APPENDICES

APPENDIX 1: SCOPE FOR THE DEVELOPMENT OF THE CLINICAL GUIDELINE

Guideline title: Psychosis and schizophrenia in adults: treatment and management

Short title: Psychosis and schizophrenia in adults

1. Introduction

1.1 Clinical guidelines

Clinical guidelines are recommendations by NICE on the appropriate treatment and care of people with specific diseases and conditions within the NHS. They are based on the best available evidence.

This scope defines what the guideline will (and will not) examine, and what the guideline developers will consider.

This is a partial update of 'Schizophrenia' (NICE clinical guideline 82). See section 3.3.1 for details of which sections will be updated. We will also carry out an editorial review of all recommendations to ensure that they comply with NICE's duties under equalities legislation.

This update is being undertaken because new evidence has emerged on service-level interventions, interventions that improve the ability of people to undertake employment (including supported employment and pre-vocational training) and cognitive remediation therapy (in particular, its combination with pre-vocational training). In addition, the scope has been broadened to include psychosis because it was recognised that service-level interventions are not generally limited to people with a diagnosis of schizophrenia.

1.2 Quality standards

Quality standards are a set of specific, concise quality statements and measures that act as markers of high-quality, cost-effective patient care, covering the treatment and prevention of different diseases and conditions.
For this clinical guideline a NICE quality standard will be produced during the guideline development process, after the development of the clinical guideline recommendations.

This scope defines the areas of care for which specific quality statements and measures will (and will not) be developed.

The guideline and quality standard development processes are described in detail on the NICE website (see section 7).

2 Need for guidance

2.1 Epidemiology

a) Psychosis is a broad category that includes schizophrenia. 'Psychosis' is a major psychiatric disorder (or cluster of disorders) that alters an individual's perception, thoughts, affect and behaviour. The symptoms of psychosis are usually divided into positive symptoms, including hallucinations and delusions, and negative symptoms, such as emotional apathy, lack of drive, poverty of speech, social withdrawal and self-neglect. Nevertheless, people who develop psychosis and schizophrenia will have their own unique combination of symptoms and experiences, the precise pattern of which will be influenced by their own particular circumstances and which may call for flexibility in services' response.

b) The symptoms and experience of psychosis and schizophrenia are often distressing and the effects of the illness are pervasive, with a significant number of people experiencing long-term disability. Psychosis and schizophrenia can have a major detrimental effect on people's personal, social and occupational functioning, placing a heavy burden on individuals and their carers, dependents and extended families, as well as making potentially large demands on the social and healthcare system.

c) A recent systematic review found that in England the pooled incidence of broadly defined psychotic disorder was 31.72 per 100,000 person-years. The pooled estimate of the annual prevalence rate of psychosis was 4.1 per 1000, the same rate as for schizophrenia. It should be noted that in this review there was considerable variation between study estimates.

2.2 Current practice

a) Since the 1950s there have been significant changes in the way psychosis is treated. Following de-institutionalisation service users were often treated in outpatient clinics, however since the 1970s there have been moves towards treatment in home- and community-based settings.

b) Services in England and Wales have a range of teams available for the treatment of people with psychosis and schizophrenia, which may include Assertive Community Treatment teams, early intervention teams, crisis resolution and home treatment teams and community mental health teams. Other service-level interventions include case management, acute day hospitals and crisis houses.

c) Available pharmacological treatments usually have limited effects on cognitive impairments associated with schizophrenia. Cognitive remediation is specifically

focussed on basic cognitive processes such as attention, working memory or executive functioning, and aims to improve performance in these areas in order to improve outcomes for daily living and social or vocational skills. Limited evidence for cognitive remediation has been found although there is additional US-based evidence for combined cognitive remediation and vocational training programmes; however, there is a lack of longer-term follow-up data in this area.

d) The cumulative cost of the care of individuals with psychosis and schizophrenia is high. In 2004/05, the total annual societal cost of schizophrenia in England was £6.7 billion, made up of £2 billion in the direct cost of treatment and an estimated £4.7 billion in indirect costs. The cost of lost productivity owing to unemployment, absence from work and premature death accounted for 72% of the total indirect cost.

e) Two UK studies found that after the first episode of illness, unemployment rates for people with schizophrenia increased from on average 42% to 63%. Other UK studies have found that unemployment rates may be as high as 96% for people with schizophrenia in some areas. Carers also have a very significant burden socially, financially and personally. There are work-related interventions for people with psychosis and schizophrenia, including supported employment, pre-vocational training and other approaches to enhance employment prospects in the longer term.

f) A systematic review of ethnic variations in use of specialist mental health services in the UK found higher rates of inpatient admission among African-Caribbean service users than white service users. In addition, African-Caribbean people on inpatient units were four times more likely to experience a compulsory admission than white people. Variations in gaining access to mental health services may explain some of these differences. Furthermore, other studies suggest that there may be variation in response to treatment among people with psychosis and schizophrenia from different ethnic groups.

g) Some people with schizophrenia and psychosis may have exceptionally difficult lives, facing stigma and with high levels of need for health and social care. The care and treatment of people with schizophrenia has improved since the first NICE guideline was published in 2002; however, the treatments they receive and the fact that they continue to be subject to compulsory admission, at relatively high levels, highlights the stigma and social exclusion they often have to face. The need for a quality standard to enhance the ability of the NHS to meet their needs remains a top priority.

3. Clinical guideline

3.1 Population

3.1.1 Groups that will be covered

a) Adults (18 years and older) who have a clinical working diagnosis of psychosis or schizophrenia, including schizoaffective disorder and delusional disorder, and those

with an established diagnosis of schizophrenia (with onset before age 60) who require treatment beyond age 60.

b) People in early intervention services, which may include people 14 years and older. However, the guideline will not make recommendations about the specific treatment of people under 18 years of age.

3.1.2 Groups that will not be covered

a) Very late onset schizophrenia (onset from age 60 onwards).

b) Children and young people, unless they are being treated in early intervention services. However, the guideline will not address early interventions services in Child and Adolescent Mental Health Services (CAMHS).

c) People diagnosed with bipolar disorder.

d) People with transient psychotic symptoms.

3.2 Healthcare settings

a) NHS-commissioned care that is received from health and social care professionals in community settings.

b) The guideline will also be relevant to the work of, but will not cover the practice of, A&E departments, paramedic services, prison medical services, the police and those who work in the criminal justice and education sectors.

