

# Structural neuroimaging in first-episode psychosis

Technology appraisal guidance

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# Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the [Yellow Card Scheme](#).

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should [assess and reduce the environmental impact of implementing NICE recommendations](#) wherever possible.

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# 1 Recommendations

- 1.1 Structural neuroimaging techniques (either magnetic resonance imaging [MRI] or computed axial tomography [CT] scanning) are not recommended as a routine part of the initial investigations for the management of first-episode psychosis.

## 2 Clinical need and practice

- 2.1 Psychosis is not a diagnosis in itself but 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 experiences and reality. Usually, people with psychotic symptoms lack insight into their condition. Psychosis can develop at any age from childhood to late old age. First-episode psychosis refers to the first time that a person presents with psychotic symptoms. However, it is often difficult to identify the precise time of onset. The current definition of 'first episode' could include people who have been treated for many years without remission as well as those who have had psychosis for only a short time and have not yet received treatment.
- 2.2 Psychosis sometimes occurs in association with the use of psychoactive drugs or with certain conditions, such as space-occupying lesions in the brain (a benign or malignant tumour, a cyst or an abscess), strokes, Alzheimer's disease, head injury or encephalitis. Psychoses that occur as a result of physical illness and are associated with structural changes to the brain are sometimes referred to as 'organic psychoses'. All other psychoses, including those where the diagnosis is schizophrenia or bipolar disorder, are referred to as 'functional psychoses'. The causes of psychosis vary with age and sex. Young adults who develop psychotic symptoms are most often diagnosed with functional psychoses, while organic psychoses are more common in older people. It is thought that psychosis is associated with an organic cause in 5 to 10% of people who present with symptoms.
- 2.3 The prevalence of psychosis varies with age and sex. Hospital Episode Statistics from the UK show that 0.2% of episodes of psychosis occur in people in the age range 0 to 14 years, 83.3% in the age range 15 to 59 years, and 16.5% in people aged 60 years and above. In the UK, 59% of finished consultant episodes (a period of admitted patient care under a consultant or allied healthcare professional within an NHS trust) for psychosis occur in men and 41% in women. Information on the incidence of psychosis in the UK is mostly related to schizophrenia and other functional psychoses rather than all psychoses. A study in Nottingham on the incidence of first-episode psychotic disorders in 2 cohorts (1978 to 1980, and 1992 to 1994) found that the age-standardised incidence rate

for schizophrenia and related disorders was 0.14 per 1,000 per year.

- 2.4 Mortality figures for all psychoses are not available; however, the mortality rates with schizophrenia as an underlying cause in the UK (1996 to 2004) were estimated at 0.7 per million for men and 0.8 per million for women. It is also estimated that the suicide rate for psychosis is around 7.52 per 1,000 patient years (based on a small sample study), that the lifetime suicide rate for people with psychosis is 4% and that the lifetime suicide attempt rate is 22%.
- 2.5 People with psychosis tend to have a poor quality of life as a result of severe problems with social functioning and meeting the demands of daily life. People with psychosis may be reluctant to disclose or accept their condition because of lack of insight or the stigma attached to mental illness. The problems associated with psychosis can also place a significant burden on the person's family and carers.
- 2.6 Current management for psychosis aims to promote functional recovery and reduce relapse rates; it includes standard physical, mental state, neurological and laboratory examinations. Acute onset and delirium can be indications of an organic cause of psychosis. Where an organic cause is suspected, standard practice of care involves appropriate confirmatory tests. This may or may not include routine use of structural neuroimaging techniques. Where no organic cause for psychosis is found, it is assumed that a person has functional psychosis. Treatment of psychosis usually involves psychological and pharmacological approaches. There is, however, variation in service structure and delivery, the treatment and support offered, and the resources available across clinical practices.

