accuracy study, which reports sensitivity, specificity or other diagnostic outcomes. However, the question in this review was of a phase IV type, i.e. whether patients who undergo this diagnostic test in addition to a standard diagnostic workup fare better (in their ultimate health outcomes) than those patients who have a standard diagnostic workup alone.[128] This type of question has also been described as providing a diagnostic yield. There is little published research about the type of studies required to answer this type of question. The main options are RCTs or before-after studies. RCTs are often the best type of study design in most instances but may not be appropriate here. However, before-after studies have a number of inherent weaknesses which cannot all be solved by careful study design and conduct.[83] The included studies in this systematic review were all similar to before-after studies.
- There was one study included that was a review of published case reports rather than a before-after type study. The review of misidentification syndromes was included because it was likely to be the best evidence available on the use of structural neuroimaging on these rare manifestations of psychosis. However, this review may be biased in that it is likely that only the more unusual examples may have been written up for publication. The review employed a systematic search for appropriate studies published between 1955 to approximately 1990 so structural neuroimaging would not have been available for some of the earlier cases. However, there was a very high rate of scans affecting clinical management (25%) and it is unknown if this would also be true in a before-after study of misidentification syndromes.
- In the case of structural neuroimaging in psychosis there is no single target condition sought. When a CT or MRI is ordered, it is unknown whether the patient will have a bony lesion that will be picked out better in a CT scan or a soft-tissue lesion that will more likely be found on MRI. Therefore, for each patient it is difficult to determine at the outset whether CT or MRI will be more

appropriate. In some instances patients will undergo CT first then MRI. We have not been able to evaluate this strategy because of lack of evidence. It could be argued that an appropriate study to address this difficulty would be an RCT of CT vs MRI in patients with psychosis. Different results would be obtained in patients with psychosis who have no symptoms and signs of additional pathology compared to those with signs of organic psychosis or localising symptoms and signs, depending on the exact nature of the clinical picture.

- There was no readily available quality assessment tool that was completely appropriate for the included studies. Therefore it was necessary to find a relatively appropriate tool (QUADAS – designed for test accuracy studies) and adapt it to the current review. This was done in two ways – removal of two of the items and changing the wording of index and reference tests to relate more accurately to the current review so that it could be argued that the modified QUADAS tool that we used will have different properties from the full tool. However, the QUADAS description does mention situations where each item may not apply.[84] The two items that were not used were whether the reference standard was likely to classify the target condition correctly (item 3) and was the reference standard independent of the index test (item 7). For item 3, it was presumed in all cases that the reference test would classify the target condition correctly so did not distinguish one study from another within the systematic review. Secondly, we have included a mini-systematic review looking at the sensitivity and specificity of CT and MRI to accurately diagnose brain tumours, temporal lobe epilepsy and Alzheimer's dementia. For item 7, the index test (clinical history and examination) could not form part of the reference test (brain scan) because we would then not be able to report the additional value of structural neuroimaging.
- Because the quality of the included studies was poor, no meta-analysis was possible. Therefore, the summary estimate of the number of scans affecting clinical management of patients was derived from an estimate from the results table and correspondingly wide ranges were also estimated.
- A major limitation of the economic model is that it is a threshold analysis. This type of analysis is limited in its ability to consider the detailed progress of patients through treatment pathways and the impact that scanning would have on this process
- A weakness in the threshold analysis is that it only considers the effects of scanning all patients over 12 months. This is largely due to data limitations, as there was no information on the impact of early scanning upon the prognosis of a brain tumour/cyst patient. However it is likely that the QoL gain from early diagnosis will go beyond 12 months and this has been ignored in the analysis but further supports the implementation of routine scanning
- The treatment costs only take into account the costs of antipsychotic medication. They do not include the cost of subsequent treatment should another condition be found following neuroimaging or the cost of inappropriate treatment following a false positive result
- Another limitation of the analysis is the assumption of no mortality affects within the cohort. Also the model assumes that there is no deterioration in disease state from being detected at a later stage with standard practice compared to being detected earlier from routine neuroimaging. This may be approximately correct only if the disease state is relatively slow to develop

8.3 Uncertainties

- There is uncertainty around the prevalence of organic psychosis or the proportions of organic to functional psychosis in the different agegroups. Although it is known that most younger people experience a functional psychosis and many more older people have organic causes, the precise prevalence in the different age groups is currently uncertain.
- There remains considerable uncertainty around the true added value of structural neuroimaging in patients with psychosis (including first episode psychosis) where there are no symptoms and signs of additional pathology. This is because of the poor quality of the evidence found. As mentioned in Section 4, if a before-after study has found no clinical benefit of the new intervention, it is unlikely that a stronger study design on the same question will find a benefit. However, this cannot be known for certain. Also the before-after type studies were mostly of poor quality for this study design so the results found here may not be generalisable to a better quality before-after study.
- For the threshold analysis there were considerable uncertainties around the model parameters, particularly the time delay between diagnosis of psychosis and the scanning undertaken, whether more patients are treated in hospital or at home, the average dose of antipsychotic medication and the prevalence of organic pathology that could be found by structural neuroimaging. If the MRI studies found in the clinical effectiveness review are the most accurate at determining prevalence, then it appears from the threshold analysis that structural neuroimaging with cT or MRI is cost saving. However, if the prevalence is more akin to 0.5%, as suggested by the CT studies in the clinical effectiveness review, then MRI is no longer cost saving and CT is only cost saving if 50% patients are admitted to hospital.
- The model was developed from the NHS perspective. There may be societal benefits of structural neuroimaging to patients such as the quality of life benefit of having a definitive diagnosis where a patient has a condition such as a brain tumour that may in part explain the psychotic symptoms they are experiencing.
- We have no information on the utility gain or loss that would be experienced by patients with psychosis who undergo structural neuroimaging. Potential gains could be from having a more accurate diagnosis or from ruling out serious pathology. Also, there may be psychological gains from having the condition being taken as potentially a physical condition that would warrant an investigative procedure. Potential quality of life losses could arise for CT from the dose of radiation to the head to all who are scanned and from missed pathology as CT is not 100% sensitive. Potential quality of life losses could arise for MRI from the noise and claustrophobic nature of the investigation and from incidental findings that could seriously worry a psychotic patient. These could be seen as the equivalent of false positive findings. If a person with psychosis is very ill they may not be able to cope with the investigation. Also if serious, inoperable pathology is found, an early scan may cause loss of quality of life compared to a later scan.

8.4 Other relevant factors

If CT or structural MRI was used to check for serious pathology, such as brain tumours, that would affect clinical management in patients with psychosis and no

other symptoms and signs of an organic cause of psychosis and/or symptoms of a space occupying lesion of the brain, then in effect this could be seen as being more similar to a screening test than a diagnostic test. As such it could be useful to examine the features of such a programme to determine whether the established criteria for screening tests could be used to assess the programme. Some of the relevant issues are discussed in Table 43 below.

Table 43. National Screening Committee criteria for appraising the viability, effectiveness and appropriateness of a screening programme

Criteria	Discussion
1. The condition should be an important health problem	It is undoubtedly true that the conditions being screened for are important health problems in terms of severity rather than prevalence.
2. The epidemiology and natural history should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage	We know a great deal about the epidemiology and particularly the natural history of the conditions being screened for but not in their manifestations with psychosis as the principle presentation. However, this group of patients with psychosis specifically do not have any symptoms and signs of additional conditions. The only detectable risk factor is that found in the CT or structural MRI scan
3. All of the cost-effective primary prevention interventions should have been implemented as far as practicable	Not relevant in this situation
4. There should be a simple, safe, precise and validated screening test	Both CT and structural MRI are relatively simple and safe procedures and are also extremely precise and well validated. Head CT does result in ionising radiation to the head which can cause further morbidity. There is the potential for CT to cause more harm than good if there is no pathology found in the scan.
5. The distribution of test values within the target population should be known and a suitable cut-off level defined and agreed	From the systematic review of before-after studies we estimate that the proportions of scans that affect clinical treatment are approximately 5% (range 0-10%) for MRI and 0.5% (range 0-5%) for CT. Also the proportions of incidental findings (false positives) are approximately 10% for MRI and 5% for CT. We can also estimate that MRI is 100% sensitive and CT is approximately 95% sensitive in the detection of the target conditions. These are relatively wide ranges. However, it is acknowledged that the knowledge of test values needed for diagnosis is less than that required for a screening programme. However, there are some causes of organic psychosis where CT or MRI cannot be used for diagnosis, particularly in temporal lobe epilepsy
6. The test should be acceptable to the population	MRI is generally acceptable to the population and is only contraindicated in those patients with indwelling metal parts. There is a refusal rate in the general public of approximately 5-10% due to anxiety or claustrophobia and this rate may be higher in people with psychosis

7. There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals	Further diagnostic investigation depends on the condition found. There does not seem to be an evidence base of the options for people with incidental findings following brain scanning and whether and how these should be communicated to patients in order to prevent anxiety
8. There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment	Once serious morbidity is detected by scanning, further treatment follows according to the condition found. It is assumed that early treatment, particularly for malignant brain tumours would almost always lead to better outcomes than late treatment. For other organic causes, eg dementia, this is not necessarily the case as early diagnosis may make no difference to the subsequent disease course
9. There should be agreed evidence based policies covering which individuals should be offered treatment and the appropriate treatment offered	It is generally assumed that all patients with serious conditions discovered by scanning should be offered appropriate treatment
10. Clinical management of the condition and patient outcomes should be optimised by all health care providers prior to participation in a screening programme	Not relevant in this situation
11. There should be evidence from high quality RCTs that the screening programme is effective in reducing mortality or morbidity	To date the only evidence is from before-after studies
12. There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/intervention) is clinically, socially and ethically acceptable to health professionals and the public	Although screening using brain scanning is clinically acceptable to health professionals and the public, this is based on the understanding that it is a useful exercise. There is a comment to NICE on the scope for this project from a member of the Royal College of Psychiatrists "I suspect that doing a scan in first episode psychosis is generally encouraged but it is done more to ease the anxiety of the clinician than for any obvious benefit of the patient." There is also an issue of whether it is possible to obtain fully informed consent in patients who are very psychotic
13. The benefit of the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment)	If a patient with psychosis has a serious condition found from brain scanning, this is obviously of benefit. However, we do not know if there is much psychological harm from the relatively high rates of false positives and incidental findings.
14. The opportunity cost of the screening programme (including testing, diagnosis and treatment) should be economically balanced in relation to expenditure on medical care as a whole	The opportunity cost of this screening programme is considerable (see section 7 of this report). It appear that screening for patients with psychosis and no other symptoms and signs of addition pathology is not a cost-effective strategy
15. There should be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards	To date, it appears that the decision to screen varies around the country and from one psychiatrist to another, partly depending on availability and waiting times
16. Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening programme	There would be considerable costs if this screening strategy was implemented (see section 7)
17. All other options for managing the condition should have been considered (eg improving treatment, providing other services)	The other main option for management is to rely on clinical acumen to detect when patients develop early signs of additional pathology

Although it is acknowledged here that structural neuroimaging is used for diagnosis rather than screening, the issues discussed above suggest that there would be a considerable number of issues and uncertainties that would need to be investigated.

9. Conclusions

9.1 Implications for service provision

The current Local Delivery Plan for mental health early intervention services includes the requirement for psychosis services to provide a quick diagnosis of the first onset of a psychotic disorder and appropriate treatment including intensive support in the early years.[129] The intention is to reduce the duration of untreated psychosis to a service median of less than 3 months (individual maximum less than six months). At the moment, structural neuroimaging cannot help with the diagnosis and treatment of psychosis per se. There is no current requirement for all new psychosis patients to undergo neuroimaging to screen for unsuspected pathology. The evidence to date suggests that if this type of screening were implemented, very little would be found to affect clinical management in addition to that suspected by a full clinical history and neurological examination. If it is agreed that the effects of routine scanning would not cause a QoL loss overall, and the prevalence of organic causes is approximately 5%, then the analysis has shown that the intervention could be cost-saving. This is because of the expense of antipsychotic medication and the associated cost of treatment following a delayed diagnosis. It assumes that once an organic cause of psychosis is discovered, the patients will no longer need antipsychotic medication, but does not take into account the treatment costs associated with the change in diagnosis. If, however, the prevalence of organic causes is similar to 0.5%, then structural neuroimaging is no longer cost saving in most scenarios. As the prevalence of organic psychosis varies with age, where younger patients rarely have organic conditions, this has implications for service provision

9.2 Suggested research priorities

- There needs to be an assessment of which patients with psychosis in the different age groups are currently being sent for CT and MRI and reasons for referral.
- There needs to be much better quality research to answer the question of whether patients with psychosis and no symptoms and signs of additional pathology should have a routine CT or structural MRI scan. Ordinarily, the best study design to answer this type of decision problem would be an RCT. However, in this situation, where neuroimaging is looking for a wide range of conditions, it would be very difficult to determine the appropriate outcomes. This is because multiple conditions are being sought. If health-related quality of life and mortality due to undetected treatable conditions were the outcomes measured, the sample size would need to be massive. Because of this, a much more appropriate study design would be a diagnostic before and after study, which also incorporated costs. If a properly conducted before and after study showed little positive benefit of structural neuroimaging, then it is likely that there is no benefit. Paradoxically, it may require that all new psychotic patients under the age of 65 be enrolled in such a study to clearly prove that structural neuroimaging is not warranted in these patients. There are potential ethical problems because the evidence base at the moment suggests little benefit from screening and potential harm, particularly from ionising radiation if CT was used.

- There needs to be a suitable study of the additional benefits of structural neuroimaging in patients over the age of 65. Anecdotal evidence suggests that there is a higher relative frequency of findings in this age group so it is likely that this study may not need to be quite as large as for the younger age groups. It is also possible that, pecause of the higher prevalence of organic psychosis in this group, structural neuroimaging may be cost saving
- There needs to be further research on whether CT or structural MRI should be used in patients with psychosis. This could be an RCT of CT vs MRI. Different results would be obtained in patients with psychosis who have no symptoms and signs of additional pathology compared to those with signs of organic psychosis or localising symptoms and signs, depending on the exact nature of the clinical picture. So both those with and without additional symptoms and signs would need to be enrolled and then assessed separately. Alternatively, this could be a diagnostic before and after study where all patients get both CT and MRI.
- The only evidence available of misidentification syndromes (review of published case reports) suggested a higher rate of scans affecting clinical management (25%). It would be useful to know if this would also be found in a before-after study of misidentification syndromes.