3.3 Clinical management

3.3.1 Key issues that will be covered

a) Low intensity interventions specifically for people with psychosis and schizophrenia, for example, befriending, peer support, exercise and diet, smoking cessation interventions, interventions for anxiety and depression, self-management and hearing voices self-help groups.

b) All the range of teams and service level interventions currently used in the treatment of people with psychosis and schizophrenia, including Assertive Community Treatment teams, early intervention teams, crisis resolution and home treatment teams, community mental health teams, case management, acute day hospitals and crisis houses.

c) Key aspects of teams delivering interventions that are associated with good outcomes.

d) Interventions that improve the ability of people to undertake employment, including supported employment and pre-vocational training.

e) Cognitive remediation, in particular its combination with vocational rehabilitation.

f) The psychological management of previous trauma.

3.3.2 Key issues that will not be covered

a) Psychological (with the exception of cognitive remediation) and pharmacological interventions.

b) Specific interventions that are delivered in primary care services.

c) Rapid tranquillisation.

d) The specific management of affective disorders.

e) The treatment of people with schizophrenia whose illness has not responded adequately to pharmacological or psychological treatment.

f) The management of coexisting learning disabilities, significant physical or sensory difficulties, or substance misuse.

3.4 Main outcomes

a) Relapse rates and days in recovery.

b) Quality of life and functioning.

c) Engagement with services.

d) Symptom measures, including affective outcomes as a result of interventions.

e) Physical health.

f) Experience of care.

g) Experience of carers.

h) Rate of employment/ occupational activity.

i) Accommodation.

3.5 Economic aspects

Developers will take into account both clinical and cost effectiveness when making recommendations involving a choice between alternative interventions. A review of the economic evidence will be conducted and analyses will be carried out as appropriate. The preferred unit of effectiveness is the quality-adjusted life year (QALY), and the costs considered will usually be only from an NHS and personal social services (PSS) perspective. Further detail on the methods can be found in section 8 of 'The guidelines manual'.

4. Quality Standard

Information on the NICE quality standards development process is available on the NICE website, see section 7.

4.1 Areas of care

The areas of care of a patient's pathway used to inform the development of the quality statements are set out in section 4.1.1. The content of the quality standard statements may change during the process and may differ after consultation with stakeholders.

4.1.1 Areas of care that will be considered

a) Service-level interventions.

b) Initiating treatment (first episode).

c) Treating the acute episode.

d) Promoting recovery across all phases.

e) Treatment in primary and secondary care

f) Delivery of services, including the components of effective teams.

4.1.2 Areas of care that will not be considered

a) Primary prevention.

b) Diagnosis of schizophrenia.

c) Schizophrenia in people with moderate to severe learning disabilities, and physical or sensory disabilities.

4.2 Economic aspects

Developers will take into account both clinical and cost effectiveness when prioritising the quality statements to be included in the quality standard. The

economic evidence will be considered, and the cost and commissioning impact of implementing the quality standard will be assessed.

5. Status

5.1 Scope

This is the final version of the scope.

5.2 Timing

The development of the guideline recommendations and the quality standard will begin in February 2012.

6. Related NICE guidance

6.1 NICE that will be incorporated in or updated by the clinical guideline

- Schizophrenia. NICE clinical guideline 82 (2009). Available from

www.nice.org.uk/guidance/CG82

6.2 Related NICE guidance

This guideline will incorporate the following NICE guidance:

Published

- Psychosis with coexisting substance misuse. NICE clinical guideline 120 (2011). Available from: www.nice.org.uk/guidance/CG120
- Medicines adherence. NICE clinical guideline 76 (2009). Available from www.nice.org.uk/guidance/CG76
- Psychosis and schizophrenia in adults final version
- Violence. NICE clinical guideline 25 (2005). Available fromwww.nice.org.uk/guidance/CG25
- Service user experience in adult mental health. NICE clinical guideline 136 (2011). Available from www.nice.org.uk/guidance/CG136

NICE guidance under development

NICE is currently developing the following related guidance (details available from the NICE website):

- Psychosis and Schizophrenia in Children & Young People. NICE clinical guideline. Publication expected January 2013.

7. Further information

Information on the guideline development process is provided in:

- How NICE clinical guidelines are developed: an overview for stakeholders the public and the NHS
- The guidelines manual
- Developing NICE quality standards: interim process guide.

Information on the progress of the guideline and quality standards is also available from the NICE website.

APPENDIX 2: DECLARATIONS OF INTERESTS BY GUIDELINE DEVELOPMENT GROUP MEMBERS

With a range of practical experience relevant to Psychosis & Schizophrenia in Adults in the GDG, members were appointed because of their understanding and expertise in healthcare for people with Psychosis & Schizophrenia in Adults and support for their families and carers, including: scientific issues; health research; the delivery and receipt of healthcare, along with the work of the healthcare industry; and the role of professional organisations and organisations for people with Psychosis & Schizophrenia in Adults and their families and carers.

To minimise and manage any potential conflicts of interest, and to avoid any public concern that commercial or other financial interests have affected the work of the GDG and influenced guidance, members of the GDG must declare as a matter of public record any interests held by themselves or their families which fall under specified categories (see below). These categories include any relationships they have with the healthcare industries, professional organisations and organisations for people with Psychosis & Schizophrenia in Adults and their families/carers.

Individuals invited to join the GDG were asked to declare their interests before being appointed. To allow the management of any potential conflicts of interest that might arise during the development of the guideline, GDG members were also asked to declare their interests at each GDG meeting throughout the guideline development process. The interests of all the members of the GDG are listed below, including interests declared prior to appointment and during the guideline development process.

Categories of interest to be written in third person

Paid employment

Personal pecuniary interest: financial payments or other benefits from either the manufacturer or the owner of the product or service under consideration in this guideline, or the industry or sector from which the product or service comes. This includes holding a directorship or other paid position; carrying out consultancy or fee paid work; having shareholdings or other beneficial interests; receiving expenses and hospitality over and above what would be reasonably expected to attend meetings and conferences.

Personal family interest: financial payments or other benefits from the healthcare industry that were received by a member of your family.

Non-personal pecuniary interest: financial payments or other benefits received by the GDG member's organisation or department, but where the GDG member has not personally received payment, including fellowships and other support provided by the healthcare industry. This includes a grant or fellowship or other payment to

sponsor a post, or contribute to the running costs of the department; commissioning of research or other work; contracts with, or grants from, NICE.

Personal non-pecuniary interest: these include, but are not limited to, clear opinions or public statements you have made about Psychosis & Schizophrenia in Adults, holding office in a professional organisation or advocacy group with a direct interest in Psychosis & Schizophrenia in Adults, other reputational risks relevant to Psychosis & Schizophrenia in Adults.