## 3 The technologies

- 3.1 Structural neuroimaging involves non-invasive visualisation of the anatomical structure of the brain, in contrast to functional neuroimaging, which involves visualisation of the neurophysiological function of the brain. Two structural neuroimaging techniques that are currently used in the NHS are magnetic resonance imaging (MRI) and computed axial tomography (CT) scanning. MRI exploits the nuclear magnetic resonance phenomenon while CT scanning is based on a series of X-rays.
- 3.2 MRI is considered to be the preferred option for neuroimaging because it provides higher image resolutions than CT scans. It is also better able to picture the soft tissues of the brain, whereas CT scanning is more effective for picturing bone and hard tissues. MRI is generally a safe diagnostic technique and few safety concerns are reported in practice. Safety concerns usually relate to interactions of MRI scanners with magnetic objects (for instance, pacemakers) and patients may be subjected to noise, hyperthermia and peripheral nerve stimulation causing muscle twitching. There is a refusal rate in the general patient population of 5 to 10% because of anxiety and claustrophobia (this rate may be much higher for people with psychosis). MRI scanning results in a number of false positive tests. In a retrospective study of 1,000 healthy volunteers, 82% of MRI results were completely normal, and 1.1% required urgent referral. The remaining 16.9% may therefore have been unduly worried by a false positive MRI result of no medical consequence.
- 3.3 CT scanning can only detect differences in tissue density; lesions that have the same density as adjoining tissues will not be detected. However, in this case, an iodine-based contrast dye may be used for better visualisation. Contrast dyes may cause allergic reactions in some people, and in others may impair renal function. In some situations, MRI scanning may also require contrast enhancement. However, it is not generally expected that contrast enhancement would be required for evaluation of first-episode psychosis. One disadvantage of CT scanning is the dose of radiation absorbed during the process.
- 3.4 The acquisition cost of an MRI scanner is £1 to 2 million and that of a CT machine is approximately £500,000. Other costs associated with an MRI scanner include

the space that the scanner and other computerised equipment occupy. Additional costs associated with both technologies include regular maintenance, additional clinical support, and staff costs and training to use the technologies. The costs of individual MRI and CT scans are estimated at £244 and £78, respectively (2005 to 2006 NHS Reference costs, codes RBF1 and RBC5, respectively).



## 4 Evidence and interpretation

The [Appraisal Committee](#) considered [evidence from a number of sources](#). No submissions were received from the manufacturers of the technologies considered. The evidence base comprised the evidence presented by the Assessment Group and the personal perspectives of the nominated experts. The objective of the appraisal was to determine whether it is clinically and cost effective to scan routinely all those with first-episode psychosis by either structural MRI or CT techniques compared with the standard practice of carrying out selective radiological examinations contingent on clinical findings suggestive of an underlying structural cause.

### 4.1 Clinical effectiveness

- 4.1.1 The Assessment Group identified 25 studies that had been conducted for different purposes and had a wide range of study populations. The relevant studies identified had varying objectives and only 2 of the studies were conducted in the UK. Nine studies were considered to relate to first-episode psychosis. Two of the studies in first-episode psychosis involved MRI scanning, 6 involved CT scanning and 1 study involved both techniques. All the studies included for the clinical effectiveness review by the Assessment Group had varying patient populations, and a high level of methodological heterogeneity. There was incomplete reporting of results and sampling bias, which the Assessment Group thought was likely to affect the results. Consequently, a quantitative meta-analysis of the study results was not possible.
- 4.1.2 Studies that included people with first-episode psychosis did not generally explain how this term was defined, and this could be important given the lack of precision in defining what is meant by the term first-episode psychosis (see more about the definition in [section 2.1](#)). Based on a review of the 25 studies identified, the Assessment Group estimated that MRI scanning resulted in findings that would influence clinical management in approximately 5% of people with psychosis (range of 0 to 10%). The corresponding figure for CT scanning was approximately 0.5% (range of 0 to 5%). However, these estimates are subject to considerable uncertainty, given the nature of the studies and also the possibility that studies that do not demonstrate the usefulness of the technology remain

unpublished.