10. Appendices

Appendix 1. ARIF search protocol (October 2006 version)

In the first instance the focus of ARIF's response to requests is to identify systematic reviews of research. The following will generally be searched, with the addition of any specialist sources as appropriate to the request.

1. Cochrane Library
- Cochrane Database of Systematic Reviews (CDSR)
- Database of Abstracts of Reviews of Effects (DARE)
- Cochrane Central Register of Controlled Trials (CENTRAL)
- Health Technology Assessment (HTA) database

2. ARIF Database
An in-house database of reviews compiled by scanning current journals and appropriate www sites. Many reviews produced by the organisations listed below are included.

3. NHS CRD
- DARE
- Health Technology Assessment Database
- Completed and ongoing CRD reviews

4. Health Technology Assessments and Evidence Based guidelines
- NICE appraisals and work plans for TARs, Interventional Procedures and Guidelines programmes, Public Health excellence
- SBU – Swedish Council on Technology Assessment in Health Care
- NHS Coordinating Centre for Health Technology Assessments
- Canadian Agency for Drugs and Technologies in Health
- New Zealand Health Technology Assessment
- STEER Reports (no longer published)
- Agency for Healthcare Research and Quality (AHRQ)
- Alberta Heritage Foundation
- McGill Medicine Technology Assessment Unit of MUHC (McGill University Health Centre)
- Monash reports – Centre for Clinical Effectiveness, Monash University
- US Department of Veterans Affairs
- NHS QIS (Quality Improvement Scotland)
- SIGN (Scottish Intercollegiate Guidelines Network)

5. Clinical Evidence

6. Bandolier

7. National Horizon Scanning Centre

8. TRIP Database

9. Bibliographic Databases
- Medline – systematic reviews
- Embase – systematic reviews
- Other specialist databases

10. Contacts

- Cochrane Collaboration (via Cochrane Library)
- Regional experts, especially Pharmacy Prescribing Unit, Keele University (& MTRAC) and West Midlands Drug Information Service for any enquiry involving drug products.

Appendix 2. Search strategies

Clinical effectiveness searches

Database: MEDLINE (Ovid) In-Process & Other Non-Indexed Citations December 04, 2006
Search Strategy:

1 MRI.mp. or exp Magnetic Resonance Imaging/
2 magnetic resonance imag$.mp.
3 computeri?ed axial tomography.tw.
4 X ray computed tomography.mp. or exp Tomography, X-Ray Computed/
5 structural neuroimag$.tw.
6 neuroimag$.tw.
7 CT scan$.mp.
8 CAT.mp.
9 brain imag$.mp.
10 or/1-9
11 first episode.mp.
12 structural.mp.
13 organic.mp.
14 secondary.mp.
15 or/11-14
16 psychosis.mp.
17 psychotic$.mp.
18 mental disorder$.mp.
19 or/16-18
20 10 and 15 and 19

Database: MEDLINE (Ovid) 1966 to November Week 3 2006
Search Strategy:

1 MRI.mp. or exp Magnetic Resonance Imaging/
2 magnetic resonance imag$.mp.
3 computeri?ed axial tomography.tw.
4 X ray computed tomography.mp. or exp Tomography, X-Ray Computed/
5 structural neuroimag$.tw.
6 neuroimag$.tw.
7 CT scan$.mp.
8 CAT.mp.
9 brain imag$.mp.
10 or/1-9
11 exp Psychotic Disorders/ or psychosis.mp.
12 exp Psychoses, Substance-Induced/
13 exp Mental Disorders/
14 or/11-13
15 10 and 14
16 (systematic adj review$).tw.
17 (data adj synthesis).tw.
18 (published adj studies).ab.
19 (data adj extraction).ab.
20 meta-analysis/
21 meta-analysis.ti.
22 comment.pt.
23 letter.pt.
24 editorial.pt.

25 animal/
26 human/
27 25 not (25 and 26)
28 15 not (22 or 23 or 24 or 27)
29 or/16-21
30 28 and 29
31 first episode.mp.
32 structural.mp.
33 organic.mp.
34 secondary.mp.
35 or/31-34
36 30 and 35
37 30 or 36

Database: Ovid MEDLINE(R) 1966 to November Week 3 2006
Search Strategy:

1 MRI.mp. or exp Magnetic Resonance Imaging/
2 magnetic resonance imag$.mp.
3 computeri?ed axial tomography.tw.
4 X ray computed tomography.mp. or exp Tomography, X-Ray Computed/
5 structural neuroimag$.tw.
6 neuroimag$.tw.
7 CT scan$.mp.
8 CAT.mp.
9 brain imag$.mp.
10 or/1-9
11 exp Psychotic Disorders/ or psychosis.mp.
12 exp Psychoses, Substance-Induced/
13 exp Mental Disorders/
14 or/11-13
15 10 and 14
16 first episode.mp.
17 structural.mp.
18 organic.mp.
19 secondary.mp.
20 or/16-19
21 randomized controlled trial.pt.
22 controlled clinical trial.pt.
23 randomized controlled trials.sh.
24 random allocation.sh.
25 double blind method.sh.
26 single-blind method.sh.
27 or/21-26
28 (animals not human).sh.
29 27 not 28
30 clinical trial.pt.
31 exp clinical trials/
32 (clin$ adj25 trial$).ti,ab.
33 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
34 placebos.sh.
35 placebo$.ti,ab.
36 random$.ti,ab.
37 research design.sh.
38 or/30-37

39 38 not 28
40 39 not 29
41 comparative study.sh.
42 exp evaluation studies/
43 follow up studies.sh.
44 prospective studies.sh.
45 (control$ or prospectiv$ or volunteer$).ti,ab.
46 or/41-45
47 46 not 28
48 47 not (29 or 40)
49 29 or 40 or 48
50 exp Case-Control Studies/ or exp "Case Reports [Publication Type]"/
51 exp Cohort Studies/
52 49 or 50 or 51
53 15 and 20
54 52 and 53

Database: EMBASE 1980 to 2006 Week 48
Search Strategy:

1 MRI.mp. or exp Nuclear Magnetic Resonance Imaging/
2 magnetic resonance imag$.mp.
3 computeri?ed axial tomography.tw.
4 exp COMPUTER ASSISTED TOMOGRAPHY/ or exp COMPUTED TOMOGRAPHY SCANNER/ or exp BRAIN TOMOGRAPHY/
5 structural neuroimag$.tw.
6 neuroimag$.tw.
7 CT scan$.mp.
8 CAT.mp.
9 brain imag$.mp.
10 or/1-9
11 psychosis.mp. or exp PSYCHOSIS/
12 exp Mental Disease/
13 psychotic$.mp.
14 or/11-13
15 first episode.mp.
16 structural.mp.
17 organic.mp.
18 secondary.mp.
19 or/15-18
20 10 and 14 and 19
21 randomized controlled trial/
22 exp clinical trial/
23 exp controlled study/
24 double blind procedure/
25 randomization/
26 placebo/
27 single blind procedure/
28 (control$ adj (trial$ or stud$ or evaluation$ or experiment$)).mp.
29 ((singl$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$)).mp.
30 (placebo$ or matched communities or matched schools or matched populations).mp.
31 (comparison group$ or control group$).mp.
32 (clinical trial$ or random$).mp.
33 (quasiexperimental or quasi experimental or pseudo experimental).mp.
34 matched pairs.mp.

35 or/21-34
36 exp CASE CONTROL STUDY/ or exp CASE STUDY/
37 35 or 36
38 20 and 37

Database: CINAHL - Cumulative Index to Nursing & Allied Health Literature 1982 to November Week 4 2006
Search Strategy:

1 MRI.mp. or exp Magnetic Resonance Imaging/
2 magnetic resonance imag$.tw.
3 computeri?ed axial tomography.tw.
4 CAT.mp.
5 CT scan$.mp. or exp Tomography, X-Ray Computed/
6 structural neuroimag$.tw.
7 neuroimag$.tw.
8 brain imag$.mp.
9 or/1-8
10 psychosis.mp. or exp Psychotic Disorders/
11 exp mental disorders/ or psychotic disorders/
12 psychotic$.mp.
13 or/10-12
14 first episode.mp.
15 structural.mp.
16 organic.mp.
17 secondary.mp.
18 or/14-17
19 9 and 13 and 18
20 9 and 13
21 exp Clinical Trials/
22 randomi?ed.tw.
23 CASE CONTROL STUDIES/ or exp CASE STUDIES/ or case.mp.
24 cohort.mp.
25 or/21-24
26 20 and 25

Database: PsycINFO 1967 to November Week 4 2006
Search Strategy:

1 exp Neuropathology/
2 ct scan$.mp.
3 CAT.mp.
4 mri.mp. or exp Magnetic Resonance Imaging/
5 neuroimag$.tw.
6 exp Tomography/
7 or/1-6
8 exp mental disorders/
9 psychosis.mp. or exp Psychosis/
10 psychotic$.mp.
11 or/8-10
12 7 and 11
13 first episode.mp.
14 structural.mp.
15 secondary.mp.
16 exp organic brain syndromes/

17 organic.mp.
18 or/13-17
19 12 and 18
20 randomi?ed.tw.
21 exp Clinical Trials/
22 cohort.mp.
23 case.mp.
24 or/20-23
25 19 and 24

Cochrane Library (Wiley) 2006 Issue 4 (CENTRAL)
Search strategy

#1 mri
#2 magnetic next resonance
#3 ct
#4 cat
#5 axial next tomography
#6 MeSH descriptor Tomography, X-Ray Computed explode all trees
#7 MeSH descriptor Magnetic Resonance Imaging explode all trees
#8 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)
#9 psychosis
#10 psychotic
#11 MeSH descriptor Psychotic Disorders explode all trees
#12 MeSH descriptor Mental Disorders explode all trees
#13 (#9 OR #10 OR #11 OR #12)
#14 (#8 AND #13)

Cost effectiveness searches

Database: Ovid MEDLINE(R) 1966 to November Week 3 2006
Search Strategy:

1 CAT.ti.
2 CT.ti.
3 tomography.ti.
4 brain.tw.
5 neuro$.tw.
6 cost.ti.
7 or/1-3
8 or/4-5
9 7 and 6
10 9 and 8

Database: Ovid MEDLINE(R) 1966 to November Week 3 2006
Search Strategy:

1 MRI.mp. or exp Magnetic Resonance Imaging/
2 cost effectiveness.mp. or exp Cost-Benefit Analysis/
3 1 and 2
4 MRI.mp. or exp Magnetic Resonance Imaging/
5 exp Cost-Benefit Analysis/ or cost effective$.mp.
6 4 and 5
7 MRI.ti.
8 magnetic resonance.ti.

9 7 or 8
10 cost effect$.ti.
11 9 and 10

Database: Ovid MEDLINE(R) 1966 to November Week 3 2006
Search Strategy:

1 MRI.mp. or exp Magnetic Resonance Imaging/
2 magnetic resonance imag$.mp.
3 computeri?ed axial tomography.tw.
4 X ray computed tomography.mp. or exp Tomography, X-Ray Computed/
5 structural neuroimag$.tw.
6 neuroimag$.tw.
7 CT scan$.mp.
8 CAT.mp.
9 brain imag$.mp.
10 or/1-9
11 exp Psychotic Disorders/ or psychosis.mp.
12 exp Psychoses, Substance-Induced/
13 exp Mental Disorders/
14 or/11-13
15 10 and 14
16 economics/
17 exp "costs and cost analysis"/
18 cost of illness/
19 exp health care costs/
20 economic value of life/
21 exp economics medical/
22 exp economics hospital/
23 economics pharmaceutical/
24 exp "fees and charges"/
25 or/16-24
26 15 and 25

Database: Ovid MEDLINE(R) 1966 to November Week 3 2006
Search Strategy:

1 MRI.mp. or exp Magnetic Resonance Imaging/
2 magnetic resonance imag$.mp.
3 computeri?ed axial tomography.tw.
4 X ray computed tomography.mp. or exp Tomography, X-Ray Computed/
5 structural neuroimag$.tw.
6 neuroimag$.tw.
7 CT scan$.mp.
8 CAT.mp.
9 brain imag$.mp.
10 or/1-9
11 exp Psychotic Disorders/ or psychosis.mp.
12 exp Psychoses, Substance-Induced/
13 exp Mental Disorders/
14 or/11-13
15 10 and 14
16 decision support techniques/
17 markov.mp.
18 exp models economic/

19 decision analysis.mp.
20 cost benefit analysis/
21 or/16-20
22 15 and 21

Database: Ovid MEDLINE(R) 1966 to November Week 3 2006
Search Strategy:

1 decision support techniques/
2 markov.mp.
3 exp models economic/
4 decision analysis.mp.
5 cost benefit analysis/
6 or/1-5
7 exp Psychotic Disorders/ or first episode psychosis.mp.
8 exp Psychoses, Substance-Induced/ or psychosis.mp.
9 or/7-8
10 6 and 9

Database: Ovid MEDLINE(R) 1966 to November Week 3 2006
Search Strategy:

1 MRI.mp. or exp Magnetic Resonance Imaging/
2 magnetic resonance imag$.mp.
3 computeri?ed axial tomography.tw.
4 X ray computed tomography.mp. or exp Tomography, X-Ray Computed/
5 structural neuroimag$.tw.
6 neuroimag$.tw.
7 CT scan$.mp.
8 CAT.mp.
9 brain imag$.mp.
10 or/1-9
11 quality of life/
12 life style/
13 health status/
14 health status indicators/
15 or/11-14
16 exp Psychoses, Substance-Induced/ or exp Psychotic Disorders/ or psychosis.mp.
17 first episode psychosis.mp.
18 or/16-17
19 15 and 17
20 10 and 15
21 18 and 15
22 19 or 20 or 21

Database: EMBASE (Ovid) 1980 to 2006 Week 47
Search Strategy:

1 exp "COST BENEFIT ANALYSIS"/ or exp "COST EFFECTIVENESS ANALYSIS"/ or exp "COST"/ or cost$.mp.
2 cost.ti.
3 brain$.mp.
4 neuro$.mp.
5 or/3-4
6 CAT.mp.