Declarations of interest	
Professor Elizabeth Kuipers- Chair, Guideline Development Group	
Employment	Professor of Clinical Psychology, Institute of Psychiatry, King's College London.
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	From July 2007 – mid 2012 Elizabeth was a Patron of Making Space who provides family/carer support, residential care home provision, supported housing, day & employment services and clinical provision via their independent hospital and volunteer aided CBT provision. Elizabeth also helped re-launch the mentalhealthcare.org.uk website which is publically funded
Actions taken	
Prof Max Birchwood	
Employment	Professor of Clinical Psychology and Youth Mental Health, School of Psychology,University of Birmingham; Clinical Director: Birmingham Youth Mental Health Services, Birmingham and Solihull Mental Health Foundation Trust; Director of R&D, Birmingham and Solihull Mental Health Foundation Trust
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Actions taken	None
Dr Alison Brabban	

Employment	Consultant Clinical Psychologist, Tees, Esk & Wear Valleys NHS Foundation Trust; Honorary Senior Clinical Lecturer. Durham University; National Advisor for Severe Mental Illness (IAPT); Department of Health
Personal pecuniary interest	Alison has been involved in randomised control trials for CBT and has taught in New York- Bellevue. National Advisor of Bipolar...etc
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Actions taken	None
Ms Debbie Green	
Employment	Directorate Lead for Occupational Therapy and Social Inclusion, Adult Mental Health, Oxleas NHS Foundation Trust, London
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	Debbie has a personal interest in assertive outreach programmes. Attending and contributing to the NHS Confederation and ImROC briefing paper on peer support workers.
Actions taken	None
Dr Zaffer Iqbal	
Employment	Head of Psychology and Consultant Clinical Psychologist, Navigo NHS Health & Social Care CiC
Personal pecuniary interest	Zaffer has links with medical suicidedology which gets funding from a pharmaceutical company.
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	Zaffer, publically advocates particular models of suicidology. Undertakes clinical teaching which may be paid by a trust of pharma- but not currently receiving money
Actions taken	
Prof Sonia Johnson	
Employment	Professor of Social and Community Psychiatry, Mental Health Sciences, University College London; Consultant Psychiatrist, Camden and Islington Early Intervention Service, Camden and Islington NHS Foundation Trust
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Actions taken	None
Mr Tom Lochhead	

Employment	Mental Health Lead Professional for Social Work in Bath & North East Somerset
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Actions taken	None
Prof Max Marshall	
Employment	Professor of Community Psychiatry, University of Manchester. Honorary Consultant, Lancashire Care NHS Trust; Medical Director Lancashire Care NHS Trust; Deputy Director/Associate Director Mental Health Research Network England
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	Max is the medical director of Lancashire Care NHS Foundation Trust, which provides mental health services in Lancashire. A Professor of Psychiatry at the University of Manchester, and an executive director of the Mental Health Research Network. Max currently holds a programme grant on early psychosis from the NIHR and is a co-applicant on several other NIHR grants in the area of psychosis.
Personal non-pecuniary interest	Max is an author of a number of Cochrane reviews, including reviews of care management and interventions for early psychosis. He has generally been supportive of introducing new services for people with psychosis including early intervention teams, crisis teams and assertive community treatment; although he believes that this support has been tempered by a rational evaluation of the evidence base.
Actions taken	None
Dr Jonathan Mitchell	
Employment	Consultant Psychiatrist, Sheffield Health and Social Care NHS Foundation Trust
Personal pecuniary interest	Is working on a HTA examining non-pharmacological ways to prevent weight gain for people with Schizophrenia.
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Actions taken	None
Prof Tony Morrison	
Employment	Professor of Clinical Psychology, Division of Psychology, University of Manchester
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Actions taken	None
Dr David Shiers	

Employment	GP Advisor to the National Audit of Schizophrenia (the Royal College of Psychiatrists), London; Rethink Mental Illness Trustee (2010-2012)
Personal pecuniary interest	Received a lecture fee of £450 for presenting to a specialist mental health audience in Southampton, organised and paid for by Janssen-Cilag on September 22nd 2010. Title of keynote presentation was "Early intervention in psychosis – looking after the body as well as the mind." (declared December 2010) Joint editor of '**Promoting Recovery in Early Psychosis**' Wiley-Blackwell ISBN978-1-4051-4894-8. Published 2010 (Royalties received [for first time] £169.14 on March 23rd 2012) Nov 27- Dec 2nd 2011 Tokyo: Attended the Japanese DIET inaugural meeting of the all-party parliamentary group on mental illness providing keynote presentation on UK Early Intervention service reforms; followed by my presenting similar keynote at a two day National Japanese Society for prevention and early intervention in psychosis; fee £1893.81 Dec 13th 2011; Consultancy on early intervention in psychosis provided to Second Step Trust Bristol (voluntary sector); fee £412 Nov 11th 2012; Bolton AqUA group of Salford Royal NHS Foundation Trust: Presentation on early intervention in physical health of people with psychosis; fee £500 February 18th 2013: Fee for NSW Health presentation (Sydney) £407.07 March 13th 2013: Fee AqUA group of Salford Royal NHS Foundation Trust: Presentation on early intervention in physical health of people with psychosis; fee £500 March 23rd 2013: Fee for presentation at EPION network of Ontario – Toronto £947.05
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	Co-author of **Tobacco Use Before, At, and After First-Episode Psychosis: A Systematic Meta-Analysis**. (declared May 2011 –*Myles, N., Newall, H, Curtis, J., Olav Nielssen, O., PhD, David Shiers, D., Large,* M. accepted for publication by J Clin Psychiatry) Co-authoring an early intervention in psychosis guidelines produced by IRIS Initative Ltd (a social enterprise) Co-author **Efficacy of metformin for prevention of weight gain in psychiatric populations: a review** Hannah Newall, Nicholas Mylesa, Philip B. Ward,

