Technology Assessment Report commissioned by the NHS R&D HTA Programme on behalf of the National Institute for Health and Clinical Excellence

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1. Title of the project:
Structural neuroimaging in first episode psychosis.

2. Name of TAR team and 'lead'
West Midlands Health Technology Assessment Collaboration (WMHTAC)

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3. Plain English summary
Psychosis is considered to be a symptom of severe mental illness but not a diagnosis in itself. It includes lack of insight and an inability to distinguish between subjective experience and external reality as shown by the presence of delusions and hallucinations. A person may have been experiencing psychotic episodes for some time before coming into contact with a health professional either through accident and emergency, general practice or the criminal justice system. When medical contact is made for the first time, the term 'first episode psychosis' is used.

In the UK, a standard examination is carried out (history, physical, mental state and neurological examinations and blood and urine tests) to assess possible causes of first episode psychosis. The neurological history and examination looks for motor, sensory or cognitive deficits.

Historically, there have been two main categories of psychosis – organic and functional. Organic psychoses were those where a change in brain tissue could be seen on examination by light microscopy whereas functional psychoses had no obvious differences from normal brain tissue that could be seen with this technique. Organic psychoses can be caused by a variety of conditions including strokes, brain injury, encephalitis, Alzheimer's disease, Parkinson's disease, multiple sclerosis, temporal lobe epilepsy or brain tumours. Functional psychoses include schizophrenia and mood disorders such as manic-depression.

Neuroimaging (also called brain imaging) can be categorized as either structural (MRI and CT scanning) or functional (functional MRI and PET scanning). This project will investigate the two structural brain imaging techniques only. Magnetic resonance imaging (MRI) employs radio-waves and a strong magnetic field to assemble highly detailed cross-sectional pictures of the brain. Computed (axial) tomography (CT or CAT) scanning uses a series of x-rays to visualize 'slices' through the brain.

This project will determine whether the information provided by neuroimaging improves diagnosis and management of first episode psychosis. It will assess research evidence to establish circumstances where MRI and CT scanning should be used for individuals presenting with first episode psychosis and whether these techniques provide good value for money.

4. Decision problem

4.1 Purpose of the decision to be made

The purpose of this project is to determine whether the use of structural neuroimaging, also known as brain imaging (MRI and CT or CAT scan), gives any clinical benefit above standard current practice in the differential diagnosis and management of the various causes of first episode psychosis and whether it is a cost effective diagnostic strategy.

4.2 Definition of the intervention

The interventions are structural imaging techniques of standard magnetic resonance imaging (MRI) and standard computed (axial) tomography (CT) scanning. MRI uses radio-waves and a strong magnetic field to assemble highly detailed cross-sectional pictures of the brain. CT scanning uses a series of x-rays to visualize slices through the brain. 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.

Functional imaging techniques such as functional MRI (fMRI) and Positron Emission Tomography (PET) scanning and all other forms of research scanning will not be included in this project (see Scope).

4.3 Place of the intervention in the treatment pathway(s)

A patient may suffer one or several episodes of psychosis of varying lengths before they come to the attention of the health services.(1) Referral usually comes via the criminal justice system or family or friends to the accident and emergency or general practitioner services.(2,3) The first time that a person presents with psychosis is termed first episode psychosis. A thorough history is taken from patients and their relatives and patients are given a physical examination, mental state examination and neurological examination. Following this, laboratory investigations (haematological, biochemical, microbiological) and an electroencephalogram (EEG) may be required, depending on possible diagnoses.