## 4.2 Cost effectiveness

- 4.2.1 A systematic review of studies on the cost effectiveness of structural neuroimaging in first-episode psychosis found no relevant economic evaluations. Nor was any evidence found on differential treatment responses to antipsychotic drugs in organic and functional psychoses or on quality-of-life benefits following early diagnosis (from routine screening). Because of the lack of data to populate a comprehensive decision-analytical model, the Assessment Group used a threshold analysis to estimate the cost effectiveness of routine scanning as compared with the standard diagnostic strategy of selective scanning contingent on clinical findings suggestive of an underlying structural cause of first-episode psychosis. A threshold analysis predicts the quality-adjusted life year (QALY) gain required for a technology to be regarded as cost effective. By combining the incremental cost of routine scanning with cost-effectiveness thresholds of £20,000 and £30,000 per QALY, the QALY gains needed to make routine scanning cost effective (or the QALY losses that could be tolerated if the strategy is cost saving) are estimated. A 12-month time horizon was assumed in the Assessment Group's threshold analysis. It was assumed that people considered to have functional psychoses will receive a predefined sequence of atypical antipsychotic medications.
- 4.2.2 The Assessment Group noted that some organic causes of psychosis cannot be diagnosed using MRI or CT scans. The Assessment Group's threshold analysis therefore considered the case of an organic psychosis caused by a brain tumour or cyst diagnosed after routine or selective scanning. The threshold analysis assumed that treatment of a brain tumour was not altered as a result of earlier detection with an MRI or CT scan. The analysis also assumed no deterioration in disease state when detected at a later stage with selective scanning compared with early-stage detection with routine scanning.
- 4.2.3 The cost of treatment for a brain tumour or cyst is common to both the routine and selective scanning strategies (using MRI or CT), because it was assumed that, even with selective scanning, diagnosis (and subsequent treatment) of a brain tumour or cyst would be achieved within the 12-month time horizon of the

threshold analysis. It was assumed that patients' response to antipsychotic medications is monitored over an 8-week period. The costs associated with this monitoring phase were determined by a proportional split of people receiving either hospital care or home care. The Assessment Group estimated test accuracy rates for detecting brain tumours or cysts to be 100% for MRI and above 90% for CT scans. It was assumed that the prevalence of brain tumours or cysts in a population of people with psychosis was 5%. This was based on MRI scanning having a sensitivity rate at or close to 100%. Also, the probability of detecting a brain tumour or cyst after an MRI scan was estimated to be 5% based on the Assessment Group's review of the evidence from studies that reported scans affecting clinical management.

- 4.2.4 The base-case threshold analysis incorporating the above assumptions found that the strategy of routine scanning with MRI was cost saving. These cost savings were sensitive to the following assumptions: the time period during which a brain tumour or cyst is undetected and antipsychotic medications are provided under selective scanning; the dosage and costs of antipsychotic medications; and the proportional split of people receiving hospital and home care during the monitoring phase. The greatest cost saving was apparent when the largest proportion of people were hospitalised during the monitoring phase. A 50 out of 50 split between hospital and home care had the largest impact on incremental costs. Under a conservative assumption that no people were hospitalised (0 out of 100 split), routine structural neuroimaging using MRI was still cost saving.
- 4.2.5 At a threshold value for willingness to pay for an additional QALY of £20,000, and under the conservative scenario of a 0 out of 100 split in hospital or home care, a QALY loss of 0.011 for the full cohort and 0.228 for people with brain tumours or cysts only is needed to offset cost savings. The Assessment Group stated that, under its base-case assumptions, QALY losses needed to render routine MRI scanning not cost effective would have to be large.
- 4.2.6 The base-case threshold analysis for CT scanning also showed that the scenario that achieved the greatest cost saving was that with the largest proportion of people receiving hospitalised care. However, even when this proportion was assumed to be zero, the antipsychotic drug dosage was assumed to be low and the duration of antipsychotic treatment was assumed to be only 6 months, a routine scanning strategy remained cost saving. Threshold analysis suggested