	Katherine Samaras, David Shiers and Jackie Curtis International Journal of Clinical Psychopharmacology 27(2):69-75 DOI: 10.1097/YIC.0b013e32834d0a5b Co-authoring with Tony Morrison and others an editorial regarding antipsychotics and patient choice (submitted to The British Journal of Psychiatry in March 2012) A collaboration with Tim Kendall and others on a study of Health Economic model on the key drivers for physical ill health for LSE and the Institute of Psychiatry 5th Sept 2012 and ongoing; funded by Southampton University to attend Diabetes Research Network/Mental Health Research Network writing group. March 2013: Approval for HTA grant number 12/28 examining non-pharmacological ways to prevent weight gain for people with Schizophrenia –lead PI = Prof Richard Holt May 24th 2013: Travel and accommodation to present at Australian Ministerial Summit on Physical / Mental Health Co-author on an international consensus statement of the importance of intervening early to prevent future CVD, obesity and diabetes. Entitled HeAL (Healthy Active Lives), this was launched at RC Psych event led by Sue Bailey on 19 June 2013.
Actions taken	None
Dr Clive Travis	

Employment	SUC
Personal pecuniary interest	Public governor SEPT. About to undertake paid work for SEPT. Due to publish an autobiographical novel about his journey through paranoid schizophrenia. It is entitled *Looking for Prince Charles's Dog*. Due to the title and the story line all of the royalties are going to charities as follows: The Prince of Wales International Centre for SANE Research The Prince's Trust The Diana Princess of Wales Memorial Fund Catholic Aid Overseas Development (CAFOD) The Salvation Army Build Africa UNICEF Medecins Sans Frontieres Comic Relief The Speedwell Trust The Dog's Trust Look- Charity for Blind and Partially Sighted Children
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	Has a website www.paranoidschizophrenia.co.uk Clive believes that in some suicides of psychiatric patients, side effects of prescribed medication are a factor.
Actions taken	None
Ms Rachel Waddingham	
Employment	Service User Representative; London Hearing Voices Project Manager
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	Rachel is a trustee of the national Hearing Voices Network. And is an employee of MIND in Camden, a local MIND Organisation.
Personal non-pecuniary interest	Has spoken in public about her reservations about the scientific validity of the diagnosis of schizophrenia. Rachel has also spoken about the need for more alternatives to medication, and the need to provide better support and advice for those choosing to withdraw from medication. However, she has no clear views with respect to the guidance update and is open to reviewing the evidence gathered.
Actions taken	None
Mr Peter Woodhams	

Employment	SUC
Personal pecuniary interest	Peter has a contract as a self employed Carer Consultant with the Meriden Family Programme within Birmingham and Solihull Mental Health Foundation Trust and so he has an interest in Family Interventions
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Actions taken	None
Mr Norman Young	
Employment	Nurse Consultant, Cardiff and Vale UHB & Cardiff University
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Actions taken	None

NCCMH staff

Tim Kendall – Facilitator, Guideline Development Group	
Employment	Director, NCCMH
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	Tim is a co-applicant for a £1.7-2 million NIHR HTA grant for a multicentre, randomised controlled trial of a diabetes intervention to induce weight loss (DESMOND) for people who are overweight and have a SMI, including people with schizophrenia and bipolar disorder.
Personal non-pecuniary interest	None
Actions taken	None
Nadir Cheema	
Employment	Health Economist (until November 2012)
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Actions taken	None
Bronwyn Harrison	
Employment	Research Assistant
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Actions taken	None
Evan Mayo-Wilson	

Employment	Senior Systematic Reviewer (until March 2012)
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Actions taken	None
Maryla Moulin	
Employment	Project Manager
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Actions taken	None
Eric Slade	
Employment	Health Economist (from January 2013)
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Actions taken	None
Sarah Stockton	
Employment	Senior Information Scientist
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Actions taken	None
Clare Taylor	
Employment	Senior Editor
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Actions taken	None
Amina Yesufu -Udechuku	
Employment	Systematic Reviewer (from March 2012)
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Actions taken	None

APPENDIX 3: SPECIAL ADVISORS TO THE GUIDELINE DEVELOPMENT GROUP

To be completed after stakeholder consultation

Table caption

Table title	Table text

Table title	Table text
Table title	Table text
Table title	Table text

APPENDIX 4: STAKEHOLDERS WHO RESPONDED TO EARLY REQUESTS FOR EVIDENCE

To be completed after stakeholder consultation

APPENDIX 5: RESEARCHERS CONTACTED TO REQUEST INFORMATION ABOUT UNPUBLISHED OR SOON-TO-BE PUBLISHED STUDIES

Dr Maryanne O'Donnell
Dr David Griffiths
Dr A. J. Marx
Dr Alex Kopelowicz
Dr Ali Gholipour
Dr Anna Aberg
Dr B. N. Gangadhar
Dr Benjamin Druss
Dr Bente Berget
Dr Bernard Audini
Dr Bush
Dr Cathaleene Macias
Dr Chandler
Dr Cheng Y. Chu
Dr Cheryl Forchuk
Dr Christine McKibbin
Dr David L. Penn
Dr David Salkever
Dr David Sells
Dr David Shern
Dr Deborah Perlick
Dr E. Sally Rogers
Dr Eileen Edmundson
Dr Elizabeth McCay
Dr Elizabeth Visceglia
Dr Elizabeth W. Twamley
Dr Eóin Killackey
Dr Eric Latimer
Dr F. Holloway
Dr Farkhondeh Sharif
Dr Fiona Lobban
Dr Frank-Gerald Pajonk
Dr Gail Daumit
Dr Gary Bond
Dr Gary Gerber
Dr Gary R Bond
Dr Gary S. Skrinar
Dr George H. Wolkon
Dr George Szmukler
Dr Gerard Leavey

Dr Gregory Clarke
Dr Gutierrez-Maldonado
Dr Hanneke van Gestel-Timmermans
Dr Heidi Herinckx
Dr Helen Killaspy
Dr Holger Hoffmann
Dr Ilanit Hasson-Ohayon
Dr Ingrid Doherty
Dr Jack Franklin
Dr Jagadisha Thirthalli
Dr James L. Curtis
Dr James Rivera
Dr Jaspreet Brar
Dr Jeanette Jerrell
Dr Jean-Pierre Lindenmayer.
Dr Jerry Dincin
Dr Jing-Ping Zhao
Dr John Gleeson
Dr John H Beard
Dr John M. Kuldau
Dr Jonathan Cole
Dr Judith A. Cook
Dr Jun Soo Kwon
Dr Junichiro Ito
Dr Kenny Kin Wong
Dr Khodabakhshi
Dr Kim T. Mueser
Dr Kimberly Littrell
Dr Kuei-Ru Chou
Dr Kyung Hee Shon
Dr L. Blankertz
Dr Larry Davidson
Dr Linda Chafetz
Dr Lora Humphrey Beebe
Dr Louis John Cozolino
Dr M. Kline
Dr Mario Alvarez-Jimenez
Dr Mark S. Bauer
Dr Mark Salzer
Dr Mary Ann Test
Dr Mary T. Weber
Dr Matthew Muijen
Dr Mauro Mauri
Dr Merete Nordentoft
Dr Michelle Salyers
Dr Morris Bell