7 CT scan$.mp. or exp Computer Assisted Tomography/
8 (computeri?ed adj2 tomography).mp.
9 or/6-8
10 9 and 1 and 5
11 9 and 2 and 5

Database: EMBASE (Ovid) 1980 to 2006 Week 47
Search Strategy:

1 MRI.mp. or exp Nuclear Magnetic Resonance Imaging/
2 magnetic resonance imag$.mp.
3 or/1-2
4 exp "COST BENEFIT ANALYSIS"/ or exp "COST EFFECTIVENESS ANALYSIS"/ or exp "COST"/ or cost$.mp.
5 4 and 3
6 cost.ti.
7 3 and 6
8 brain$.mp.
9 neuro$.mp.
10 or/8-9
11 10 and 7

Database: EMBASE (Ovid) 1980 to 2006 Week 47
Search Strategy:

1 psychosis.mp. or exp PSYCHOSIS/
2 first episode psychosis.mp.
3 or/1-2
4 cost benefit analysis/
5 cost effectiveness analysis/
6 cost minimization analysis/
7 cost utility analysis/
8 economic evaluation/
9 (cost or costs or costed or costly or costing).tw.
10 (economic$ or pharmacoeconomic$ or price$ or pricing).tw.
11 (technology adj assessment$).tw.
12 or/4-11
13 3 and 12
14 2 and 12

Database: EMBASE 1980 to 2006 Week 47
Search Strategy:

1 quality of life.mp. or exp "Quality of Life"/
2 health status.mp. or exp Health Status/
3 life style.mp. or exp Lifestyle/
4 or/1-3
5 exp Organic Brain Syndrome/
6 organic psychosis.mp.
7 first episode.mp.
8 or/5-7
9 4 and 8

Cochrane Library (Wiley) 2006 Issue 4 (CENTRAL)
Search strategy

ID	Search
#1	mri
#2	magnetic next resonance
#3	ct
#4	cat
#5	axial next tomography
#6	MeSH descriptor Tomography, X-Ray Computed explode all trees
#7	MeSH descriptor Magnetic Resonance Imaging explode all trees
#8	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)
#9	psychosis
#10	psychotic
#11	MeSH descriptor Psychotic Disorders explode all trees
#12	MeSH descriptor Mental Disorders explode all trees
#13	(#9 OR #10 OR #11 OR #12)
#14	(#8 AND #13)

Database: OHE HEED November 2006 issue
Terms used:

Psychosis or psychotic and first or organic or structural

Appendix 3. Categorisation of conditions as psychotic or otherwise

Disorder	Conditions required for an included study
Delusional misidentification syndromes in which psychosis is always a feature	
Capgras syndrome	Should meet criteria for first episode
Frégoli syndrome	Should meet criteria for first episode
Delusion of subjective doubles	Should meet criteria for first episode
Intermetamorphosis	Should meet criteria for first episode
Reduplicative paramnesia	Should meet criteria for first episode
Psychotic syndromes in which psychosis is always a feature	
Cotard's Syndrome	Should meet criteria for first episode
Charles Bonnet Syndrome	Should meet criteria for first episode
Body dysmorphic disorder or Dysmorphobia	Should meet criteria for first episode
Othello Syndrome	Should meet criteria for first episode
Pathological jealousy	Should meet criteria for first episode
Erotomania	Should meet criteria for first episode
Psychotic depression	Should meet criteria for first episode
Schizophrenia	Should meet criteria for first episode
Conditions in which psychosis is a possible feature	
Depression (including severe or major)	Must mention "psychotic" in abstract
Unipolar depression	Must mention "psychotic" in abstract
Dementia	Must mention "psychotic" in abstract
Alzheimer's Disease	Must mention "psychotic" in abstract
Frontotemporal dementia (FTD)	Must mention "psychotic" in abstract
Systemic lupus erythematosus (SLE)	Must mention "psychotic" in abstract
Delirium	Must mention "psychotic" in abstract
Mood disorders	Must mention "psychotic" in abstract
Personality disorder	Must mention "psychotic" in abstract
Borderline personality disorder	Must mention "psychotic" in abstract
Bipolar	Must mention "psychotic" in abstract
Schizotypal personality disorder	Must mention "psychotic" in abstract
Temporal lobe epilepsy	Must mention "psychotic" in abstract
Conditions in which psychosis is not a feature	
Parkinson's disease (iatrogenic psychosis)	Exclude in all circumstances
Mild cognitive impairment	Exclude in all circumstances
Post traumatic stress disorder	Exclude in all circumstances
Tardive dyskinesia	Exclude in all circumstances
Autism	Exclude in all circumstances
Obsessive compulsive disorder (OCD)	Exclude in all circumstances

Appendix 4. Data extraction form

Trial details

Author, year [Trial name] Ref manager no	
Country(ies) and yrs of recruitment	
Trial design	
CT/ MRI system used	
Reason for scanning given	
Comparator	
Standard examination	
Setting	
Comments:	

Patient characteristics

Author, year, [Trial name]	
Population	
Patient numbers	
Age (years) Mean (SD) [range]	
Sex Proportion male (%)	
Presenting diagnoses/ previous diagnosis and criteria (eg DSM-IV or DSM-III-R or ICD-10)	
Duration of illness Mean (SD) [range]	
Age at diagnosis Mean (SD) [range]	
Previous treatment for psychosis	
Concomitant condition	
Diagnosis and proportions of sample at start of study	
Diagnosis and proportions at end of study	
Change in diagnosis following scan	
Inclusion/exclusion criteria	
Follow up points (e.g. 3m, 6m, 12m…)	
Comments	

Outcomes extracted data in red calculated data in blue

Author, year, [Trial name]	
Time point	
Mortality in scanned group due to undetected treatable causes of FEP	
Morbidity in scanned group due to undetected treatable causes of FEP	
Proportion of scans identifying unknown or unsuspected organic causes of FEP	
Pathology found (number)	
Proportion of scans that 'rule-out' organic causes of FEP	
Proportion of scans revealing information of clinical value	
Proportion of scans identifying abnormal pathology of no clinical importance	
Severity and progression of FEP	
Subsequent service use	
Proportion did not scan (reasons)	
Major adverse events due to scanning	
Health-related quality of life	
Length of untreated psychosis	
Who performed clinical evaluation/ image analysis	
Were clinical variables collected prospectively or retrospectively?	
No. patients with/ without potentially reversible cause of psychosis as defined by the neuroimaging results	
Comments	

Subgroup analyses

Author, year, [Trial name]	
Age	
Gender	
Comments	

Appendix 5. QUADAS quality assessment tool

	Author, year, [Trial name]	
No	Item	y/n/unclear
1	Was the spectrum of patients representative of patients who will receive the test in practice?	
2	Were the selection criteria clearly described?	
3	Is the reference standard likely to classify the target condition correctly?	
4	Is the period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	
5	Did the whole sample or a random selection of the sample receive verification using a reference standard of diagnosis?	
6	Did the patients receive the same reference standard regardless of index test?	
7	Was the reference standard independent of the index test (ie the index test did not form part of the reference standard)?	
8	Was the execution of the index test described in sufficient detail to permit replication of the test?	
9	Was the execution of the reference standard described in sufficient detail to permit its replication?	
10	Were the index test results interpreted without knowledge of the results of the reference standard?	
11	Were the reference standard results interpreted without knowledge of the index test?	
12	Were the same clinical results available when test results were interpreted as would be available when the test is used in practice?	
13	Were uninterpretable/intermediate test results reported?	
14	Were withdrawals from the study explained?	

Appendix 6. Quality assessment tables used

Table 44. Modified QUADAS tool

Item*	Question
1	Was the spectrum of patients representative of patients who will receive the test in practice?
2	Were the selection criteria clearly described?
4	Is the period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?
5	Did the whole sample (W) or a random selection (R) of the sample receive verification using a reference standard of diagnosis?
6	Did the patients receive the same reference standard regardless of index test?
8	Was the execution of the index test described in sufficient detail to permit replication of the test?
9	Was the execution of the reference standard described in sufficient detail to permit its replication?
10	Were the index test results interpreted without knowledge of the results of the reference standard?
11	Were the reference standard results interpreted without knowledge of the index test?
12	Were the same clinical results available when test results were interpreted as would be available when the test is used in practice?
13	Were uninterpretable/intermediate test results reported?
14	Were withdrawals from the study explained?
* Question numbers refer to original QUADAS tool	

Table 45. QUADAS quality assessment for CT studies

	*1	2	4	5	6	8	9	10	11	12	13	14
Adams et al., 1996[85] (Canada)	Yes	Yes	Yes	W	Yes	No	No	No	Unclear	Yes	Yes Actual pathology NR	No
Agzarian et al., 2006[86] (Australia)	No	Yes	Unclear	W	No Some contrast/ some non-contrast	No	No	Unclear	Unclear	Unclear	Yes (3 scans showed non-specific abnormalities which were followed up with MRI), actual pathology NR for psychosis patients.	Withdraw-als NR
Ananth etal., 1992[87] (USA)	No	No	Yes	R	Yes	No	No	Unclear	Unclear	Unclear	No	No
Ananth etal., 1993[57] (USA)	No	No	Yes	W	Yes	No	No	Unclear	Yes	Unclear	No	Withdraw als NR
Bain et al., 1998[88] (USA)	?Yes	No	Yes	W	Yes	No	No	Unclear	Unclear	Unclear	No	Withdraw als NR

Battaglia & Spector, 1988[89] (USA)	Yes	Yes	Yes	W	Yes	No	No	Unclear	Unclear	Unclear	No	Withdrawals NR
Colohan et al., 1989[91] (Ireland)	Unclear	No	Unclear	W	Yes	No	No	Unclear	Unclear	Unclear	No	Withdrawals NR
Emsley et al., 1986[92] (South Africa)	No	Yes	Unclear	W	Yes	No	No	Unclear	Yes	Unclear	No	Withdrawals NR
Evans et al., 1982[93] (UK)	No	No	Unclear	W	Yes	No	No	Unclear	Unclear	Unclear	No	No
Gewirtz et al., 1994[94] (USA)	No	Yes	Yes	W	Yes	No	No	Unclear	Unclear	Unclear	No	Yes
Jeenah et al., 2007[95] (South Africa)	?Yes	Yes	Unclear	W	Yes	No	No	Unclear	Yes	Unclear	Yes Actual pathology for FEP patients NR.	Withdrawals NR
Larson et al., 1981[96] (USA)	Unclear	Yes	Unclear	W	Yes	No	No	Unclear	Unclear	Unclear	Yes Actual pathology NR	Withdrawals NR
McClellan et al., 1988[100] (USA)	No	Yes	Unclear	W	Yes	No	No	Unclear	Unclear	Unclear	No	Withdrawals NR
Roberts & Lishman, 1984[103] (UK)	Unclear	No	Unclear	W	Yes	No	No	Unclear	No	Unclear	Yes Actual pathology NR	Withdrawals NR

Schemmer et al., 1999[104] (Canada)	Unclear	No	Unclear	W	Yes	No	No	Unclear	Unclear	Unclear	Yes Actual pathology NR	Withdrawals NR
Vavilov et al., 1993[107] (Russia)	No	No	Unclear	W	Yes	No	No	Unclear	Unclear	Unclear	No	Withdrawals NR

Table 46. Quality for CT scan studies

Reference	Non-scans explained? (n not scanned)	Consecutive recruitment?	Prospective collection of clinical variables?	Who performed clinical evaluation/ image analysis?
Adams et al., 1996[85] (Canada)	No (13)	Yes	Yes	Radiologist Medical diagnosis was assigned by the senior staff psychiatrist after all information, including histories, physical exams, labs and neuroimaging were complete.
Agzarian et al., 2006[86] (Australia)	NR	Yes	No	NR
Ananth etal., 1992[87] (USA)	No (38)	Unclear	Scans Yes Diagnosis No	Physical and neurological exams were carried out by board certified internist and neurologist. In all cases the ward physicians had completed diagnostic evaluations (both physical and psychiatric) and formulated treatment plans.
Ananth etal., 1993[57] (USA)	NR	Unclear	Yes Initial diagnosis No	CT scans were read by 2 neurologists who were blind to the patients' history and the initial diagnosis. In all cases the ward physicians had completed diagnostic evaluations (both physical and psychiatric) and formulated treatment plans.
Bain et al., 1998[88] (USA)	NR	Unclear	No	Neurological exam by psychiatrist within 24h of admission. Psychiatrist also obtained medical history. Admission diagnoses performed by psychiatric resident/ board-certified psychiatrist. Discharge diagnoses made by board-certified psychiatrist using DSM-III-R criteria. CT read by neuroradiologist and also radiology resident for some films (number NR).
Battaglia & Spector, 1988[89] (USA)	NR	Unclear	Yes	Neuroradiologist No details

Colohan et al., 1989[91] (Ireland)	NR	Unclear	No	Consultant neuroradiologist No details
Emsley et al., 1986[92] (South Africa)	NR	Yes	No	CTs assessed by one of the study authors (radiologist) without reference to the original reports and in the absence of clinical information.
Evans et al., 1982[93] (UK)	No	Yes	No	Consultant radiologist
Gewirtz et al., 1994[94] (USA)	NR	Yes	Re-evaluation of scan report Yes Psychiatric diagnostic data No	Neuroradiologist blind to original scan report. Other assessments by ward psychiatrists.
Jeenah et al., 2007[95] (South Africa)	NR	Unclear	Yes	Scan read by radiologist blind to patients history and initial diagnosis.
Larson et al., 1981[96] (USA)	NR	Yes	No	NR
McClellan et al., 1988[100] (USA)	NR	Unclear	No	NR
Roberts & Lishman, 1984[103] (UK)	NR	Unclear	No	Routine scan reporting by one of two consultant neuroradiologists not blind to salient clinical details.
Schemmer et al., 1999[104] (Canada)	NR	Unclear	No	NR
Vavilov et al., 1993[107] (Russia)	NR	Unclear	No	NR

Table 47. QUADAS quality assessment for MRI studies

	1*	2	4	5	6	8	9	10	11	12	13	14
Borgwardt et al., 2006[90] (Switzerland)	Yes	Yes	Yes	W	Yes	No	Yes	Unclear	Yes	Unclear	No	No
Lesser et al., 1991[97] (USA)	No	Yes	Yes	W	Yes	No	Yes	Unclear	Yes	Unclear	No	Withdrawals NR
Lubman et al., 2002[99] (Australia)	Unclear	Yes	Unclear	W	Yes	No	Yes	Unclear	Yes	Unclear	No	Withdrawals NR
Wahlund et al., 1992[105] (Sweden)	Unclear	No	Unclear	W	Unclear	No	No	Unclear	Unclear	Unclear	Yes	Withdrawals NR

Table 48. Quality for MRI scan studies

Reference	Scan refusals explained? (n not scanned)	Consecutive recruitment?	Prospective collection of clinical variables?	Who performed clinical evaluation/ image analysis?
Borgwardt et al., 2006[90] (Switzerland)	No (6)	Unclear	Yes	MRI scans were read by 2 neuroradiologists (authors) for the presence of normal variants and pathological findings. Blind to group status (control, FEP etc). Inter-rater reliability based on 30 scans. Kappa 0.932. Only 4% findings rated differently.
Lesser et al., 1991[97] (USA)	NR	Unclear	Yes	Neuroradiologist and neurologist read 15 randomly selected MRIs, blind to subject status. Intra-class correlation 0.97.
Lubman et al., 2002[99] (Australia)	NR	No	?Yes	Neuroradiologist blind to diagnostic group. Categorisation of each scan based on consensus by 2 authors. 70 scans done blindly. Inter-rater reliability 0.864.
Wahlund et al., 1992[105] (Sweden)	NR	Unclear	No	MRI scans read by psychiatrist together with a neuroradiologist.