that the QALY loss (needed to render routine CT scanning not cost effective) is greatest in the scenario where the proportion of hospitalised care is largest (50%), the dose of antipsychotics is highest, and the duration of antipsychotic treatment is 12 months under selective scanning and for people with false negative routine CT scans. Under a conservative assumption of no hospitalised care, the QALY loss needed to render routine CT scanning not cost effective would have to be large, if the base-case assumptions regarding the probability of detecting a brain tumour or cyst after a scan are correct.

- 4.2.7 The Assessment Group conducted a number of sensitivity analyses, 1 of which varied the prevalence rate of brain tumours or cysts to 0.5% and 1%, respectively. The results of this sensitivity analysis showed that for MRI routine scanning was no longer cost saving at these prevalence rates. Therefore, for MRI to be cost effective, a QALY gain would be needed. Under all scenarios (duration of untreated psychosis, hospital and home care split, dose of antipsychotic medications), the maximum QALY gain needed to make MRI cost effective at an incremental cost-effectiveness threshold of £30,000 per QALY was small: 0.007 and 0.005 for the full cohort at 0.5% and 1% prevalences of brain tumours or cysts, respectively. At an incremental cost-effectiveness threshold of £20,000 per QALY, the corresponding maximum QALY gains were 0.010 and 0.007 for the full cohort at 0.5% and 1% prevalences of brain tumours or cysts, respectively.
- 4.2.8 When the prevalence rate of brain tumours or cysts was set at 0.5% and hospital care was given in 20% of cases or fewer, routine scanning was no longer cost saving and a QALY gain was needed to make CT scanning cost effective at conventional thresholds. For all scenarios with a 50 out of 50 split of hospital or home care, routine CT scanning was cost saving. When prevalence was set to 1%, routine CT scanning was cost saving under all scenarios.
- 4.2.9 The analyses carried out by the Assessment Group suggest that routine structural neuroimaging would be cost saving if the base-case assumptions regarding the probability of detecting a brain tumour or cyst after a scan are plausible. The maximum acceptable QALY loss for MRI to be cost effective ranged from 0.011 to 0.039, and for CT the maximum acceptable QALY loss ranged from 0.017 to 0.043. These results appear robust to variations in the various parameters investigated, except for variations in the prevalence rates of brain tumours or cysts in people with psychosis.

- 4.2.10 In conclusion, the threshold analysis showed that, if the prevalence of organic psychosis due to a brain tumour or cyst lies in the region of 5%, then, under the Assessment Group's assumptions, routine structural neuroimaging is cost saving. If the prevalence of organic psychoses is close to 0.5%, then, under the Assessment Group's assumptions, MRI is no longer cost saving, and CT is only cost saving if 50% of people receive hospital care. However, evidence for determining the true prevalence of treatable lesions in the population under test is extremely limited.

## 4.3 Consideration of the evidence

- 4.3.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of structural neuroimaging (using MRI or CT scanning) in first-episode psychosis, having considered evidence on the nature of the condition and the value placed on the benefits of structural neuroimaging by clinical specialists. It was also mindful of the need to take account of the effective use of NHS resources.
- 4.3.2 The Committee agreed that, because structural abnormalities in the brain progress over time, for people with a first episode of psychosis without signs or symptoms of additional pathology, the early positive detection and management of structural lesions after routine scanning could have health benefits where a treatable cause is found. The Committee expressed concern about whether it would be feasible to scan people who were particularly disturbed when they presented with acute psychosis. The Committee was reassured by the clinical specialist that some people may be more willing to undergo a neuroimaging scan than to have thorough clinical examinations, viewing it as less intrusive.
- 4.3.3 The Committee concluded from the evidence presented that there was substantial uncertainty about the true prevalence of structural lesions in the population under test. The Committee heard from the clinical specialist that the assumption of a 5% prevalence of organic psychosis may be an underestimate and that the figure could be as high as 10% because the studies reported had excluded people with any clinical sign of neurological abnormalities, which would reduce the likelihood of including people with psychosis of an organic cause in the study population. However, the clinical specialist considered that the figure