Dr O'Callaghan
Dr Orhan Doğan
Dr Paolo Scocco
Dr Paul B. Gold
Dr Paul Lysaker
Dr Peter J.Tyrer
Dr Phil Harrison-Read
Dr Phyllis Solomon
Dr Puihan Joyce Chao
Dr R Becker
Dr Richard Cerniglia
Dr Richard Ford
Dr Richard Gater
Dr Robert E. Drake
Dr Robert Gervey
Dr Robert J. Calsyn
Dr Robert Liberman
Dr Robert Quinlivan
Dr Robert Rosenheck
Dr Robert Walker
Dr Roland Vauth
Dr Rolf W. Grawe
Dr S. Merson
Dr Samuel Okpaku
Dr Sherryn Evans
Dr Shin-Da Lee
Dr Sjoerd Sytema
Dr Stephen R. Marder
Dr Susan Essock
Dr Susan Johnston
Dr Susan R. McGurk
Dr Suzanne Archie
Dr Tania Lecomte
Dr Tanya Park
Dr Terence Mccann
Dr Thad Eckman
Dr Thomas L. Patterson
Dr Tommy Bjorkman
Dr Tricia Nagel
Dr Ulla A. Botha
Dr Varambally
Dr Victoria Villalta-Gil
Dr Wagner Farid Gattaz
Dr Werner Muller-Clemm
Dr William Hurt Sledge
Dr William R. McFarlane

Dr Wolff
Dr Yu-Tao Xiang
Mr Sunny Ho-Wan Chan
Mr Aaron Levitt
Mr Nobuo Anzai
Mr Rickard Färdig
Mr Kamran Gholinia
Ms Stynke Castelein
Ms Betty Vreeland
Ms Skye Barbic
Ms Lisa Guzik
Ms Shelagh McDougall
Ms Susan Marzolini
Professor Tom Craig
Prof. Hector Tsang
Profesor Eduard Vieta
Professor Anthony F Lehman
Professor Elizabeth Kuipers
Professor Louise M Howard
Professor Max Marshall
Professor Peter J Tyrer
Professor Steven P. Segal.
Professor Tom Burns
Professor W.T. Chien
Thomas W. Pelham

APPENDIX 6: REVIEW QUESTIONS AND PROTOCOLS

1. Carer experience of care

Review question(s)	1a. What factors improve or diminish the experience of health and social services for carers of people with severe mental illness? 1b. What modification to health and social services improve the experience of using services for carers of adults with severe mental illness?
Sub-question(s)	-
Chapter	Chapter 4
Objectives	To identify factors that improve or diminish carers' experiences of health and social services. To evaluate the effectiveness of interventions for improving the experience of health and social services for carers of people with severe mental illness
Criteria for considering studies for the review	
• **Population**	Carers of any age who care for adults (18 years of age and over) with severe mental illness who use health and social services in community settings ***Included*** Carers of adults (18+) and people in early intervention services (which may include people 14 years and older) with schizophrenia (including schizoaffective disorder and delusional disorder) or psychosis. *Include papers with a service user population of **AT LEAST**:* 66% Schizophrenia or 66% (Schizophrenia + Bipolar disorder) or 66% (Schizophrenia + "Mood disorders") or 66% Undefined severe mental illness 66% Bipolar disorder

	Excluded Carers of adults (18+) with very late onset schizophrenia (onset from age 60 onwards) Carers of children and young people (unless they are being treated in early intervention services, as above) Carers of people with transient psychotic symptoms
• **Intervention**	**Review question 1a** Actions by health and social services that could improve or diminish the carer experience of health and social services for example:- • Form, frequency, and content of interactions with carers • Organisation of services and interactions with carers • Sharing information with carers and receiving information from carers **Review question 1b** **Included interventions** Only interventions delivered directly to carers of people with severe mental illness will be included. These may include, for example: • Specific interventions for carers • Peer-led interventions for carers (e.g. carer support groups) • Changes in the delivery and organisation of services for the benefit of carers **Excluded interventions** This review will not evaluate any interventions delivered directly to people receiving care targeted at the person receiving care, which are included elsewhere in the guideline. This review will not evaluate any interventions that are not provided by health and social care services. In addition, it will not include interventions which aim to improve service user therapeutic outcomes as this are included elsewhere in the guideline. Psychosocial and pharmacological interventions for carers with specific mental health problems will not be included as they are addressed in other guidelines. The provision of financial and practical support (for example personal assistance or direct payments) are outside of the scope of this guideline and will not be included.
• **Comparison**	Existing services and alternative strategies
Critical Outcomes	**Review question 1a** Themes and specific issues that caregivers identify as improving or diminishing their experience of health and social care

	Review question 1b Carers':- • Quality of Life • Mental health (anxiety or depression) • Burden of care (including burnout, stress, and coping) • Carer satisfaction with services (validated measures only, specific items will not be analysed)
Important, but not critical, outcomes	• **Drop-out (any reason)**
• Study design	**Review question 1a** • Metasynthesis of focus groups including people who care for persons with severe mental illness • Qualitative primary studies (focus group and case series) including people who care for persons with severe mental illness **Review question 1b** • Systematic reviews of RCTs • Primary RCTs
• Include unpublished data?	Yes but only where: • the evidence was accompanied by a study report containing sufficient detail to properly assess the quality of the data • the evidence was submitted with the understanding that data from the study and a summary of the study's characteristics will be published in the full guideline. Therefore, the GDG should not accept evidence submitted as commercial in confidence. However, the GDG should recognise that unpublished evidence submitted by investigators, might later be retracted by those investigators if the inclusion of such data would jeopardise publication of their research.
• Restriction by date	**Review question 1a** 2002 – to present The GDG decided that knowledge, understanding and experience of health and social care prior to this dates would not be relevant to present day services. **Review question 1b** 1950– (systematic review: 1995 to June 2013; RCT: 1950 to June 2013) The GDG decided that interventions and services in health and social care prior to this date would not be relevant to present day services.
• Minimum sample size	N/A