Table 49. QUADAS quality assessment for MRI or CT studies

	1*	2	4	5	6	8	9	10	11	12	13	14
Lesser et al., 1992[98] (USA)	No	Yes	Unclear	12/16 Unclear how selected	No	No	Yes	Unclear	Yes	Unclear	No	No
McKay et al., 2006[101] (Australia)	Yes	Yes	Unclear	52/117 Unclear how selected	No	No	No	Unclear	Unclear	Unclear	Yes	Withdrawals NR
Miller et al., 1991[102] (USA)	No	Yes	Yes	W	No	No	Yes	Unclear	Yes	Unclear	No	Yes

Table 50. Quality for the study using MRI or CT scan

Reference	Scan refusals explained? (n not scanned)	Consecutive recruitment?	Prospective collection of clinical variables?	Who performed clinical evaluation/ image analysis?
Lesser et al., 1992[98] (USA)	No (4)	Yes	Yes	Scans read by neuroradiologist blind to clinical diagnosis.
McKay et al., 2006[101] (Australia)	NR	Unclear	No	NR
Miller et al., 1991[102] (USA)	Yes (1- too large for MRI or CT scan)	Unclear	Yes	Scans read for clinical diagnoses by 2 independent raters (a neuroradiologist and a neurologist) blind to subject status (diagnosis). 2 independent observers each read MRI scans from 15 randomly selected cases- intraclass correlation of 0.97 then one read the remainder.

Table 51. QUADAS quality for treatment refractory psychosis

	1	2	4	5	6	8	9	10	11	12	13	14
Cunningham-Owens et al., 1980[106] (UK)	Unclear	No	Unclear	W	Yes	No	Yes	Unclear	Unclear	Unclear	No	NR

Table 52. Quality of treatment refractory psychosis patients

Reference	Non-scans explained? (n not scanned)	Consecutive recruitment?	Prospective collection of clinical variables?	Who performed clinical evaluation/ image analysis?
Cunningham-Owens et al., 1980[106] (UK)	NR	No	?Yes	NR

Appendix 7. Review of published economic evaluations

Mushlin et al., 1997[130]
This American study was designed to determine the incremental cost-effectiveness of magnetic resonance imaging and computed tomography in young adults presenting with equivocal neurological signs and symptoms. It is based on results produced from a decision-analytic Markov simulation model that is fully described in Mooney et al., 1990. As a consequence Mooney et al., 1990 is reviewed instead.

Mooney et al., 1990[110]
This study was designed to explore the costs and benefits of routine versus selective (only if symptoms recur) use of magnetic resonance imaging for adults who have symptoms suggestive of multiple sclerosis (MS). The authors used a decision-analytic model to produce an incremental cost-effectiveness ratio of using immediate MRI compared to selective MRI. The study is based in the US and therefore expressed in US dollars (1987 dollars). For the base case, both costs and benefits are discounted at 2.5% per year. Outcomes are expressed using QALYs. Probabilities of outcomes are estimated from incidence rates of disease, data on test characteristics and on treatment effects. Sensitivity rates and false positive rates of MRI to detect various conditions are reported. The base case analysis does not consider patients over 40 years of age (changes of MRI suggestive of MS are not specific for people aged over 40). MRI is modelled to suggest either MS, infarct, tumour, or 'other disease'. Treatment and quality of life gains dependant upon the MRI findings are reported. For example patients who test positive for tumour are assumed to undergo angiography associated with a reduction in QoL of 0.14 for 3 days. It is assumed that angiography has perfect specificity therefore if patient tests positive then will immediately undergo surgery. In the base case the model assumes that MRI is never false-positive for tumour (this assumption is relaxed in sensitivity analysis).

Utility values for the model were based on assumptions related to the disease state characteristics and then derived from a utility function derived by Torrance. These utility values were subject to extensive sensitivity analysis.

A separate Markov-model for each of the conditions detected by MRI is reported. The results reported suggest that assuming MRI is a perfect test (100% sensitivity and specificity) then the ICER is $4,877 per QALY. The analysis then progresses to identifying parameters in the model at which the cost-effective threshold for immediate MRI versus selective MRI use is most sensitive. Recommendations are then made as to where more information is required to improve the accuracy of information. This form of analysis suggests that more information is required on the accuracy of MRI at detecting MS and also on the value that patients place on early diagnosis and the impact this has on the patient's well-being.

This study provides an in-depth analysis adopting value of information analysis to report the cost-effectiveness of immediate versus selective MRI for detecting MS. Assuming a perfect MRI test, the ICER is reported to be cost-effective. The corresponding ICER for a less than perfect test is however nested within several assumptions that more information is required on. The study does provide information on test accuracy for MRI in detecting several conditions which could potentially be useful for our economic evaluation. Costs and QoL values are also reported which may be adaptable to our model. This study therefore has potential to be beneficial for our economic evaluation.

Simon and Lubin, 1985[111]
This paper estimates the costs and benefits associated with using CT to diagnose surgically treatable causes of dementia (normal pressure hydrocephalus (NPH), primary brain tumours, or subdural haematomas (SDH)) as a routine scanning tool versus using it as a selective

scanning tool. The decision analytic model measures the economic impact within a hypothetical cohort at 60, 70 and 80 years of age. The model also considers the impact of replacing CT with MRI assuming MRI is a perfect test.

Initially the cohort can be exposed to either the routine-care strategy using either MRI or CT or the selective care strategy (scanning only performed when historical or physical findings suggest a need). There are seven possible outcomes to the routine care diagnostic pathway using CT – diagnosis of NPH or SDH (2 separate arms), diagnosis of brain tumour, or four other arms indicating why a scan may fail to detect treatable causes comprising depression, irreversible dementia, false negative for SDH and false negative result for brain tumour. Where a brain tumour has been diagnosed with the routine care strategy, the model assumes that all false positive tests results arise from the group with 'irreversible' dementia. This is because they have assumed that a CT scan has a 100% specificity (i.e. no false positives) for NPH and SDH therefore the only sources for a false positive CT result is that arising from a patient with depression or irreversible dementia. (The paper reports that excluding depression as a source of false positive had a negligible effect on the cost effectiveness ratio). Routine scanning using MRI is assumed to produce the same treatment pathways as CT, only MRI is treated as a perfect diagnostic test (100% sensitive and specific). Neither CT nor MRI results influence the outcome of treating depression therefore the model assumes that costs and outcomes for patients with depression are identical for all strategies.

Health outcomes are reported as either Quality-Adjusted Life Expectancy (QALE) or 'number of surgically treatable cases' that would be diagnosed under each strategy. To calculate the QALEs, life expectancy for each outcome is estimated as percentage of life expectancy predicted for persons 60, 70 and 80 years in the general population and then a quality-adjustment factor applied. For estimated years in an improved state a quality-adjustment factor of 0.8 (0.8-0.9) is applied, for a demented state a quality-adjustment factor of 0.1 (0-0.2) is applied. The sum of these terms gives the QALE. The QALE is discounted at annual rate of 5%.

Costs are split into 3 parts; the cost of a MRI or CT procedure, the cost of surgery, and the cost of health problems occurring during a person's remaining lifetime. For CT, the costs are described as charges for scans and are assumed to be $300 per procedure (source of inflation rates not reported), for MRI, a baseline value of $600 is used and is varied between $500 and $1000 in a sensitivity analysis. Treatment costs comprise hospitalisation costs (estimated from DRG prospective payment rates) and professional fees (estimated from 1982 Medicare Part B charge information for Georgia). To estimate the health costs over the remaining years of life a number of assumptions relating to the number of years spent in a state of relative independence and number of years spent in a nursing home for each outcome are applied. The costs for nursing home care were estimated to be $20,000 a year and adjusted to $15,000 in the sensitivity analysis.

The model shows that if routine MRI replaces routine CT then an additional 70 to 150 persons who have surgically treatable causes for dementia would be detected per 100,000 persons scanned. Regardless of age, the cost per additional year of QALE in moving from selective scanning to routine scanning using CT, is below $50,000. In comparing routine scanning with MRI to CT, the incremental cost ranges from $46K for 60 year olds to $144K for 80 year olds. The authors conclude by deducing that use of MRI on a routine basis would add little to the clinical benefit as it only discovers very few additional surgically treatable cases out of a large proportion of people who develop dementia on an annual basis. However the authors do acknowledge that the model is sensitive to prevalence estimates for the surgically treatable conditions and when these are lowered the marginal cost of routine CT scanning becomes a lot higher.

Overall, this paper provides a useful framework to measure the costs and benefits of using CT/MRI to detect surgically treatable causes of dementia and can be likened to the clinical problem facing first-episode psychosis in terms of model structure. However there are a number of assumptions contained within the model which are not justified and/or are not subject to a sensitivity analysis. It is not clear for example how appropriate it is to assume that CT has a 100% specificity for NPH and SDH therefore the only source for false positive CT results stems from patients with depression or irreversible dementia. It is not clear why the authors have chosen 0.8 and 0.1 as a quality-adjustment factor for the QALE calculations and what evidence this estimate is based on. Also the discount rate of 5% is not justified nor varied in a sensitivity analysis. The number of years spent in a state of relative independence and number of years spent in a nursing home are also not justified and it is not clear how appropriate these assumptions are.

In addition to the uncertainty surrounding the assumptions, the model has been developed for a US setting and cost estimates (due to differences in clinical practice) are not directly generalisable to a UK setting.

McMahon and Araki et al., 2000[112]

This study sets out to explore the incremental cost-effectiveness of a standard diagnostic strategy versus a strategy that involves a functional neuroimaging examination within a setting of a specialised Alzheimer disease centre. The analysis takes a societal perspective thus includes costs such as time and travel costs.

The costs and benefits of the following diagnostic strategies for Alzheimer disease are compared:

- Standard examination (detailed history, assessment of cognition and functional status, laboratory testing, structural brain imaging (non-enhanced CT)).
- MR imaging plus DSC MR imaging (assumed to be performed simultaneously)
- Visual SPECT (assumed to be performed in 2nd visit)
- Computed SPECT (assumed to be performed in 2nd visit)

The Markov model operates on a 6-week cycle with patients being classified into the following disease states: no Alzheimer disease, mild Alzheimer disease, severe Alzheimer disease, or dead. A full model description alongside transition probabilities are reported in another paper that reports the cost-effectiveness of donepezil for mild or moderate Alzheimer disease (Neumann et al., 1999 (8)). The model assumes that all patients diagnosed with Alzheimer disease will receive treatment with either donepezil or with a hypothetical higher-efficacy drug. As donepezil is only recommended in mild-moderate Alzheimer patients, severe Alzheimer patients are assumed to discontinue treatment and have no further drug-related costs or benefits. Estimated sensitivity and specificity of the standard diagnostic work-up strategy for the base-case analysis were estimated as 0.75 and 0.9 respectively (adjusted to 0.5 and 0.8 in the sensitivity analyses).

The cost of the average series of laboratory tests for the initial work up was estimated at $70 on the basis of resource use data from Massachusetts General Hospital. CT and MR imaging costs were based on Medicare reimbursement rates and estimated to be $212 for CT (non-enhanced) and $1139 for MR imaging plus DSC MR imaging. These cost estimates are subject to a sensitivity analysis and a range of cost estimates are explored. The time taken to complete the standard diagnostic work up was estimated to be 1 day (8 hours plus travel). Patient travel expenses were included and estimated at $40 a day. Time costs were also included for patients and estimated at $50 per day (derived from the median income of persons aged 65 and over). The sensitivity analysis explores the different strategies assuming no cost for patient and no travel costs.

Quality of life weights for patients without Alzheimer disease was estimated at 0.826 (varied to 0.796 in sensitivity analysis) using the mean of the time trade-off scores for men and women 65-84 years of age derived from study of community preferences (Fryback et al., 1993 (24)). QoL weights for Alzheimer patients were based on Health Utilities Index Mark 2 (HUI:2) scores published previously in Neumann et al., 1999 (8)) and varied between 0.710 for mild disease to 0.310 for severe disease.

The sensitivity analysis performed on the model is extensive and explores drug effects and duration, disease progression, prevalence, cost and quality of life estimates in detail.

The strategy of MR imaging plus dynamic susceptibility contrast enhanced MR imaging compared with standard examination had an ICER of $479,500 per QALY. The visual SPECT strategy and computed SPECT were dominated by the standard examination. Therefore base-case analysis suggests that it is not cost-effective to add functional imaging to the standard diagnostic work-up of Alzheimer disease. This is a well-developed model that explores the diagnostic strategy of Alzheimer disease that can be likened to first-episode psychosis in that it is a 'diagnosis of exclusion' (series of tests performed to rule out any structural abnormalities causing symptoms). The estimates contained within the model however are heavily dependant upon a set of assumptions and it was found that if the sensitivity/specificity of the standard examination are less than base case and/or the treatment effectiveness or the duration of effectiveness improves then the ICER resulting from the inclusion of functional imaging improves. The model is also based on US practice with all data inputs sought from a US source. The model provides a useful framework with potentially valuable data inputs (such as QoL figures for Alzheimer states and sensitivity/specificity values for examination procedures) for modelling the diagnosis of first-episode psychosis. The decision problem considered in this model assumes that non-enhanced CT is used on all patients as part of the standard diagnostic strategy and compares this strategy (in terms of costs and benefits) to one that adds an MR imaging test within patients suspected of Alzheimer disease. The decision problem addressed in this report however is slightly different in that CT and/or MRI will be modelled in patients where the initial physical and neurological findings suggest a need (selective strategy) compared to routine use of CT and/or MRI. The results therefore will not be directly comparable.