There are two main categories of psychosis – organic and functional. Organic psychoses are those where a change in brain tissue can be seen on examination by light microscopy whereas functional psychoses have no obvious differences from normal brain tissue that can be seen with this technique. Organic causes of psychosis include as stroke, Alzheimer's disease, Parkinson's disease, multiple sclerosis, temporal lobe epilepsy, or primary or secondary brain tumours. Functional causes of psychosis include schizophrenia and mood disorders such as manic depression or puerperal psychosis. The main factors that would lead the clinician to suspect an organic cause should be discovered during the initial clinical process. Indication of an organic cause of psychosis from a mental state examination includes memory impairment, episodic confusion or loss of lucidity and/or disorientation in time, place or person. Indication of an organic cause of psychosis in a neurological history and examination include 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 frequently not in the UK.(4,5) However, 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.(5)

If no organic cause of psychosis is suspected following the standard clinical process, it is assumed that the patient has a functional psychosis.(6) 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. MRI or CT scanning could possibly be used in this situation to find cases of psychosis with an organic cause missed in the initial clinical process. However, it is very rare to find an organic cause of psychosis missed in the initial clinical process in younger age groups (personal communication, F. Oyebode, Queen Elizabeth Psychiatric Hospital Birmingham, October 2006). MRI and CT scans at the moment cannot be

used to diagnose schizophrenia (or other forms of functional psychoses) because any structural changes seen, such as generalised atrophy or enlarged ventricles, have not been found to be specific to schizophrenia so far.(7)

It is unlikely that MRI or CT scanning would be used where patients do not initially respond to treatment because a relatively high proportion of people with schizophrenia and mood disorders do not initially respond to treatment anyway. For example, 39% of people diagnosed with schizophrenia do not respond after up to eight weeks of chlorpromazine treatment.(8) MRI or CT scanning may be used where patients initially respond to treatment but then seem to deteriorate in the presence of symptoms or signs of a suspected organic cause of psychosis.

4.4 Relevant comparators
The comparators for the interventions under assessment are standard clinical history, mental state examination and neurological examination, additional laboratory investigations (haematological, biochemical, microbiological) and possibly an EEG.

4.5 Population and relevant sub-groups
The population is adults and children who present with first episode psychosis.

The most common causes of psychosis vary by age and gender, for example schizophrenia usually develops in the young adult(9) whereas most causes of psychosis in the elderly are organic.(10) Potential subgroups include gender and different age groups such as adolescent, young adult, older adult and the elderly. As psychosis is rare in children under the age of 12 years, there may be no evidence available in this age group. If evidence allows, variation in outcomes will be investigated in the subgroups of age and gender.

4.6 Key factors to be addressed
The primary focus of this assessment will be the clinical and cost outcomes from the perspective of the healthcare system and personal social services. Direct costs will include all costs of healthcare resources consumed in the provision of the interventions, administration and monitoring costs as well as the consequences of scanning such as adverse events and false positive diagnoses.

4.7 Areas of agreement at the scoping workshop that are outside the scope of the appraisal and therefore do not require any detailed assessment
It was agreed that atypical psychosis was not a useful term so first episode psychosis was substituted.

5. Report methods for synthesis of evidence of clinical effectiveness

1.1 5.1 Search strategy
A scoping search has already been undertaken to identify any existing systematic reviews and to estimate the volume and nature of primary studies. The search for systematic reviews was carried out based on the ARIF search protocol (Appendix 1). No published systematic reviews assessing structural neuroimaging in first episode psychosis were identified in The Cochrane Library.

Selected subject terms to be used in the searches for primary studies are illustrated in the sample search strategy for MEDLINE (Appendix 1). Filters to identify particular study designs may be used depending on the yield of references. No language or date restrictions will be applied.

The following resources will be searched:

- Bibliographic databases: Cochrane Library (Wiley), MEDLINE (Ovid), MEDLINE In-Process & Other Non-Indexed Citations (Ovid), EMBASE (Ovid), CINAHL (Ovid), PsycINFO (Ovid).
- Citations of relevant studies.

- Research registries of ongoing trials including National Research Register, Current Controlled Trials, Clinical Trials.gov
- Relevant internet resources
- Hand search of appropriate journals such as Magnetic Resonance in Medicine and Journal of Computer Assisted Tomography
- Industry submissions
- Further information from contact with experts.

1.2 5.2. Types of studies included

Primary studies suitable for inclusion will be selected from those identified as potentially relevant by the search strategy, using the criteria listed below:

Inclusion criteria

Population:
Persons (adults or children) presenting with first episode psychosis.