• Study setting	Health and social care in community settings excluding A&E, paramedic services, medicals services, the police and those who work for the criminal justice system.
Databases searched	Core: CDSR, CENTRAL, DARE, Embase, HTA, MEDLINE, PreMedline Topic specific: AEI, ASSIA, BEI, CINAHL, ERIC, IBSS, PsycINFO, Sociological Abstracts, Social Services Abstracts
Other resources searched	
Search filters used	**Review question 1a** Qualitative systematic review, qualitative primary studies **Review question 1b** Quantitative systematic review, RCT
The review strategy	**Review question 1a** Thematic synthesis of qualitative studies and sub-analyses of those caring for people with schizophrenia compared with other severe mental illnesses. We will use a modified matrix of service user experience to organise themes. **Review question 1b** **If reviews are found, the GDG will assess their quality, completeness, and applicability to the NHS and to the scope of the guideline. If the GDG identify a systematic review appropriate to the review question, we will search for RCTs conducted or published since the review was conducted, and the GDG will assess if any additional studies could affect the conclusions of the previous review. If new studies could change the conclusions, we will update the review and conduct a new analysis. If new studies could not change the conclusions of an existing review, the GDG will use the existing review to inform their recommendations.** In no reviews are found, we plan to compare all eligible interventions using pairwise meta-analyses. Data will be included in analyses if >66% of the sample have a primary diagnosis of schizophrenia, psychosis, or bipolar disorder. If data are available, sub-analyses will be conducted of studies with >75% of the sample described as having a primary diagnosis of schizophrenia.

2. Preventing psychosis

Review question(s)	**RQ B1** For people who are at risk of developing psychosis[1] and schizophrenia (at risk mental state), does the provision of pharmacological and/or psychological or psychosocial interventions improve outcomes?

Sub-question(s)	**RQ A1** What are the specific behaviours and symptoms that are associated with an increased risk of developing psychosis[1] and schizophrenia (at risk mental state): What is the course of these behaviours and symptoms? What are the specific behaviours and symptoms that prompt initial recognition of psychoses[1] or prompt diagnosis of schizophrenia?
Chapter	Chapter 5
Objectives	To provide evidence based recommendations, via GDG-consensus, regarding early recognition and management of at risk mental states and early psychosis before a formal diagnosis of psychosis and schizophrenia has been made.
Criteria for considering studies for the review	
Population	**Inclusion:** People who are considered to be 'at risk' of developing psychosis and more specifically schizophrenia. Consideration will be given to individuals with mild learning disability; and those from black and minority ethnic groups. **Exclusion:** Study samples consisting only of individuals with a formal diagnosis of Bipolar Disorder.
Intervention	For RCTs or systematic reviews of RCTs, pharmacological and psychological interventions will be considered. *Pharmacological interventions include:* all antipsychotic medication licensed in the UK for the treatment of people with psychosis or schizophrenia. Off label use may be considered if clearly supported by evidence (e.g. those licensed only for adults with psychosis and schizophrenia). Note that guideline recommendations will not normally fall outside licensed indications. Exceptionally, and only if clearly supported by evidence, use outside a licensed indication may be recommended. Licensed antipsychotics include: • Amisulpride • Aripiprazole • Benperidol • Chlorpromazine hydrochloride • Clozapine • Flupentixol • Haloperidol

	• Levomepromazine • Pericyazine • Paliperidone • Pimozide • Prochlorperazine • Promazine hydrochloride • Olanzapine • Quetiapine • Risperidone • Sulpiride • Trifluoperazine • Zuclopenthixol • Zuclopenthixol acetate *Psychological interventions include:* • Cognitive Behavioural Therapy • Cognitive Remediation • Counselling and Supportive Psychotherapy • Family Interventions (including family therapy) • Psychodynamic Psychotherapy and Psychoanalysis • Psychoeducation • Social Skills TrainingArt Therapies *Dietary interventions, including:* • Any dietary/nutritional supplements
Comparison	Alternative management strategies
Critical outcomes	Transition to psychosis Time to transition to psychosis

Important but not critical outcomes	• Mental state (symptoms, depression, anxiety, mania) • Mortality (including suicide) • Global state • Psychosocial functioning • Social functioning • Leaving the study early for any reason • Adverse events (including effects on metabolism; extrapyramidal side effects; hormonal changes; and , cardiotoxicity)
Study design	• Systematic reviews of RCTs • Primary RCTs
Include unpublished data?	Yes (if criteria met). The GDG will use a number of criteria when deciding whether or not to accept unpublished data. First, the evidence must be accompanied by a trial report containing sufficient detail to properly assess the quality of the data. Second, the evidence must be submitted with the understanding that data from the study and a summary of the study's characteristics will be published in the full guideline. Therefore, the GDG will not accept evidence submitted as commercial in confidence. However, the GDG recognises that unpublished evidence submitted by investigators, might later be retracted by those investigators if the inclusion of such data would jeopardise publication of their research.
Restriction by date?	Systematic review: 1995 to May 2012 RCT: inception of databases to May 2012
Minimum sample size	RCTs: >10 per arm. Exclude studies with > 50% attrition from either arm of trial (unless adequate statistical methodology has been applied to account for missing data)
Study setting	Any
Databases searched	Core: CDSR, DARE, CENTRAL, Embase, HTA, MEDLINE, PreMedline Topic specific: CINAHL, PsycINFO
Other resources searched	Hand-reference searching of reference lists of included studies. GDG members will be asked to confirm that the list of included studies includes key papers. Drug companies will be requested to provide relevant published and unpublished data.
Search filter used	Quantitative SR, RCT
The review strategy	If reviews are found, the GDG will assess their quality, completeness, and applicability to the NHS and to the scope of the guideline. If the GDG identify a systematic review appropriate to the review question, we will search for RCTs conducted or published since the review was conducted, and the GDG will assess if any additional studies could affect the conclusions of the previous review. If new studies could change the conclusions, we will update the review and conduct a new analysis. If new studies could not change the conclusions of an existing review, the GDG will use the existing review to inform their recommendations.

	In no reviews are found, we plan to compare all eligible interventions using pairwise meta-analyses.