Wortzman, Holgate and Morgan, 1975[131]

This paper reports a general analysis designed to investigate the impact of cranial computed tomography (CCT) upon the cost-effectiveness of a neuro-diagnostic work-up. The objective was to provide information on the cost-effectiveness to the Ministry of Health of the Province of Ontario so as to assist in future decisions concerning need and distribution of an EMI scanner. The study directly explores the impact of CCT upon the (a) number of angiograms and air studies, (b) length of hospital stay, and (c) rate of admission of neurological outpatients.

This cost-effectiveness study was performed in 1975 therefore is rather dated. It is focused on the impact of CCT upon the diagnostic work-up of general patients not patients with a neurological disorder therefore has been excluded from any further review.

Evens and Jost, 1977[113]

This study explores the cost effectiveness of cranial computed tomography (CCT) compared to the radionuclide brain scan (RBS) as a diagnostic tool in patients with suspected intracranial pathology. The clinical efficacy of RBS and CCT is reviewed with sensitivity, specificity and accuracy rates for both tests reported. A detailed costing analysis is undertaken of CCT and categorised into equipment cost, fixed costs (such as maintenance, space, updating equipment), technical personnel required to operate the equipment and variable costs (Polaroid film, magnetic tape etc) leading to an annual estimate of technical costs for CCT assuming 50 patients per week of $337K ($130 per patient). The total costs of

a RBS facility using a similar costing exercise to that used for CCT, is estimated as $132K/year ($51 per patient) - 40% of a CCT examination.

Taking into consideration the clinical efficacy data, CCT will improve the overall accuracy of diagnosis (92% versus 70%) by detecting patients with atrophy and ventricular abnormalities that will be false-negative with RBS. The cost of CCT divided by its accuracy ($131/92%) is $141 per correct diagnosis, the corresponding figure for RBS is estimated as $51. The decision therefore is described as a value judgement to assess if the increased cost of CCT is offset by the increase in accuracy. The authors believe that substituting CCT for RBS as the first diagnostic radiological study in patients with neurological signs or symptoms is cost beneficial.

This study is limited as the results are sensitive to 1) higher or lower direct and indirect costs and 2) higher or lower patient volumes. The cost estimate for CCT is based on a full national study whereas for RBS,it is based on the clinician's experience. It is a US study (that is dated as based in 1977) and costs and clinical practice are different from the UK. The study explores the cost effectiveness of CCT versus the radionuclide brain scan therefore addresses an economic question which is different from that focused on in this report. The study therefore has little information to aid the economic evaluation.

Szczepura, Fletcher and Fitz-Patrick, 1991[114]

This paper reports some of the findings from a large service evaluation designed to measure the extent to which MRI in routine neuroscience clinical practice is worth its costs. The effect of MRI on diagnosis, diagnostic certainty, and patient management in the neurosciences are reported. Estimates of the cost per patient scanned, the impact upon quality of life and the diagnostic pathway leading to a MRI are also reported.

A total of 782 scanned patients were entered into the study. To measure the impact of MRI, a controlled observational study was adopted requiring clinicians to specify differential diagnosis and treatment plan before and after an MRI. Before scan, patients were asked to complete a health status questionnaire using the Rosser 29 state classification based on disability and distress (scores range from +1.00 for no disability or distress to a minimum of -0.49). Medical records of the 158 of the 782 patients were examined in detail (representative sampling frame to ensure that records were representative in terms of total requests per centre and level of use per consultant). Costs were converted to 1989-90 prices using several British sources and averaged to produce a representative cost.

Most scans were requested to confirm existing diagnosis (44%) or to exclude a suspected disease (35%). The average cost of scanning a patient in Coventry was £176.40 (£179.20 including direct costs). The authors note that the high level of fixed costs makes 'cost per patient' sensitive to throughput. The average QoL score at the time of scan was 0.904 (based on 410 patients) reducing to 0.845 six months later.

When radiologists expected the MRI to yield 'increased accuracy in measuring extent of disease', 88% of scans delivered this; when 'increased accuracy in location' was predicted, 82% of scans delivered this, and finally when 'improved identification' was expected, only 45% of scans delivered this. Changes in management were reported in 27% of cases.

Overall cost savings of procedures replaced by MRI amounted to £80.90 per patient (includes radiographic procedures, inpatient stays, surgical savings). There are cost savings to be had by including MRI in the diagnostic work up but using it too early may also not be cost effective as suitable patients (for MRI) are not correctly identified. Overall diagnosis was altered in 20% of cases after MRI. Management was changed in 27% of cases and it is estimated that these management changes reduced the cost of imaging from £206 per patient

to a marginal cost of £125 per patient. There was no indication that patients QoL improved after MRI.

This paper provides an interesting economic analysis of the costs (and diagnostic benefits) of including MRI as part of the diagnostic pathway for patients within the neurosciences. A thorough cost analysis of MRI is reported (with international comparisons) alongside the diagnostic benefits. Interestingly the paper offers a suggestion as to how the benefits of MRI can be offset again costs and describes this in terms of marginal cost per diagnostic change (estimated to be £626). As the study is done from a UK perspective and provides cost estimates alongside diagnostic benefits the data reported will be potentially useful for estimating the cost effectiveness of MRI/CT in a UK setting from a NHS/PSS perspective.

Kulasingam and Samsa et al, 2003[132]

This paper reports the benefits of using positron emission tomography (PET) scanning as a diagnostic tool in patients with Alzheimer's disease. As the economic model does not consider the use of MRI or CT scanning, the paper has been excluded from the literature review as it is not relevant to the economic question addressed in this report.

Table 53. Summary of reviewed economic evaluations

	Wortzman, Holgate & Morgan, 1975[131]	Simon and Lubin, 1985[111]	McMahon and Araki et al, 2000[112]	Evens and Jost, 1977[113]	Szczepura, Fletcher & Fitz-Patrick, 1991[114]	Mooney et al, 1990[110]
Country	Canada	US	US	US	UK	US
Year of study and currency	1974, Canadian dollars	1986, US dollars	1998, US dollars	1977, US dollars	1989, UK Sterling	1987, US dollars
Objective	To investigate the impact of cranial computed tomography (CCT) on the cost-effectiveness of a neuro-diagnostic work-up.	Analyse the cost-effectiveness of routine-use of CT or MRI compared to selective-use.	Compare the cost-effectiveness of a diagnostic work-up strategy that involves a neuroimaging test with standard diagnostic strategy in an Alzheimer disease centre setting.	To assess the cost effectiveness of cranial computed tomography (CCT) compared to the radionuclide brain scan (RBS).	To measure in a service setting the effect of magnetic resonance imaging on diagnosis, diagnostic certainty, and patient management in the neurosciences; cost per patient scanned; impact upon quality of life; and to record diagnostic pathway leading to MRI.	To explore the costs and benefits of routine versus selective use of MRI for adults who have symptoms suggestive of MS.
Patient group	Review of 203 inpatient and 241 outpatient records from Toronto General Hospital	Cohort of individuals aged 60,70 or 80 presenting with dementing illness but without historical, physical and lab findings.	Patients referred to Alzheimer disease centre.	Not defined	782 patients	Patients < 40 years of age

Treatment comparison	Clinical opinion on what action would have been taken had CCT not been available. Exploration of CCT upon: (a) number of angiograms and air studies, (b) length of hospital stay, and (c) rate of admission of neurological outpatients	Routine scanning versus selective scanning (scan only when physical and historical findings suggest increased likelihood of surgically treatable illness).	1.Standard examination (detailed history, assessment of cognition and functional status, laboratory testing, structural brain imagining (non-enhanced CT). 2. MR imaging plus DSC MR imaging (assumed to be performed simultaneously) 3. Visual SPECT (assumed to be performed in 2nd visit) 4. Computed SPECT (assumed to be performed in 2nd visit)	CCT versus RBS	Controlled observational study to measure impact requiring clinicians to specify differential diagnosis and treatment plan before and after an investigation.	Routine versus selective scanning with MRI.
Analysis	Cost-savings analysis	Cost per QALE (Quality-Adjusted Life Expectancy)	Cost-Utility Analysis	Cost-effectiveness analysis	Cost/Outcome description	Cost Utility Analysis
Model	None	Decision Tree	Markov model (6 wk cycle)	None	None	Decision-analytic model for basecase. Separate markov model for each condition.
Time horizon		Life-time	Base case = 18 months		12 month analysis	Life-time

Model description	N/A	The model assumes that if a condition is undiagnosed (due to false negative or failure to scan) then by the time additional symptoms develop that dictate ordering a scan, surgical treatment is ineffective.	Model operates on a 6-week cycle with patients being classified into the following disease states: no Alzheimer disease, mild Alzheimer disease, severe Alzheimer disease, or dead. Transition probabilities derived from data from the Consortium to Establish a Registry for Alzheimer Disease	N/A	N/A	Waiting time model – decision-analytic model. Markov models for MS, infarct, other disease and no disease. DEALE methodology for tumour patients
Outcome measure	Dollars saved	'No. of surgically treatable cases' and Quality Adjusted Life Expectancy (QALE)	QALYs	Accuracy of diagnosis (proportion of correct outcomes (true positives and true negatives) to all outcomes (all patients with and without disease)	Cost per diagnostic change/cost savings of procedures replaced by MRI.	Cost/QALY.

Health state valuation	None	QALE: Life expectancies for each outcome estimated as percentages of the life expectancies predicted for persons 60, 70 and 80 yrs. Estimated number of remaining life years in an improved state and in a demented state. Remaining years in an improved state were multiplied by 0.8 and the years spent in a demented state by 0.1. Sum of these terms = QALE.	QoL weights for patients without Alzheimers disease estimated at 0.826. QoL weights for mild, moderate and severe health states based on Health Utilities Index Mark 2 scores published previously.	None	QoL - Rosser 29 state classification	Derived from Torrance utility function
Source of resource data	Surgical tariff rate (Ontario). Toronto General Hospital Day cost.	Scanning costs taken from the Office of Technology Assessment. Hospitilisation costs estimated from DRG perspective and professional fees from 1982 medicare Part B charge information for Georgia. Nursing home costs based on the 1977 National Nursing Home Survey.	Laboratory tests estimated on resource use from Massachusetts General Hospital. CT and MR imaging costs were based on Medicare reimbursement rates	Location-specific costs based on CCT equipment installations.	Costs were converted to 1989-90 prices using several British sources and averaged to produce a representative cost	Estimated from the literature and converted into 1987 dollars.
Discounting	None	Discounted QALE at annual rate of 5%.	Costs and QALYs discounted at 3%.	None	None	2.5% on both costs and QALYs

Sensitivity analysis	None	Altered the baseline estimates for the prevalence of otherwise undetectable NPH, brain tumour and SDH. Altered the parameters on degree and duration of improvement and life expectancy for a number of the outcomes. Varied the cost of a MRI scan.	No sensitivity analysis on discount rate as base-case analysis only 18 months. Sensitivity analysis on costs, sensitivity/specificity of diagnostic tests, disease prevalence, quality of life, drug effects and duration.	None	None	Extensive, reporting the parameters at which the cost effectiveness is most sensitive.
Model base case results	The authors deduce that given the cost savings by avoiding neuroradiological procedures, the reduction of hospital stay and hospital admissions leads to a total net savings in the region of $2,000,000.	Regardless of age, the cost per additional year of QALE in moving from selective scanning to routine scanning using CT, is below $50K. In comparing routine scanning with MRI to CT, the incremental cost ranges from $46K for 60 year olds to $144K for 80 year olds.	The strategy of MR imaging plus dynamic susceptibility contrast enhanced MR imaging compared with standard examination had an ICER of $479,500 per QALY. The visual SPECT strategy and computed SPECT were dominated by the standard examination.	The cost of CCT divided by its accuracy ($131/92%) is $141 per correct diagnosis. For RBS the corresponding figure is estimated as $51.	Overall cost savings of procedures replaced by MRI amounted to £80.90 per patient (includes radiographic procedures, inpatient stays, surgical savings).Marginal cost per diagnostic change – calculated to be £626.	Assuming MRI is a perfect test, the ICER is $4,877 per QALY.

Appendix 8. Review of quality of life studies

Table 54. Review of QoL values for patients with schizophrenia

Instrument	Schizophrenia		Country of study	Sample	Source
	Treated	Untreated			
SF-36: Score (SD) Physical function Role-physical Bodily Pain General Health Vitality Social-Functioning Role-emotional Mental Health		 88.4 (14.1) 46.2 (39.3) 74.2 (26.7) 52.2 (20.9) 49.4 (19.7) 60.6 (30.0) 37.6 (41.0) 48.8 (22.1)	Hong Kong	117 patients aged: 14-28 yrs before treatment	Law et al., 2005[133]
SF-36: Score (SD) Physical function Role-physical Bodily Pain General Health Vitality Social-Functioning Role-emotional Mental Health	Read from graph: 93 76 82 72 56 77 65 75	Baseline: 91 (18) 72 (39) 79 (27) 66 (21) 51 (21) 47 (31) 33 (40) 54 (20)	North America & Western Europe	195 patients with 1st episode schizophrenia treated with olanzapine or haloperidol; 16-40 yrs Treated: 12 months from baseline.	Strakowski et al, 2005[134]
SF-36: - Baseline (n=254): Physical (PCS) mean (SD) Mental (MCS) mean (SD) - 2 years after treatment (n=265): Physical (PCS) mean (SD) Mental (MCS) mean (SD)	 72.0 (20.7) 64.9 (22.5)	 69.6 (20.2) 61.5 (21.4)	Canada	254/265 patients for baseline/2 yrs following trt: mean age = 37.9 yrs.	Malla et al, 2006[135]

SF-36: Score (SD) Physical function Role-physical Bodily Pain General Health Vitality Social-Functioning Role-emotional Mental Health	 65.0 (27.8) 54.44 (39.9) 68.9 (28.0) 62.8 (22.9) 54.8 (21.9) 68.7 (26.8) 62.5 (40.7) 66.1 (21.5)		USA	137 outpatients who met DSM-IV criteria or schizoaffective disorder. Mean age = 57.9 yrs.	Sciolla et al, 2003[136]
- Standard Gamble: Mild Moderate Severe - Linear Analogue Mild Moderate Severe	Trt status not specified. 0.61 0.36 0.29 0.58 0.35 0.25		USA	3 health profiles rated (mild, moderate and severe) by psychiatric nurses using SG and VA.	Chouinard and Albright, 1997[118]
SG-weighted utilities across 8 health states VAS-weighted utilities across 8 health states	0.775 0.596	0.729 (before trt) 0.538	Europe and Canada	725 patients aged 18-85 yrs treated for at least 1 mth with risperidone.	Lenert et al, 2005[119]