Intervention:
Structural neuroimaging techniques (Magnetic Resonance Imaging (MRI) and Computerised (Axial) Tomography (CT))

- as a routine screening tool in all individuals presenting with first episode psychosis
- as an assessment tool in patients with clinical suspicion of organic cause of first episode psychosis
- as an assessment tool when standard examination methods fail to identify causes of first episode psychosis in patients with clinical suspicion of an organic cause of psychosis
- as an assessment tool in individuals who have not responded to treatment
- as an assessment tool in individuals who have previously responded to treatment then deteriorated in the presence (or absence) of focal neurological symptoms and signs

Comparator:
The comparator is current standard NHS practice in the assessment of individuals presenting with first episode psychosis without structural neuroimaging for all i.e. thorough history, physical examination, mental state examination, neurological examination and additional laboratory investigations as appropriate (haematological, biochemical, microbiological). Current standard NHS practice may or may not include EEG and/or MRI/CT scanning where appropriate.

Outcomes – studies that investigate at least one of the following outcomes:

- Morbidity and mortality due to undetected treatable cause of first episode psychosis
- Proportion of scans that lead to the identification of otherwise unknown or previously unsuspected organic causes of first episode psychosis
- Proportion of scans that pick up structural abnormalities thought to be aetiologically related to or unrelated to the psychosis
- Proportion of scans that reveal information of clinical value in terms of supporting clinical care and management
- Proportion of scans that rule out organic causes of first episode psychosis
- Severity and progression of first episode psychoses
- Subsequent service use (including frequency and duration of hospital admissions)
- Health-related quality of life
- Major adverse effects due to the use of MRI/CT imaging

Age and gender subgroups will be examined for the outcomes listed above where possible

Types of studies:
Fully published RCTs, cohort studies, case-control studies or case series will be included. Based on the volume and nature of observational evidence identified, a suitable cut-off for inclusion (such as study design, then number of study participants) may be chosen. The hierarchy would be cohort studies, then case control studies then case series.

Studies published only as abstracts or conference presentations will be included only if there are sufficient details presented to enable appraisal of the methodology used and assessment of results. Studies in all languages will be considered for inclusion. If studies are in languages where translation expertise is not available and there are insufficient details to enable appraisal of the methodology used and assessment of results, the studies will be listed in an appendix of potentially includable studies.

Exclusion criteria
Study Design:
Case reports.

Population:
Patients presenting with focal neurological signs and symptoms where first episode psychosis is not the principal clinical problem or where only some patients have first episode psychosis.

Studies where the patient population is a subset of patients with first episode psychosis, eg where all patients have already been diagnosed with schizophrenia.

Intervention:
Functional brain imaging techniques (PET and fMRI) and all other forms of research scanning.

Comparator
Functional brain imaging techniques (PET and fMRI) and all other forms of research scanning.

Outcomes
-

5.3 Inclusion and data extraction strategies
Reference lists of titles and abstracts will be checked for inclusion by two reviewers independently and discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary.

Data will be extracted independently by more than one reviewer using a standardised data extraction form (see Appendix 2) and compared. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary. Details of study characteristics, study participants, intervention, comparator and outcome results will be extracted as necessary.

5.4 Quality assessment strategy
The quality of included studies will be assessed by one reviewer and independently checked for agreement by a second reviewer. Any disagreements will be resolved by consensus and if necessary a third reviewer will be consulted. The quality of included studies will be assessed according to criteria based on, for example, NHS CRD Report No.4.(11) and the assessment framework for RCTs developed by Jadad.(12)

5.5 Methods of analysis/synthesis
It is likely that there will be a variety of study designs and these will be synthesised through narrative review and tabulation. Where results are of sufficient quantity and are homogeneous, an

appropriate method of meta-analysis will be performed, using appropriate software. Analysis of subgroups will be explored should evidence allow.