3. Peer Provided Interventions

Review question(s)	For adults with psychosis and schizophrenia, what are the benefits and/or potential harms of peer-provided interventions compared to treatment as usual or other intervention?
Sub-question(s)	• Mutual Support • Peer Support • Peer Mental Health Service Providers
Chapter	Chapter 8
Objectives	To evaluate the clinical effectiveness of peer provided interventions in the treatment of psychosis and schizophrenia .
Criteria for considering studies for the review	
• **Population**	***Included*** Adults (18+) with schizophrenia (including schizophrenia-related disorders such as schizoaffective disorder and delusional disorder) or psychosis. *Include papers with at least:* 66% Schizophrenia or 66% (Schizophrenia + Bipolar disorder) or 66% (Schizophrenia + "Mood disorders") or 66% Undefined severe mental illness ***Excluded*** Papers with >66% bipolar sample diagnosis Papers with >66% bipolar + mood disorder diagnosis Interventions *specifically* for people with bipolar disorder Very late onset schizophrenia (onset from age 60 onwards) Children and young people (unless they are being treated in early intervention services)

	People with transient psychotic symptoms
• **Intervention**	Peer-provided interventions
• **Comparison**	Any alternative management strategy

Critical Outcomes	• Empowerment/ Recovery
	• Functional disability
	• Quality of life
	• Service use
	  o GP visits
	  o A&E visits
	  o Hospitalisation (admissions, days)
	• User satisfaction (validated measures only)

Important but not critical outcomes	• Response / Relapse
	  o Relapse (as defined in study)
	  o Response (improvement in symptoms)
	• Symptoms of psychosis
	  o Total symptoms
	  o Positive symptoms
	  o Negative symptoms
	• Duration of untreated psychosis
	• Employment and Education
	  o Competitive employment
	  o Occupation (any)
	  o Attendance at school/college
	• Accommodation
	  o Homelessness
	  o Stable accommodation
	• Anxiety or Depression
	• Leaving study early
	• Adverse effects
	  o Suicide
	  o Mortality, all cause
	  o Self-harm
	  o Violent acts

	• Carer-focused outcomes
	  o Quality of life
	  o Depression
	  o Burden of care (validated measures only)
	  o Employment/ Income

• Study design	• Systematic reviews of RCTs • Primary RCTs
• Include unpublished data?	Yes but only where: • the evidence was accompanied by a study report containing sufficient detail to properly assess the quality of the data • the evidence was submitted with the understanding that data from the study and a summary of the study's characteristics will be published in the full guideline. Therefore, the GDG should not accept evidence submitted as commercial in confidence. However, the GDG should recognise that unpublished evidence submitted by investigators, might later be retracted by those investigators if the inclusion of such data would jeopardise publication of their research.
• Restriction by date	RCT: database inception to June 2013 Systematic review: 1995 to June 2013
• Minimum sample size	RCT N=10 per arm (ITT) Exclude studies with > 50% attrition from either arm of study (unless adequate statistical methodology has been applied to account for missing data).
• Study setting	Primary, secondary and tertiary healthcare services that are relevant to the NHS. The guideline will also be relevant to, but not cover the practice of, A&E departments, paramedic services, prison medical services, the police and those who work in the criminal justice system.
Databases searched	Core: CDSR, CENTRAL, DARE, Embase, HTA, MEDLINE, PreMedline Topic specific: CINAHL, PsycINFO
Other resources searched	Hand-reference searching of retrieved literature
Search filters used	Quantitative SR, RCT
The review strategy	**If reviews are found, the GDG will assess their quality, completeness, and applicability to the NHS and to the scope of the guideline. If the GDG identify a systematic review appropriate to the review question, we will search for RCTs conducted or published since the review was conducted, and the GDG will assess if any additional studies could affect the conclusions of the previous review. If new studies could change the conclusions, we will update the review and conduct a new analysis. If new studies could not change the conclusions of an existing review, the GDG will use the existing review to inform their recommendations.**

	In no reviews are found, we plan to compare all eligible interventions using pairwise meta-analyses. Data will be included in analyses if >66% of the sample have a primary diagnosis as defined in the protocol above. If data are available, sub-analyses will be conducted of studies with >75% of the sample described as having a primary diagnosis of schizophrenia/ schizoaffective disorder or psychosis. If data are available, sub-analyses will be conducted for UK/Europe studies.

4. Self-Management

Review question(s)	For adults with psychosis and schizophrenia, what are the benefits and/or potential harms of self-management interventions compared to treatment as usual or other intervention?
Chapter	Chapter 8
Objectives	To evaluate the clinical effectiveness of self-management interventions in the treatment of psychosis and schizophrenia.
Criteria for considering studies for the review	
• **Population**	***Included*** Adults (18+) with schizophrenia (including schizophrenia-related disorders such as schizoaffective disorder and delusional disorder) or psychosis. *Include papers with at least:* 66% Schizophrenia or 66% (Schizophrenia + Bipolar disorder) or 66% (Schizophrenia + "Mood disorders") or 66% Undefined severe mental illness Those with an established diagnosis of schizophrenia (with onset before age 60) who require treatment beyond age 60. People in early intervention services, which may include people 14 years and older. However, the guideline will not make

	recommendations about the specific treatment of people under 18 years of age. ***Excluded*** Papers with >66% bipolar sample diagnosis Papers with >66% bipolar + mood disorder diagnosis Interventions *specifically* for people with bipolar disorder Very late onset schizophrenia (onset from age 60 onwards) Children and young people (unless they are being treated in early intervention services) People with transient psychotic symptoms
• **Intervention**	Self-management interventions
• **Comparison**	Any alternative management strategy

Critical Outcomes	• Empowerment/ Recovery
	• Functional disability
	• Hospitalisation (admissions, days)
	• Contact with secondary services
	• Quality of life
	• Symptoms of psychosis
	  o Total symptoms
	  o Positive symptoms
	  o Negative symptoms

Important but not critical outcomes	• Employment and Education
	  o Competitive employment
	  o Occupation (any)
	  o Attendance at school/college
	• Accommodation
	  o Homelessness
	  o Stable accommodation
	• Anxiety or Depression
	• Leaving study early
	• Adverse effects
	  o Suicide
	  o Mortality, all cause
	  o Self-harm