EQ-5D (Spanish version) (SD): Baseline – olanzapine Baseline - risperidone Baseline – conventional antipsychotics VAS (SD): Baseline - olanzapine Baseline - risperidone Baseline – conventional antipsychotics SIX MONTHS AFTER TRT: EQ-5D (Spanish version) : Olanzapine Risperidone Conventional antipsychotics VAS : Olanzapine Risperidone Conventional antipsychotics	 0.85 0.86 0.65 73.3 67.6 64.2	Before trt: 0.5 (0.3) 0.5 (0.2) 0.4 (0.2) 47.3 (24) 39.6 (25.1) 46.7 (20.9)	Spain	patients requiring initial treatment for 1st episode with olanzapine (n=114), risperidone (n=31), conventional antipsychotics (n=37), < 40 yrs.	Montes, 2003[120]
SF-12 scores by category: Age: 1. Younger (<38 yrs, n=315) 2. Middle (38-46 yrs, n=315) 3. Older (>46 yrs, n=315) Diagnosis 1. Schizophrenia (n=422) 2. Schizoaffective (n=183) 3. Bipolar (n=164) 4. Major depression (n=106) 5. Other (n=66)	PCS MCS 50.1(9.4) 40.0(12.9) 47.0(10.9) 39.6(12.9) 44.2(11.8) 39.0(14.0) 48.2(9.7) 42.4(11.9) 48.1(10.2) 40.7(13.6) 46.1(11.5) 39.6(12.7) 44.3(12.6) 31.8(13.4) 43.8(14.7) 31.4(14.1)		USA	Patients with diagnosis of schizophrenia, psychotic disorder or major mood disorder, >18 yrs, on treatment	Salyers et al, 2000[137]

Worst Remembered Health State: Schizophrenia group: • RS • SG • TTO Depression group: • RS • SG • TTO Current Health State: Schizophrenia group: • RS • SG • TTO Depression group: • RS • SG • TTO	 25.1(16.71) 0.19 (0.12) 0.36 (0.29) 24.5 (11.16) 0.18 (0.12) 0.24 (0.02) 77.16 (15.24) 0.85(0.12) 0.81(0.14) 69.57(9.6) 0.95(0.08) 0.73(0.19)		Canada	Patients with schizophrenia (n=120) and treated depression (n=32)	Voruganti et al., 2000[116]

Appendix 9. Systematic review of the test accuracy of CT and MRI for identifying dementia, and brain tumours amenable to surgery and focal lesionspotentially amenable to surgery in epilepsy

A review of the test accuracy of CT and MRI for these conditions was performed on the basis that differences in test accuracy will impact on the effectiveness of CT and MRI in the management of psychosis.

Note that cerebral infarctions were not included with the exception of cerebral infarcts causing vascular dementia or those that present solely with psychiatric symptoms. This is on the basis that under current practice other clinical presentations of stroke (acute clinical presentation) would usually result in an immediate neuroimaging investigation and subsequent management by stroke specialists rather than psychiatrists.

Searches on CT/MRI scanning

Database: Cochrane Library (Wiley) 2007 Issue 2

#1 magnetic.ti.
#2 mri.ti.
#3 #1 or #2
#4 ct.ti.
#5 tomography.ti.
#6 #4 or #5
#7 diagnostic.ti.
#8 sensitivity.ti.
#9 comparison.ti.
#10 effective*.ti.
#11 #7 or #8 or #9 or #10
#12 #3 and #6 and #11

Database: Ovid MEDLINE(R) 1950 to April Week 1 2007
Search Strategy:

1 exp Diagnosis/ or diagnosis.mp.
2 accuracy.mp.
3 sensitivity adj specificity.mp.
4 exp "Sensitivity and Specificity"/
5 comparison.mp.
6 effectiveness.mp.
7 or/1-6
8 computed tomography.ti.
9 ct.ti.
10 mri.ti.
11 magnetic resonance.ti.
12 8 or 9
13 10 or 11
14 12 and 13
15 14 and 4
16 stroke.mp.
17 brain.mp.
18 cerebral.mp.
19 or/16-18
20 15 and 19
21 7 and 14

22 21 and 19
23 (stroke or brain or cerebrovascular).ti.
24 21 and 23
25 limit 24 to humans

Database: Ovid MEDLINE(R) 1950 to April Week 3 2007
Search Strategy:

1 mri.ti.
2 magnetic.ti.
3 or/1-2
4 ct.ti.
5 computed tomography.ti.
6 or/4-5
7 3 and 6
8 exp Diagnosis/ or diagnosis.mp.
9 sensitivity.mp. or exp "Sensitivity and Specificity"/
10 comparison.mp.
11 effectiveness.mp.
12 accuracy.mp.
13 or/8-12
14 7 and 13
15 dementia$.mp.
16 14 and 15

Database: Ovid MEDLINE(R) 1950 to April Week 2 2007
Search Strategy:

1 mri.ti.
2 magnetic resonance.ti.
3 or/1-2
4 ct.ti.
5 computed tomography.ti.
6 or/4-5
7 3 and 6
8 exp Diagnosis/ or diagnosis.mp.
9 sensitivity.mp. or exp "Sensitivity and Specificity"/
10 comparison.mp.
11 effectiveness.mp.
12 accuracy.mp.
13 or/8-12
14 7 and 13
15 exp Epilepsy/ or epilepsy.mp.
16 tumo?r$.mp. or exp Neoplasms/
17 or/15-16
18 14 and 17
19 epilepsy.ti.
20 tumo?r$.ti.
21 or/19-20
22 18 and 21

Criteria for inclusion of studies on the basis of title and abstract:

Population:
Those with or without physical symptoms and with or without psychosis and with or without a working diagnosis of a structural brain lesion at the time of neuroimaging.

Intervention and comparator (reference standard):
Plain or contrast CT versus plain or contrast MRI
Plain or contrast CT versus clinical follow up
Plain or contrast CT versus histology
Plain or contrast CT versus post-mortem

Plain or contrast MRI versus clinical diagnosis (Alzheimer's disease)
Plain or contrast MRI versus clinical follow up
Plain or contrast MRI versus histology
Plain or contrast MRI versus post-mortem

Outcome:
Diagnostic accuracy by condition.

Quality assessment and exclusion criteria:
Studies were excluded if it was not possible to construct a 2x2 table based on clinically significant findings. Quality assessment was performed according to the criteria in Table 55.[138] Studies scoring 5 (expert opinion) following application of quality criteria in table 1 were excluded.

Table 55. Quality assessment criteria for included studies

1	An independent, masked comparison with reference standard among an appropriate population of consecutive patients
2	An independent, masked comparison with reference standard among non consecutive patients or patients confined to a narrow population of study participants
3	An independent, masked comparison of an appropriate population of patients, but reference standard not applied to all study patients
4	Reference standard not applied independently or masked
5	Expert opinion with no explicit critical appraisal, based on physiology, bench research or first principles
1= most rigorous. 5 = least rigorous	

Figure 5. Flow of papers for systematic review of the test accuracy of CT and MRI for identifying dementia, temporal lobe epilepsy and brain tumours amenable to surgery

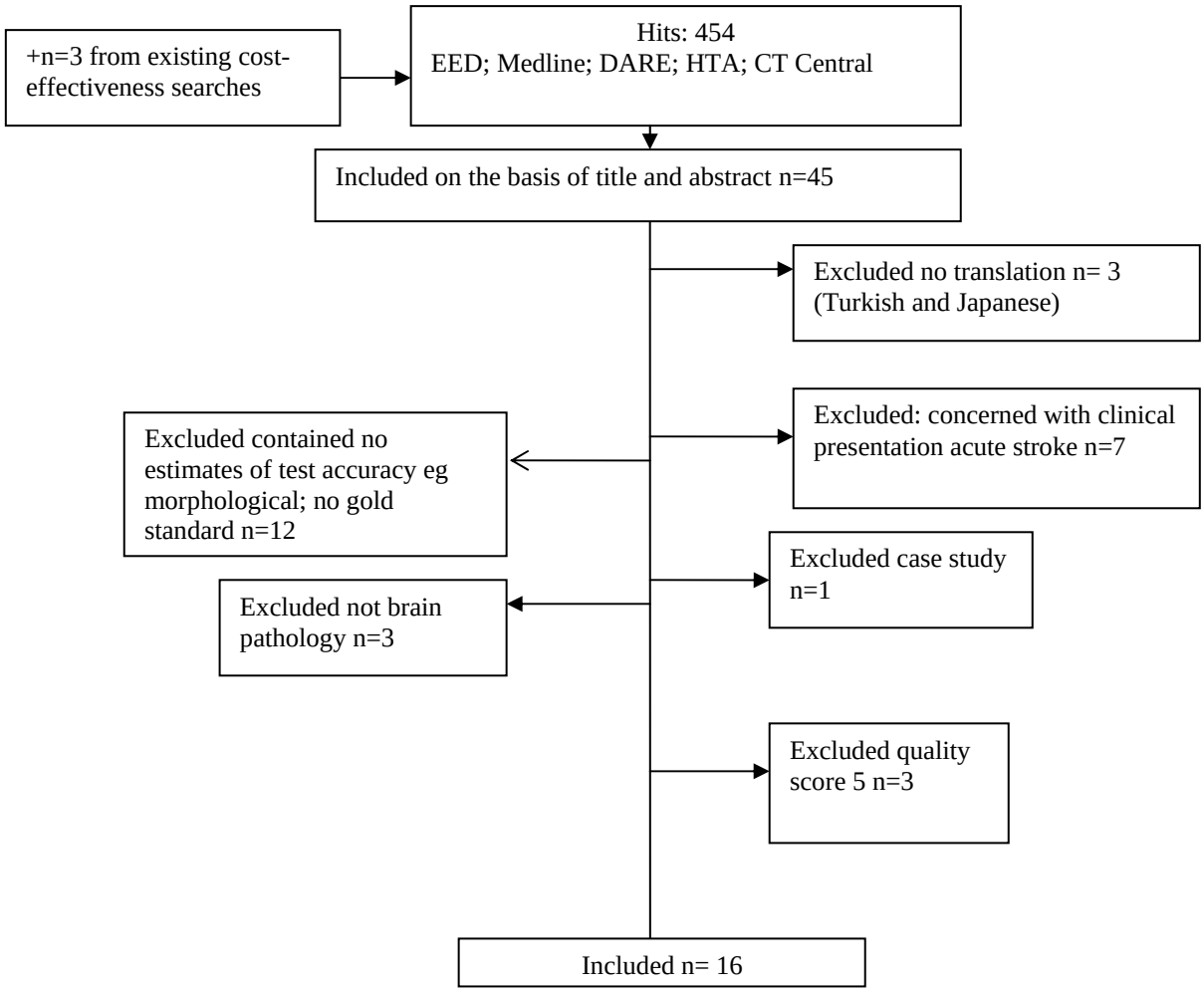


Table 56. Data extraction table for systematic review of the test accuracy of CT and MRI for identifying dementia, temporal lobe epilepsy and brain tumours

Condition	Reference	N	Target disorder	Intervention description	Contrast agent	Refusal rate	Comparator	Quality score (Sackett 1977)	Test accuracy estimate
Alzheimer's disease	Harris (1998)[139] USA. Consecutive referrals to a Memory Diagnostic clinic.	Mild = 8 Mod= 19. Control= 18	Alzheimer disease (mild and moderate). Regional cerebral blood volume images (rCBV). rCBV in temporoparietal cortex used as target disorder following logistic regression analysis on healthy and Alzheimer subjects. Cut off appears to be quantitatively measured 20% reduction in rCBV in moderate Alzheimer's and 15% reduction in rCBV in mild.	DSC MR imaging to evaluate haemodynamic deficits. (Multi-section T2 weighted echoplanar images on 1.5T scanner retrofit with whole body echo-planar coil with imaging parameters 100/2000 (TR/TE). 50 sets of 10 image planes over 100 secs, 128x256 matrix, 1.5x1.5 mm pixels and 7mm thick sections with 3 mm gap.	Yes. IV Gado-teridol	None reported	Clinical diagnosis (probable Alzheimer's disease) based on NINCDS-ADRDA criteria and the mini-mental state examination	2	Sensitivity: moderate Alzheimer's 95%. Sensitivity mild Alzheimer's 88% Specificity 94%

Condition	Reference	N	Target disorder	Intervention description	Contrast agent	Refusal rate	Comparator	Quality score (Sackett 1977)	Test accuracy estimate
Alzheimer's disease	Scheltens (1997)[140] Netherlands. Prospective cohort. 511 underwent clinical diagnosis. Randomly selected n=63 65-85 year olds with a range of cognitive function. Mean age 78.5 (4.7)	51	Medial Temporal Lobe Atrophy (MTA) score as a proxy for Alzheimers disease. 0= no atrophy. 4 = severe atrophy. (Qualitative measure by 2 raters in conference.)	MRI. Telescon I. 0.6T. Nine T1-weighted (TR 400ms; TE 28 ms) saggital slices followed by 19 T2-weighted (TR, 2740 ms; TE 60ms and 120 ms) axal slices and six T1 weighted (TR 300ms; TE 22 ms) coronal slices. Slice thickness 5mm with inter-slice gap 1mm and in-plane resolution 0.8-1.0 mm. Objective measurement of medial temporal lobe atrophy (MTA).	?	4/63=6%	Clinical diagnosis (DSMIII-R)	1	With an MTA cut off of >1 : MRI sensitivity 70%. MRI specificity 76%

Condition	Reference	N	Target disorder	Intervention description	Contrast agent	Refusal rate	Comparator	Quality score (Sackett 1977)	Test accuracy estimate
Epilepsy	Puri (1991).[141] India 1991. 67 patients with epilepsy (83.5% partial and 16.4% generalised) and isolated contrast enhanced CT abnormalities (ring or disc lesions). Sampled from a variety of institutions. 6 months – 50 yrs. Note pattern of disease in this cohort will be markedly different to those seen in the UK..	67	MRI abnormality as an indicator of lesion causing epilepsy: - Non-specific (resolved with medical therapy within 5 months). - Specific (tuberculoma; cysticercosis; abscess) as aetiological pathology in epilepsy.	CT (varying machines) with slice thickness 8-9 mm with matrix size 256x256.	Yes	None reported	No mention of contrast. Siemens Magnetron. 1.5 T; slice thickness 5-6 mm; 2.5-3 interslice gaps; 256x256 matrix; 20 cm filed of view. All transaxial images and some coronal and / or sagittal planes. T2 weighted spin (TR: 2500-3200ms) (TE: 90-112ms). T1 weighted spin (TR: 700ms; TE: 17-28mm).	4	Positive predictive value = 76% assuming CT lesions (ring or disc) described as non-specific abnormalities that resolved with medical therapy within 5 months = false +ves according to MRI.