for organic psychosis due specifically to a brain tumour or cyst may be less than 5%. The Committee noted that the prevalence estimate of 5% for organic psychosis due to a brain tumour or cyst was based on the results from studies of varying methodological quality and internal validity, and agreed that this estimate could not be relied on. The Committee further considered that incidental findings and false positives associated with neuroimaging may increase the anxiety levels of people with psychosis, leading to additional investigations and treatments, with questionable returns in terms of improved health outcomes from clinical care.

- 4.3.4 The Committee considered the evidence presented on the cost effectiveness of routine structural neuroimaging in first-episode psychosis. It discussed the tentative results of the Assessment Group's threshold analysis, which suggested that neuroimaging may be cost saving in a number of scenarios. The Committee noted that 1 limitation of the Assessment Group's threshold analysis is the uncertainty surrounding estimates of the prevalence of brain tumours or cysts in people with first-episode psychosis. It also noted that the analysis did not capture potential costs associated with false positives, the need for repeat investigations and subsequent treatments, and potential health benefits and losses. The Committee considered that, although the Assessment Group's approach was appropriate given the lack of data, substantial uncertainties existed about key parameters in the threshold analysis – in particular, the estimates of the prevalence rates of brain tumours or cysts in the population of people with first-episode psychosis.
- 4.3.5 The Committee further discussed the assumption in the Assessment Group's approach that people in whom structural lesions were identified by neuroimaging could discontinue antipsychotic medication and thereby eliminate subsequent costs for these drugs. The Committee heard from the clinical specialist that this may not routinely be the case if the lesion is not treatable and the psychotic symptoms persist. The Committee was aware that effects on mortality had not been considered in the threshold analysis and that the analysis did not consider possible deterioration in the underlying organic conditions as a result of late detection and diagnosis under selective scanning. The Committee concluded that a reliable estimate of the cost effectiveness of routine structural neuroimaging could not be made given the limitations on the data available.

- 4.3.6 On balance, the Committee agreed that, although routine scanning could have potential benefits from early detection of structural causes of first-episode psychosis, the current evidence base, particularly in relation to the prevalence of treatable lesions in the population under examination, was too weak to support a decision to implement routine use of MRI or CT scanning in people with first-episode psychosis. The Committee agreed that this decision should not affect the current practice of using structural neuroimaging techniques selectively to exclude organic causes of psychosis where people's symptoms, or other aspects of their presentation, suggest a higher likelihood of an underlying organic cause.
- 4.3.7 The Committee considered that the limited evidence base to support routine scanning using structural neuroimaging techniques made it difficult to determine the clinical and cost effectiveness of routine structural neuroimaging versus selective scanning. The Committee concluded therefore that the use of structural neuroimaging techniques (either MRI or CT scanning) should not be recommended as a routine part of the initial investigations for the management of first-episode psychosis.



## 5 Recommendations for further research

- 5.1 The Committee recommends that further evidence should be collected and systematic studies on the clinical benefits of routine scanning with structural neuroimaging in first-episode psychosis should be carried out.
- 5.2 Research studies should evaluate whether routine scanning is associated with early detection and treatment of organic causes of psychosis and improved health outcomes including effects on health-related quality of life.