5.6 Methods for estimating quality of life
See section 6.

6. Report methods for synthesising evidence of cost-effectiveness
A comprehensive search for literature on the cost and cost-effectiveness of structural neuroimaging in first episode psychosis will be carried out.

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

- Bibliographic databases: MEDLINE (Ovid), EMBASE (Ovid), CINAHL (Ovid), Cochrane Library (Wiley) DARE and NHS EED and the Office of Health Economics HEED database.
- Industry submissions
- Internet sites of national economic units

Searches will not be limited by date and there will be no language restrictions.

Standard approaches to applying inclusion/ exclusion criteria will be employed. Quality assessment for cost-effectiveness studies will be done using standard criteria.(13,14) Papers may be excluded at this stage on the basis of quality assessment. Justification for the exclusion of papers will be presented. The papers that remain in the review will be summarised on the basis of key items of information, an example of which is listed below.

- Details of the study characteristics such as form of economic analysis, comparators, perspective, time horizon and modelling used.
- Details of the effectiveness and cost parameters such as: effectiveness data; health state valuations; resource use data; unit cost data; price year; discounting assumptions; productivity costs.
- Details of the results and sensitivity analysis.

Searches for additional information regarding model parameters, patient preferences and other topics not covered within the clinical effectiveness and cost-effectiveness reviews will be based on the methodological discussion paper produced by InterTASC (January 2005).

1.3 6.1 Economic Evaluation

Where feasible and sensible the economic analysis will conform to the NICE reference case. Any major deviation from the reference case will, however, be discussed with colleagues at NICE before being implemented.

A model-based economic evaluation will be conducted as part of this appraisal. The structure of the model will be considered in light of any existing published models in this clinical area and will be developed in collaboration with clinical experts. The choice of model type has to be guided by the nature of the clinical condition and is likely to be either a decision tree or a Markov model.

The perspective for the base-case cost analysis will be the NHS and Personal Social Services but a broader perspective will be considered as part of the sensitivity analysis. The analysis will be conducted with a number of different time horizons (including both short-term, such as 1 year, and longer-term, such as 10 years), given the high levels of uncertainty that will inevitably be associated with long-term horizons in this clinical area. Longer-term analyses will be discounted in line with reference case recommendations and so a rate of 3.5% will be applied to both costs and benefits. The results are likely to be sensitive to the rate selected and so sensitivity analyses will include alternative discount rate assumptions.

Perhaps the most challenging aspect of this economic analysis will be to express effectiveness in terms of quality-adjusted life years (QALYs). It is self-evident that standard utility-based measures of health related quality of life, such as the EuroQol EQ-5D, are not ideal measures in this clinical area. For example, the EQ-5D has a single mental health dimension (Anxiety/Depression) and it seems unlikely that changes in patients with psychosis will be fully captured using such an instrument. Thus, whilst our intention is to conduct a cost-utility analysis, with QALYs as the measure of outcome, data limitations may be considerable and if this proves to be the case then the analysis will be of a cost-effectiveness format with effects expressed in more natural clinical units.

Once again, subject to the availability of suitable data, the costs and benefits of different service strategies in existing clinical practice will be explored in sensitivity analysis. In particular, the costs and benefits among different patient subgroups (identified in the clinical effectiveness evidence synthesis) will be explored.

The uncertainties in this analysis will be considerable and so extensive sensitivity analyses will be undertaken. These will take the form of both conventional one and multi-way analyses (where the values of key input parameters are varied) and probabilistic sensitivity analysis (PSA). The use of PSA will involve specifying distributions around model parameters (such as probabilities, costs, utilities, etc.) and sampling from such distributions. This analysis will then allow results to be presented as scatter plots on the CE plane and as cost-effectiveness acceptability curves.

7. Handling the company submission(s)

Company submissions by the manufacturers/sponsors will be considered if received by the TAR team no later than 14 March 2007. Company submission material of any nature arriving after this date will not be considered.

If the clinical information meets the inclusion criteria for the review it will be extracted and quality assessed in accordance with the procedures outlined in this protocol. Any economic evaluations included in the company submission, provided it complies with NICE's advice on presentation, will be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used in the economic model.