Condition	Reference	N	Target disorder	Intervention description	Contrast agent	Refusal rate	Comparator	Quality score (Sackett 1977)	Test accuracy estimate
Epilepsy	Convers (1990)[142] France. Patients attending a neurological hospital with refractory, complex partial seizures with a –ve CT scan (? contrast or plain CT). Age 5-54 (mean 27). Note ? overlap with Froment 1989.	100	MRI abnormalities as aetiological for epilepsy. Lesions reported as abnormal in this series: N=4 (13%) vascular malformations; n=13 (42%) focal increase in T2 intensity; n=8 (26%) diffuse white matter abnormalities; n=2 (7%) focal atrophy; n=4 (13%) increase in focal T1 and T2 intensity.	CT. No other details	Yes	Not stated	Plain MRI. Magniscan 5000 (GE-CGR) 0.5 Tesla magnet using 9mm thick contiguous sections and T2 weighted sequences. (TR 1800 or 2000 ms, TE 60 and 120 ms. Sections were performed on both coronal and axial planes (n=73); coronal alone (n=19); axial alone (n=8). In 82/100 patients T1 weighted sequences (TR 380ms, TE 12 ms or TR 500ms, TE 21 ms) were also performed on both coronal and axial planes (n=49; coronal alone (n=20); axial alone (n=13).	4	Selection of sample requires normal CT therefore can only calculate negative predictive value: = 70%. (31% of CT results were false –ves). However clinical significance of all abnormalities found unclear.

Condition	Reference	N	Target disorder	Intervention description	Contrast agent	Refusal rate	Comparator	Quality score (Sackett 1977)	Test accuracy estimate
Epilepsy	Salas-Puig. (1993)[143] Spanish. Patients aged 15-60 (average 35.5 years) with drug-resistant focal epilepsy and normal CT.	45	MRI abnormality assumed to be aetiological for epilepsy: n=5 mesial sclerosis (surgical intervention); n=1 low grade astrocytoma; n=1 temporal lobe atrophy; n=1 cavernous angioma; n=1 malformation of the corpus callosum; n=1 multiple sub-cortical hyper-intense signals. For 8 cases no further information given.	CT. No other information	No information on how many plain CT and how many contrast.	None reported	MRI. 0.5 or 1 Tesla. No other information and no mention of contrast.	4	17 'pathological' MRIs are reported only 9 of which are described. Assuming only 9 cases described had a clinically significant lesion: CT negative predictive value = 80%

Condition	Reference	N	Target disorder	Intervention description	Contrast agent	Refusal rate	Comparator	Quality score (Sackett 1977)	Test accuracy estimate
Epilepsy	Adams (1992)[144] Canada1992. Case series of 20 children assessed pre-operatively with EEG, SPECT, and CT. 14/20 had MRI. Otherwse no information on criteria for selection. Majority of patients had partial epilepsy (13/20)	20 (only 14 had MRI)	Epilepsy: Correct identification of 'pathology' site determined following surgical removal of a lesion. Lesions included: encephalitis; Sturge Weber syndrome; cyst (histologically normal); ganglioglioma; cortical dysplasia; porencephalic cyst / gliosis; astrocytoma; mesial temporal sclerosis; cavernous hemangioma; oligo/astrocytoma	CT or MRI. NO other details.	?	Not reported	Pathology determined at surgery. However it is unclear to what extent SPECT and EEG contributed to final diagnosis.	2	For correct identification of pathological site including identification of a cyst which was histologically normal. CT: Sensitivity 75%. Specificity 100% MRI sensitivity =93%. Specificity 100%.

Condition	Reference	N	Target disorder	Intervention description	Contrast agent	Refusal rate	Comparator	Quality score (Sackett 1977)	Test accuracy estimate
Epilepsy	Froment (1989)[145]. France. Patents attending a neurological hospital with refractory, complex partial seizures wth a – ve CT scan (? contrast or plain CT). Age 6-67 (mean 31). Note ? overlap with Convers 1990.	100	Abnormal morphology or signal on MRI as an indicator of aetiology of Epilepsy. In this case series abnormal morphology:cryptic vascular malformation, hamartoma, low grade astrocytoma. Abnormal signals: diffuse temporal lobe high intensity; localised high intensity.	CT Note that CT was re-examined or re-done with smaller sections (1mm thick) in the light of MRI findings. This is likely to lead to review bias.	?	Not stated	Plain MRI. Magniscan 5000 (GE-CGR) 0.5 Tesla magnet using 9mm thick contiguous sections and T2 weighted sequences. (TR 1800 or 2000 ms, TE 60 and 120 ms. Sections were performed on both coronal and axial planes (n=73); coronal alone (n=19); axial alone (n=8). In 82/100 patients T1 weighted sequences (TR 380ms, TE 12 ms or TR 500ms, TE 21 ms) were also performed on both coronal and axial planes (n=49; coronal alone (n=20); axial alone (n=13).	4	Some CT scans were re-read or re-done in the light of MRI findings which will introduce review bias and may overestimate sensitivity. Assuming that high signal + morphology is clinically significant but high signal alone is not: CT sensitivity 80%. Negative predictive value 99%.

Condition	Reference	N	Target disorder	Intervention description	Contrast agent	Refusal rate	Comparator	Quality score (Sackett 1977)	Test accuracy estimate
Epilepsy	Stefan (1987)[146] Germany. 10 patients with drug resistant focal epilepsy. 19-51 (median 29).All had a constant focus demonstrated by either MRI (n=2) or EEG (n=8). No other information given about selection of sample.	10	MRI abnormalities as aetiological for epilepsy. The clinical significance of these abnormalities is unclear from the paper.	CT. Phillips 2000 scanner which is described as ' not one of the most recent generation'. No other information given.	?	Not stated	MRI. No mention of contrast. Picker 2000 system with super conducting magnet operating at 0.5T. T1 weighted images sing (TR:1860ms; T1: 500ms). T2 applied with repetition times of 2320 ms and echo time of 120 ms .All transaxial images and some coronal and / or saggital planes.	4	Note CT and MRI findings are not reported in relation to a diagnosis. The only detail given is the location in the brain where CT 'abnormalities' or 'pathologically increased T2 signals' on MRI were located. The clinical significance of these are unclear. Sensitivity of CT 38%; Specificity CT 100%

Condition	Reference	N	Target disorder	Intervention description	Contrast agent	Refusal rate	Comparator	Quality score (Sackett 1977)	Test accuracy estimate
Epilepsy	Carrilho (1994)[147]. Brazil. Patients with temporal lobe epilepsy and normal 3rd generation CT. 10-63 years.	26	MRI abnormality assumed to be aetiological for epilepsy: mesial temporal sclerosis (73%); gliomas (20%); cyst (6%); diffuse atrophy (6%)	CT by 3rd generation scanner. No other details	?	None reported	No mention of contrast. Signa; GE medical systems, Milwaukee. 1.5T. T1 and T2 images were obtained on coronal, saggital and axial planes with special emphasis over temporal lobes.	4	Participants selected on the basis of a normal CT scan. On this basis negative predictive value = 73% (58% of CT results were false negatives).

Condition	Reference	N	Target disorder	Intervention description	Contrast agent	Refusal rate	Comparator	Quality score (Sackett 1977)	Test accuracy estimate
Primary tumours	Baker (1980)[148]. USA. Five University Hospitals. Unclear how selection of participants took place. I. Symptoms suggestive of tumour (n=2204) II. Known malignancy with potential for brain metastases with and without neurological symptoms (n=351) III. Controls (n=373)	?	1y tumours included: gliomas, meningiomas, acoustic neuroma, pituitary adenoma, lymphoma, craniopharyngioma, hemangioblastoma, medullablastoma, pinealoma. 2y tumours: stated as metastases.	CT. EMI Mark 1 head scanners. Plain and contrast. ? Contrast agent used.	Yes	None reported	Histology; post-mortem; initial examination and 3 year clinical follow up. No information on what proportion received what tests.	3	-1y tumours: Sensitivity CT 96% Specificity 99%. Sensitivity contrast CT 98%. Specificity contrast CT 99%. -2y tumours Sensitivity CT 47% Specificity 98%. Sensitivity contrast CT 78%. Specificity contrast CT 98%. (Calculated from paper)

Condition	Reference	N	Target disorder	Intervention description	Contrast agent	Refusal rate	Comparator	Quality score (Sackett 1977)	Test accuracy estimate
Primary tumours	Gray (1987)[149]. USA. Review of 13 children with neurofibramatosis being treated at a paediatric neurology clinic and who had had both CT and MRI Age 4-21; average 4.5.	13	Tumours, (gliomas, accoustic neuroma, brainstem glioma, dumbbell neuroma spinal cord).	Plain CT. Siemens DR3 and Siemens DRH.	No	Not stated. Note selection on the basis that patients had had both CT and MRI.	Plain MRI. Siemens Magnetron 1.0 Tesla self-shielded magnet. Note gap between application of CT and application of MRI variable. For one patient this gap was 3 years and s(he) was therefore excluded from the analysis of test accuracy for the purposes of this review.	4	For calculation of test accuracy identification of any lesion suspected to be tumour by CT and not number of lesions assumed to be diagnostic +ve Under this assumption CT = 90% sensitive and 100% specific.
Primary tumours	Grafin von Einsiedel. (1982)[150]. Germany. Patients suffering from focal or generalised seizures or from progressive focal neurological symptoms.	6	Lesions demonstrated by MRI. In this series confined to astrocytomas.	CT. No further details given	?	None reported	Experimental Siemens NMR unit. No mention of contrast. Four coil magnet used to generate a magnetic field of 0.12 Tesla. T 50ms; time delay between successive scans 0.3-1.8 s. 128x128 image matrix interpolated to 256x256 for display. Slice thickness 10mm.	4	Sensitivity of CT 50%. Specificity 100%.

Condition	Reference	N	Target disorder	Intervention description	Contrast agent	Refusal rate	Comparator	Quality score (Sackett 1977)	Test accuracy estimate
Primary and secondary tumours	Guckel (1990)[151]. Germany. Age 7 months to 13.3 years (mean 7.5 years). ? How selected.	31	Brain tumours; primary n= 25 and recurrent n= 6. Includes: astrocytoma, brain stem tumours, gliomas, endodermal tumours, embryonic carcinoma, craniopharyngioma, medulloblastoma, optical glioma.	CT MRI	Contrast CT . MRI without contrast.	Not stated	Contrast MRI. 1.5 Tesla. T1 and T2 spin sequence (TR/TE: 500ms/30ms and 1600-2200ms / 20-100ms).Transaxial, coronal and saggital sections. Slice thickness 5-8mm. Contrast: Gd-GTPA.	4	Plain MRI was 100% sensitive and 100% specific at identifying tumours compared to contrast MRI. Unable to derive sensitivity and specificity for contrast CT compared to MRI.
Secondary tumours	Suzuki (2004)[152]. Japan. Non-consecutive patients with lung cancer (various histology). No neurological symptoms.	134	Brain metastases from 1y site lung.	CT. X-Force (Toshiba Medical, Japan). 10 mm slice intervals.	Yes. Contrast= non-ionic iodine contrast agent IV.	None stated although participants included on the basis they had both CT and MRI	Contrast MRI. 1.5T (VISART/Progress, Toshiba, Medical, Japan). T2 enhances images by FSE method (TR/TE = 4400/120ms) and T1 enhanced images obtained by SE (TR/TE = 500/15) slice thickness/gap = 6.5mm/1.2mm.	4	Sensitivity contrast CT: 58%. Specificity contrast CT: 100%

Condition	Reference	N	Target disorder	Intervention description	Contrast agent	Refusal rate	Comparator	Quality score (Sackett 1977)	Test accuracy estimate
Secondary tumours	Nomoto (1994)[153]. Japan . Patents attending National Institute for Radiological Sciences with diagnosis small cell ca lung. Some patients had physical symptoms suggestive of brain occupying lesion.	25	Brain metastases of small cell lung ca.	CT-8600 (Yokokawa Medical Co., Tokyo). 10 mm thickness; 12 slices.	Yes. Contrast= Amidotri zoic acid or Iopami-dol.	None stated	Contrast MRI. Superconductive Gyroscan S15 (Phillips Co. , Eindhoven, Holland). 12-13 T1-weighted SE (TR/TE = 400/40) axal slices were obtained with 8mm thickness (gap = 0.8mm, 512X512 matrixes and 25cm field of view.	4	Sensitivity contrast CT 91%. Specificity contrast CT 100 %

Condition	Reference	N	Target disorder	Intervention description	Contrast agent	Refusal rate	Comparator	Quality score (Sackett 1977)	Test accuracy estimate
	Taphoorn (1989)[154]. Netherlands. Non-consecutive patients with brain metastases detected by plain or contrast CT. Variety of 1y tumours. Mean age 57. Selection bias as all had to have had CT to be entered into study	60 eligible. Only 50 available for compare-ison of contrast CT and contrast MR. 42 available for plain CT and contrast MRI. Four cases not included due to indeterm-inate results . Unclear why others not included.	Brain metastases of 1y tumours (variety of 1y sites).	All CT scans performed on high resolution scanners (Phillips CT 350). Slice thickness between 6mm for posterior fossa and 9mm for supratentorial region.	Yes for some ? numbers. Contrast = iohexol 100ml IV.	Patients excluded if claustro-phobic. Numbers not given.	Plain MRI 60. Contrast MRI 4. Technicare 0.6 Tesla superconductiing MR unit. (TR 500 ms; TE 32ms. Balanced and T2 (TR 3000 ms; TE 32/64/96/128 ms)weighting pulse sequences generated in all patients. Inversion recovery technique (TR 2600 ms; TE 40 ms; TI 600ms) was also used in most cases. Slice thickness varies between 2-10 mm. Contrast = Gd-DTPA IV.	4	For calculation of test accuracy from this paper identification of any lesion suspected to be tumour by CT and not number of lesions was assumed to be a diagnostic +ve on the basis that a single lesion on CT would normally result in an MRI scan under current practice. For detection of any lesion: Contrast CT sensitivity 100%. specificity 100% Plain CT sensitivity 98% specificity 100%.