# 6 Appraisal Committee members and NICE project team

## Appraisal Committee members

The Appraisal Committee is a standing advisory committee of NICE. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets twice a month except in December, when there are no meetings. The Committee membership is split into 3 branches, each with a chair and vice-chair. Each branch considers its own list of technologies and ongoing topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The [minutes of each Appraisal Committee meeting](#), which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

### **Professor Keith Abrams**

Professor of Medical Statistics, University of Leicester

### **Dr Jeff Aronson**

Reader in Clinical Pharmacology, Radcliffe Infirmary

### **Professor David Barnett (Chair)**

Professor of Clinical Pharmacology, University of Leicester

### **Professor Stirling Bryan**

Director of the Health Economics Facility, University of Birmingham

### **Professor John Cairns**

Public Health and Policy, London School of Hygiene and Tropical Medicine

**Dr Mark Charkravarty**

Head of Government Affairs and NHS Policy, Procter and Gamble Pharmaceuticals (UK) Ltd

**Ms Lynn Field**

Nurse Director, Pan Birmingham Cancer Network

**Professor Christopher Fowler**

Professor of Surgical Education, University of London

**Dr Fergus Gleeson**

Consultant Radiologist, Churchill Hospital

**Ms Sally Gooch**

Former Director of Nursing and Workforce Development, Mid Essex Hospitals Services NHS Trust

**Mrs Barbara Greggains**

Lay Member

**Mr Sanjay Gupta**

Former Service Manager in Stroke, Gastroenterology, Diabetes and Endocrinology, Basildon and Thurrock University Hospitals Foundation NHS Trust

**Mr Terence Lewis**

Mental Health Consultant, National Institute for Mental Health in England

**Professor Gary McVeigh**

Professor of Cardiovascular Medicine, Queens University, Belfast

**Dr Ruairidh Milne**

Senior Lecturer in Health Technology Assessment, National Coordinating Centre for Health Technology

**Dr Neil Milner**

General Medical Practitioner, Tramways Medical Centre, Sheffield

**Dr Rubin Minhas**

General Practitioner, CHD Clinical Lead, Medway PCT

**Dr Stephen Saltissi**

Consultant Cardiologist, Royal Liverpool University Hospital

**Dr Lindsay Smith**

General Practitioner, East Somerset Research Consortium

**Mr Cliff Snelling**

Lay Member

**Dr Ken Stein**

Senior Lecturer, Peninsula Technology Assessment Group (PenTAG), University of Exeter

**Dr Rod Taylor**

Associate Professor in Health Services Research, Peninsula Medical School, Universities of Exeter and Plymouth.

## **B NICE project team**

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

**Ebenezer Tetteh**

Technical Lead

**Janet Robertson**

Technical Adviser

**Natalie Bemrose**

Project Manager

## 7 Sources of evidence considered by the Committee

The assessment report for this appraisal was prepared by the West Midlands Health Technology Assessment Group, University of Birmingham.

- Albon E, Tsourapas A, Frew E et al. Structural neuroimaging in psychosis. Systematic review and economic evaluation, June 2007

The following organisations accepted the invitation to participate in this appraisal. They were invited to comment on the draft scope, the assessment report and the appraisal consultation document (ACD). Companies or sponsors, and professional or specialist, and patient or carer groups were also invited to make written submissions and have the opportunity to appeal against the Final Appraisal Determination.

Companies or sponsors:

- GE Medical Systems
- Phillips Medical Systems

Professional or specialist, and patient or carer groups:

- Counsel and Care
- Rethink
- British Association for Psychopharmacology
- British Neuropsychiatry Association
- British Psychological Society
- Royal College of General Practitioners
- Royal College of Nursing
- Royal College of Radiologists

Commentator organisations (without the right of appeal):

- Department of Health, Social Services and Public Safety for Northern Ireland
- EUCOMED
- NHS Quality Improvement Scotland
- Institute of Psychiatry
- National Coordinating Centre for Health Technology Assessment
- West Midlands HTA Collaboration

The following individuals were selected from clinical specialist and patient advocate nominations from the non-manufacturer or sponsor consultees and commentators. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on structural neuroimaging by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD.

- Professor Philip McGuire, Professor of Psychiatry and Cognitive Neuroscience, Institute of Psychiatry – clinical specialist
- Dr Sophia Frangou, Reader, Institute of Psychiatry – clinical specialist

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