Any 'commercial in confidence' data taken from a company submission will be underlined and highlighted in the assessment report (followed by an indication of the relevant company name e.g. in brackets).

8. Competing interests of authors

Personal specific	**Non-personal specific**
Esther Albon- None	Esther Albon- None
Theodoros Arvanitis - None	Theodoros Arvanitis - None
Stirling Bryan - None	Stirling Bryan - None
Sue Bayliss- None	Sue Bayliss- None
Clare Davenport- None	Clare Davenport- None
Catherine Meads- None	Catherine Meads- None
Femi Oyebode- None	Femi Oyebode- None

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9. Appendices

9.1. Appendix 1 DRAFT Search Strategy

9.1.1 Subject search strategy:

Database: Ovid MEDLINE(R) 1966 to October Week 3 2006

1 MRI.mp. or exp Magnetic Resonance Imaging/
2 magnetic resonance imag$.mp.
3 CAT.mp.
4 computeri?ed axial tomography.tw.
5 X ray computed tomography.mp. or exp Tomography, X-Ray Computed/
6 structural neuroimag$.tw.
7 neuroimag$.tw.
8 CT scan$.mp.
9 or/1-8
10 exp Psychotic Disorders/ or psychosis.mp.
11 exp Schizophrenia/ or schizophrenia.mp.
12 bipolar disorder$.mp. or exp Bipolar Disorder/
13 manic depression.mp.
14 exp Psychoses, Substance-Induced/ or psychosis.mp.
15 exp Delirium, Dementia, Amnestic, Cognitive Disorders/ or exp Dementia/ or dementia.mp.
16 exp Epilepsy/ or epilepsy.mp.
17 psychotic.mp.
18 exp Mental Disorders/
19 mood disorder$.mp. or exp Mood Disorders/
20 or/10-19
21 9 and 20
22 tumo?r$.mp. or exp Neoplasms/
23 infection$.mp.
24 stroke$.mp. or exp Cerebrovascular Accident/
25 pathолog$.mp.
26 (first adj2 episode).mp.
27 secondary psychosis.mp.
28 organic$.mp.
29 lesion$.mp.
30 or/20-29
31 21 and 30
32 limit 31 to "reviews (specificity)"

9.1.2 Example of a filter for identifying systematic reviews

(University of York CRD search strategy for identifying systematic reviews and meta-analyses from MEDLINE) :

1 (systematic adj review$).tw.
2 (data adj synthesis).tw.
3 (published adj studies).ab.
4 (data adj extraction).ab.
5 meta-analysis/
6 meta-analysis.ti.
7 comment.pt.
8 letter.pt.
9 editorial.pt.
10 animal/
11 human/

12 10 not (10 and 11)
13 SUBJECT TERMS not (7 or 8 or 9 or 12)
14 or/1-6
15 13 and 14

9.1.3 Example of a filter for identifying randomized controlled trials and other primary studies in the MEDLINE database

(Appendix 5b.2 *Cochrane Handbook for Systematic Reviews of Interventions 4.2.6 Updated September 2006 Cochrane Collaboration 2006* *http://www3.interscience.wiley.com/homepages/106568753/handbook.pdf*) :

1 randomized controlled trial.pt.
2 controlled clinical trial.pt.
3 randomized controlled trials.sh.
4 random allocation.sh.
5 double blind method.sh.
6 single-blind method.sh.
7 or/1-6
8 (animal not human).sh.
9 7 not 8
10 clinical trial.pt.
11 exp clinical trials/
12 (clin$ adj25 trial$).ti,ab.
13 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
14 placebos.sh.
15 placebo$.ti,ab.
16 random$.ti,ab.
17 research design.sh.
18 or/10-17
19 18 not 8
20 19 not 9
21 comparative study.sh.
22 exp evaluation studies/
23 follow up studies.sh.
24 prospective studies.sh.
25 (control$ or prospectiv$ or volunteer$).ti,ab.
26 or/21-25
27 26 not 8
28 27 not (9 or 20)
29 9 or 20 or 28

9.1.4 ARIF search protocol (September 2006 version)

1) Cochrane Library
- Cochrane Reviews
- 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.