Summary of CT and MRI test accuracy review
The search for studies evaluating the relative accuracy of CT and MRI in selected conditions (tumours, epilepsy and dementias) yielded 16 included studies. Of included studies only one was published after 2000. Ten identified studies were published in the 1990s and six in the 1980s. Studies conducted in the 1980s are likely to under-estimate test accuracy due to technological advances.

Population
The majority of research identified was carried out on highly selected populations and in most cases populations with a working diagnosis based on preliminary investigations. In four studies inclusion was based on a negative test result with the index test (12;13;18;20) and in one study based on a positive index tests result (17). Four of seven studies concerned with epilepsy were performed in drug-resistant disease. None of the identified studies included patients with psychosis thus test accuracy results may not be generalisable to patients with a first episode of psychosis. In addition only one study included in a narrative review originated from the UK.

Target condition
The majority of identified studies were concerned with the identification of primary and secondary tumours (seven studies) and focal lesions that may be amenable to surgery in epilepsy (seven studies). Two studies were concerned with the diagnosis of Alzheimer's disease.

Index test
CT: Fourteen studies were concerned with the accuracy of CT. Seven out of these assessed the accuracy of CT for identification of tumours and seven studies assessed the accuracy of CT in identifying focal lesions that may be amenable to surgery in epilepsy. In five studies contrast CT had been used and in one study plain CT. In the majority of studies (8/14) it was not clear to what degree plain CT or contrast CT had been used.

MRI: Four studies were concerned with the accuracy of MRI. Both of the studies concerned with the identification of Alzheimer's dementia assessed the accuracy of MRI for this purpose, one study concerned with identifying lesions that may be amenable to surgery in epilepsy and one study concerned with the identification of tumours. In the two studies investigating the accuracy of MRI in the diagnosis of Alzheimer's disease, one study used contrast MRI and the other plain. In the one study investigating the accuracy of MRI in the identification of focal lesions that may be amenable to surgery in epilepsy the authors did not state whether contrast had been used. In one study an assessment of the accuracy of plain versus contrast MRI in the identification of paediatric tumours was possible.

Reference tests
The reference tests for individual conditions varied across studies. For both studies concerned with the identification of Alzheimer's disease a clinical diagnosis was used as the reference standard. For studies concerned with the identification of tumours, three used contrast MRI, one used plain and contrast CT, two used plain MRI only and one used histology, post-mortem and clinical follow up. For studies concerned with the identification of lesions amenable to surgery in epilepsy, two studies used plain MRI, in four studies the use of contrast was not mentioned and one study used histology following surgery as the reference standard.

Quality
The quality of identified studies for estimation of test accuracy (see Table 55) was generally poor. However the majority of included studies were not described as being concerned with test accuracy and reported results descriptively. This may be an explanation for the poor quality rating on a scale designed for test accuracy studies. Some studies erroneously reported

correlation between tests (Altman 1991) rather than providing data in the form of a 2x2 diagnostic table.

The majority, (12) of included studies achieved a quality rating of four. One study achieved a score of three, two studies a score of two and one study a score of one.

Test accuracy
In five studies selection of the sample population was on the basis of either a negative or positive CT scan and in these instances only one dimension of test accuracy could be derived. The nature and clinical significance of target conditions or lesions used in studies for the calculation of tests accuracy were not always clear. For this reason test accuracy has been calculated separately for different lesions as far as possible. Note that if clinically insignificant lesions have been included in the calculation of test accuracy this will lead to an underestimation of the sensitivity of the index test used.

Detection of tumours
The sensitivity of plain CT for detection of primary tumours ranged from 90-96% with specificity 99-100%. All three of these studies were conducted in the 1980s. Estimates of sensitivity of plain CT for secondary tumours were lower (47-98%) but with a similar range of specificity (98-100%). One of three of these studies was conducted in the 1980s.

The sensitivity of contrast CT for the detection of primary tumours based on one study was 98% with corresponding specificity 99%. The sensitivity of contrast CT for the detection of secondary tumours was 58-100% with corresponding specificity of 98-100%.

One study allowed the comparison of plain and contrast MRI in 1y and recurrent paediatric tumours; plain MRI was 100% sensitive and 100% specific.

Detection of focal lesions potentially amenable to surgery in epilepsy
The sensitivity of CT for the detection of lesions that may be amenable to surgery in epilepsy ranged between 38 and 80% with corresponding specificity of 100%. Two of seven of these studies were conducted in the 1980s. The sensitivity of MRI for the detection of lesions that may be amenable to surgery in epilepsy was estimated as 93% with a specificity of 100%. It was unclear whether MRI was plain or contrast in this study.

Diagnosis of Alzheimer's disease
The sensitivity of plain MRI for diagnosing Alzheimer dementia reported in one study was 70% with specificity 76%. The sensitivity of contrast MRI for the detection of Alzheimer dementia was reported in one study as ranging between 88-95% with specificity of 94%.

Implications for test accuracy estimates to be used in the economic model
Plain CT, contrast CT, plain MRI and contrast MRI demonstrate sensitivities and specificities of over 90% for the detection of primary tumours in the group of studies reviewed here. In addition, all studies concerned with the detection of primary tumours were conducted in the 1980s; any technological advances since this time are likely to improve test accuracy. The sensitivity of plain CT in secondary tumours was lower. However patients with metastases are unlikely to present to a psychiatrist only with a first episode of psychosis as they will be known to other clinicians on the basis of treatment for their primary cancer.

The estimated sensitivity of CT for the identification of lesions amenable to epilepsy ranged between 38 and 80% with specificity of 100%. The majority of studies were conducted in the 1990s and so it is unlikely that these estimates of tests accuracy have been affected by technological advances. On the basis of one study the estimated sensitivity of MRI for this purpose was 93% and specificity 100%. However no studies included in the clinical effectiveness review identified these types of lesions.

No studies were identified investigating the accuracy of CT for the diagnosis of dementia. Plain MRI had sensitivities and specificities less than 80%. The estimated sensitivity of contrast MRI was higher (88-95%) with specificity of 94%. None of the studies included in the effectiveness review, where neuroimaging had been used to assist with a diagnosis of dementia, provided details of whether a contrast agent had been used.

Appendix 10. Costing of treatment for 1st Episode of Psychosis

Table 57. Treatment cost breakdown for economic model

	Dose (according to BNF unless stated otherwise)	**Drug**	**Cost Estimate (lower end – higher end)**
Oral atypical antipsychotic drugs			
Olanzapine 1st Choice	Schizophrenia: *ADULT over 18 years* 10 mg daily adjusted to usual range of 5-20 mg daily; doses greater than 10 mg daily only after reassessment; max. 20 mg daily *Assumptions (FO)*: 10mg per day: 2.5mg for 1st week 5mg for 2nd week 10mg for 6 weeks 20mg per day: 5mg for 1st week 10mg for 2nd week 20mg for 6 weeks *ELDERLY (by FO)* 5 mg daily adjusted to usual range of 2.5-5 mg daily *Assumptions (FO)*: 2.5mg per day: 2.5mg for 8weeks 5mg per day: 2.5mg for 2 weeks 5mg for 6 week	*Zyprexa (Lilly):* Tablets 2.5mg, 28-tab pack = £33.29 5mg, 28-tab pack = £48.78 7.5mg, 56-tab pack = £146.34 10mg, 28-tab pack = £79.45 15mg (blue), 28-tab pack = £119.18 20mg, 28-tab pack = £158.90	*ADULT* *Zyprexa (Lilly):* ***10mg per day** 21 tablets of 2.5mg and 42 tablets of 10mg = 1 x 28-tab pack (2.5mg) and 2 x 28-tab pack (10mg) = **£192.19** ***20mg per day** 21 tablets of 5mg and 42 tablets of 20mg = 1 x 28-tab pack (5mg) and 2 x 28-tab pack (20mg) = **£366.58** *ELDERLY* *Zyprexa (Lilly):* ***2.5mg per day** 56 tablets of 2.5mg = 2 x 28-tab pack = **£66.58** ***5mg per day** 14 tablets of 2.5mg and 42 tablets of 5mg = 1 x 28-tab pack (2.5mg) and 2 x 28-tab pack (5mg) = **£130.85**

Risperidone 2nd Choice	*Psychoses:* *ADULT* 2mg on first day 4mg on second day usual dose range 4-6 mg daily ELDERLY Initially 500 micrograms twice daily Increased in steps of 500 micrograms twice daily to 1-2 mg twice daily CHILD under 15 years not recommended	*Risperdal (Janssen-Cilag)* *Tablets* 500 micrograms, 20-tab pack = £7.06 1 mg, 20-tab pack = £11.61 1 mg, 60-tab pack = £34.84 2 mg, 60-tab pack = £68.69 3 mg, 60-tab pack = £101.01 4 mg, 60-tab pack = £133.34 6 mg, 28-tab pack = £94.28	*ADULT* *Risperdal (Janssen-Cilag)* ***2mg,4mg,4mg** 2 tablets of 1mg (for 1st day) and 55 tablets of 4mg required = 1 x 20-tab pack (1mg) and 1 x 60-tab pack (4mg) = **£144.95** ***2mg,4mg,6mg** 2 tablets of 1mg (for 1st day), 4 tablets of 1mg (for 2nd day) and 54 tablets of 6mg required = 1 x 20tab pack (1mg) and 2 x 28-tab packs (6mg) = **£200.17** ELDERLY *Risperdal (Janssen-Cilag)* ***500micrograms (1 week), then 1mg** 14 tablets of 500micrograms and 98 tablets of 1mg = 1 x 20-tab pack (500micrograms), 2 x 20-tab pack (1mg) and 1 x 60-tab pack (1mg) = **£65.12** ***500micrograms (1st week), 1mg (2nd week), then 2mg** 14 tablets of 500micrograms, 14 tablets of 1mg, and 84 tablets of 2mg = 1 x 20-tab pack (500micrograms), 1 x 20-pack (1mg), 2 x 60-tab pack (2mg) = **£156.05**

Clozapine	*Schizophrenia*: *ADULT over 16 years* 12.5 mg once ~~or twice~~ on first day 25-~~50~~ mg on second day then increased gradually (if well tolerated) in steps of 25-50 mg daily over 14-21 days up to 300 mg daily in divided doses (larger dose at night, up to 200 mg daily may be taken as a single dose at bedtime); if necessary may be further increased in steps of 50-100 mg once (preferably) or twice weekly; usual dose ~~200-450~~ 450-600 mg daily max. 900 mg daily *Assumptions* (FO) Patients are on clozapine for at least 6 months to see if the drug is effective or not. If they respond they stay on the drug for 12 months. Costing is done for 6 months 1st week: 100mg (25mg step) / 100mg (50mg step) 2nd week: 200mg (25mg step) / 200mg (50mg step) 3rd week: 300mg (25mg step) / 300mg (50mg step) 4th week: 450mg (25mg step) / 450mg (50mg step) 5th week: 450mg / 600mg (50mg step) 6th-24th week (126 days): 450mg / 600mg *ELDERLY* 12.5 mg once on first day 25-~~37.5~~ mg on second day then increased gradually (if well tolerated) in steps of 25 mg daily over 14-21 days up to 300 mg daily in divided doses; if necessary may be further increased in steps of 50-100 mg once (preferably) or twice weekly; usual dose 200-450 mg daily, max. 900 mg daily Costing is done for 6 months 1st week: 100mg / 100mg 2nd week: 200mg / 200mg 3rd week: 200mg / 300mg 4th week: 200mg / 450mg 5th-24th week (133 days): 200mg / 450mg	*Clozaril (Novartis)* Tablets 25mg, 28-tab pack = £6.17 25mg, 84-tab pack (hosp. only) = £18.49 100mg, 28-tab pack = £24.64 100mg, 84-tab pack (hosp. only) = £73.92 *Denzapine (Denfleet)* Tablets 25mg, 28-tab pack = £6.17 25mg, 84-tab pack = £18.49 100mg, 28-tab pack = £24.64 100mg, 84-tab pack = £73.92 *Zaponex (IVAX)* Tablets 25mg, 84-tab pack = £22.17 100mg, 84-tab pack = £50.00	*ADULT* *** 450 per day – 25mg step** 5 x 84-tab (25mg), 1 x 28-tab (100mg) and 6 x 84-tab (100mg) *** 600 per day – 50mg step** 3 x 84-tab (25mg), 2 x 28-tab (100mg) and 9 x 84-tab (100mg) *Clozaril (Novartis)* **£560.61 - £770.03** *Denzapine (Denfleet)* **£560.61 - £770.03** *Zaponex (IVAX)* **£460.85 - £566.51** *ELDERLY* *** 200 per day – 25mg step** 1 x 84-tab (25mg) and 5 x 84-tab (100mg) *** 450 per day – 25mg step** 5 x 84-tab (25mg), 1 x 28-tab (100mg) and 7 x 84-tab (100mg) *Clozaril (Novartis)* **£388.09 - £634.53** *Denzapine (Denfleet)* **£388.09 - £634.53** *Zaponex (IVAX)* **£272.17 - £460.85**

Source BNF 53, March 2007. Text from BNF, however, crossed out numbers are those not used in this appraisal on advice from clinical expert
Assumptions: Treatment is for 8 weeks (56 days); 2 weeks of titration and 6 weeks of maintenance

Appendix 11. Costs of treating epilepsy

Data on the costs of treatment for epilepsy have been extracted from the Health Technology Assessment report reviewing the cost-effectiveness of drugs for adults with epilepsy (Wilby et al., 2006). Costs can be split into two components:

- Costs associated with drug therapy (and monitoring related to that therapy)
- Other more general resource use and costs associated with diagnosis of epilepsy (GP consultations, outpatient consultations, A&E visits, telephone calls to clinical departments from patients (and family) for advice and inpatient stays).

The treated state assumes an initial start-up cost of £149 for patients starting a course of anti-epileptic treatment plus the cost of general resource for a patient who has achieved seizure freedom (£98) plus the cost of antiepileptic drug therapy. The cost of antiepileptic drug therapy has been averaged across all possible antiepileptic drug treatments available.

Table 58. Epilepsy treatment costs

	Treated (seizure freedom and acceptable side effects)
Annual cost for general resource use	£247
Annual cost for drug therapy	£542 (range £328-£757)
Total annual cost	**£789 (2001/02 prices)**
Total annual cost	**£920 (2005/06 prices)***
*Inflated using Unit Costs of Social Care, 2006 Pay and Prices Index	

11. References

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