3) NHSCRD (WW Web access)
- DARE
- Health Technology Assessment Database

- Completed and ongoing CRD reviews

4) Health Technology Assessments and evidence based guidelines (WW Web access)
- NICE appraisals and work plans for TARs, Interventional Procedures and Guidelines programmes (NCCHTA work pages:www.ncchta.org/nice/) Public Health excellence
- NHS Coordinating Centre for Health Technology Assessments
- Canadian Agency for Drugs and Technologies in Health Care
- SBU – Swedish Council on Technology Assessment in Health Care
- New Zealand Health Technology Assessment
- Alberta Heritage Foundation
- Agency for Healthcare Research and Quality (AHRQ)
- National Horizon Scanning Centre
- SIGN (Scottish Intercollegiate Guidelines Network)
- NHS QIS (Quality Improvement Scotland)

5) Clinical Evidence

6) Bandolier

7) TRIP Database

8) Bibliographic databases
- MEDLINE - systematic reviews
- EMBASE - systematic reviews
- Other specialist databases.

9) Contacts
- Cochrane Collaboration (via Cochrane Library)

Regional experts, especially Pharmacy Prescribing Unit, Keele University (& MTRAC) and West Midlands Drug Information Service

1.4 Appendix 2 DRAFT Data Extraction Form

Trial details	**Trial ID**	
	Intervention strategy	
	CT/ MRI and machine details	
	Comparator strategy	
	Standard examination details	
	Population	
	Type of trial design	
	Setting	
	Study start and end dates	
	Centres (n) / Country	
Trial design		
	Comments on design	
Quality assessment for RCTs	Was assignment of treatment described as random?	
	Was method of randomisation described?	
	Was the method really random?	
	Was allocation of treatment concealed?	
	Who was blinded to treatment?	
	Was method of blinding adequately described?	
	Were eligibility criteria described?	
	Were groups comparable at study entry?	
	Were groups treated identically apart from the intervention?	
	Was ITT used?	
	Were withdrawals stated?	
	Were reasons for withdrawals stated?	
	Was a power calculation done?	
	Comments	

Quality assessment for observational studies (Cohort/ Case-control)	Was the population base described?			
	Were recruitment / eligibility criteria reported?			
	Was there consideration of possible confounding factors?			
	Were losses to follow up reported?			
	Were losses to follow up > 20%?			
	Were other interventions received differentially during follow up?			
	Was missing data (group or time point data) accounted for?			
	Comments			
Eligibility criteria	Inclusion criteria (pre and post randomization)			
	Exclusion criteria			
Baseline characteristics			**[Intervention]**	**[Comparator]**
	Number randomised			
	Number analysed			
	Age (wks, mos, yrs) (mean, SD; median, range)			
	Male:female n : n			
	Duration of psychotic episode (wks, mos, yrs) (mean, SD; median, range)			
	Age at diagnosis (wks, mos, yrs) (mean, SD; median, range)			
	Previous treatment for psychosis, n (%)			
	Concomitant disease/ condition			
	Alcohol, n (%) / illicit drug use, n (%)			
	Comments			

Outcomes	Primary outcome(s) reported including timepoints if repeated			
	Secondary outcome(s) reported excluding Adverse Events			
	Frequency / type of health-care contacts			
	Ad hoc' outcomes reported (if emphasised and not in methods)			
	Comments			
Results unadjusted where available			**[Intervention]**	**[Comparator]**
	Withdrawals including reasons where specified study	reasons		
			Results (diff, or by arm)	**CI for difference; p-value**
	outcome	details to be clarified		
	outcome	details to be clarified		
	outcome	details to be clarified		
	Comments (including whether unadjusted results reported)			
Adverse Events	Criteria for reporting		**[Intervention]**	**[Comparator]**
	Events n/N			
	Comments			
Conclusions	Author's conclusions			
	Our conclusions			