	○ Violent acts • User satisfaction (validated measures only) • Carer-focused outcomes ○ Quality of life ○ Depression ○ Burden of care (validated measures only) ○ Employment/ Income
• Study design	• Systematic reviews of RCTs • Primary RCTs
• Include unpublished data?	Yes but only where: • the evidence was accompanied by a study report containing sufficient detail to properly assess the quality of the data • the evidence was submitted with the understanding that data from the study and a summary of the study's characteristics will be published in the full guideline. Therefore, the GDG should not accept evidence submitted as commercial in confidence. However, the GDG should recognise that unpublished evidence submitted by investigators, might later be retracted by those investigators if the inclusion of such data would jeopardise publication of their research.
• Restriction by date	RCT: database inception to June 2013 Systematic review: 1995 to June 2013
• Minimum sample size	RCT N=10 per arm (ITT) Exclude studies with > 50% attrition from either arm of study (unless adequate statistical methodology has been applied to account for missing data).
• Study setting	Primary, secondary and tertiary healthcare services that are relevant to the NHS. The guideline will also be relevant to, but not cover the practice of, A&E departments, paramedic services, prison medical services, the police and those who work in the criminal justice system.
Databases searched	Core: CDSR, CENTRAL, DARE, Embase, HTA, MEDLINE, PreMedline Topic specific: CINAHL, PsycINFO
Other resources searched	Hand-reference searching of retrieved literature
Search filter used	Quantitative SR, RCT
The review strategy	**If reviews are found, the GDG will assess their quality, completeness, and applicability to the NHS and to the scope of the guideline. If the GDG identify a systematic review appropriate to the review question, we will search for RCTs conducted or published since the review was conducted, and the GDG will assess if any additional studies could affect the conclusions of the previous review. If new studies could change the conclusions, we will update the review and conduct a new analysis. If**

	new studies could not change the conclusions of an existing review, the GDG will use the existing review to inform their recommendations. In no reviews are found, we plan to compare all eligible interventions using pairwise meta-analyses. Data will be included in analyses if >66% of the sample have a primary diagnosis as defined in the protocol above. If data are available, sub-analyses will be conducted of studies with >75% of the sample described as having a primary diagnosis of schizophrenia/ schizoaffective disorder or psychosis. If data are available, sub-analyses will be conducted for UK/Europe studies.

5. Interventions for Promoting Physical Health in Adults

Review question(s)	For adults with psychosis and schizophrenia, what are the benefits and/or potential harms of behavioural interventions to promote physical activity (all forms, with or without healthy eating)? For adults with psychosis and schizophrenia, what are the benefits and/or potential harms of behavioural intervention to improve healthy eating? For adults with psychosis and schizophrenia, what are the benefits and/or potential harms of pharmacological interventions for smoking cessation and reduction?
Chapter	Chapter 7
Objectives	To evaluate the clinical effectiveness of interventions to improve the health of people with psychosis and schizophrenia
Criteria for considering studies for the review	
Population	*Included* Adults (18+) with schizophrenia (including schizophrenia-related disorders such as schizoaffective disorder and delusional disorder) or psychosis *Include papers with a service user population of AT LEAST:* 66% Schizophrenia or 66% (Schizophrenia + Bipolar disorder) or 66% (Schizophrenia + "Mood disorders") or 66% Undefined severe mental illness

	Excluded Papers with >66% bipolar sample diagnosis Papers with >66% bipolar + mood disorder diagnosis Interventions *specifically* for people with bipolar disorder Very late onset schizophrenia (onset from age 60 onwards) Children and young people (unless they are being treated in early intervention services) People with transient psychotic symptoms
Intervention	& 1.2 Behavioural interventions to promote physical activity and healthy eating Pharmacological interventions for smoking reduction or cessation <u>Included interventions</u> Only pharmacologcial inteventions which aim for smoking reduction or cessation will be evaluated. These include:- • Bupropion • Transdermal Nicotine Patch (TNP) <u>Excluded interventions</u> This review will not evaluate:- • Pharmacological interventions that are contraindicated for people with psychiatric disorders (e.g. Varenicline) • Interventions which report smoking outcomes but the primary aim is not smoking reduction or cessation • Non-pharmacological interventions as they are already addressed in other guidelines • Combined non-pharmacological and pharmacological interventions
Comparison	Any alternative management strategy
Critical outcomes	Behavioural interventions to promote physical activity and healthy eating Physical health • BMI/ weight • Levels of physical activity • Service use • Primary care engagement (e.g. GP visits) • Quality of life • User satisfaction (validated measures only) Smoking cessation interventions • Anxiety and depression • Physical health • Smoking (cessation or reduction)

	• Weight / BMI • Quality of life • User satisfaction (validated measures only)

Important but not critical outcomes	• Response / Relapse
	  o Relapse (as defined in study)
	  o Response (improvement in symptoms)
	• Symptoms of psychosis
	  o Total symptoms
	  o Positive symptoms
	  o Negative symptoms
	  o Duration of untreated psychosis
	• Service use
	  o Hospitalisation (admissions, days)
	  o A&E visits
	• Functional disability
	• Anxiety or Depression
	• Leaving study early
	• Adverse effects
	  o Suicide
	  o Mortality, all cause
	  o Self-harm
	  o Violent acts
	• Carer-focused outcomes
	  o Quality of life
	  o Depression
	  o Burden of care (validated measures only)
	  o Employment/ Income

Study design	Systematic reviews of RCTs Primary RCTs
Include unpublished data?	Yes but only where: the evidence was accompanied by a study report containing sufficient detail to properly assess the quality of the data the evidence was submitted with the understanding that data from the study and a summary of the study's characteristics will be published in the full guideline. Therefore, the GDG should not accept evidence submitted as commercial in confidence. However, the GDG should recognise that unpublished evidence submitted by investigators, might later be retracted by those investigators if the inclusion of such data would jeopardise publication of their research.

Restriction by date?	RCT: database inception to June 2013 Systematic review: 1995 to June 2013
Minimum sample size	RCT N=10 per arm (ITT) Exclude studies with > 50% attrition from either arm of study (unless adequate statistical methodology has been applied to account for missing data).
Study setting	Primary, secondary and tertiary healthcare services that are relevant to the NHS. The guideline will also be relevant to, but not cover the practice of, A&E departments, paramedic services, prison medical services, the police and those who work in the criminal justice system.
Databases searched	Core: CDSR, CENTRAL, DARE, Embase, HTA, MEDLINE, PreMedline Topic specific: CINAHL, PsycINFO
Other resources searched	Hand-reference searching of retrieved literature
Search filters used	Quantitative systematic review, RCT
The review strategy	If reviews are found, the GDG will assess their quality, completeness, and applicability to the NHS and to the scope of the guideline. If the GDG identify a systematic review appropriate to the review question, we will search for RCTs conducted or published since the review was conducted, and the GDG will assess if any additional studies could affect the conclusions of the previous review. If new studies could change the conclusions, we will update the review and conduct a new analysis. If new studies could not change the conclusions of an existing review, the GDG will use the existing review to inform their recommendations. In no reviews are found, we plan to compare all eligible interventions using pairwise meta-analyses. Data will be included in analyses if >66% of the sample have a primary diagnosis as defined in the protocol above. If data are available, sub-analyses will be conducted of studies with >75% of the sample described as having a primary diagnosis of schizophrenia/ schizoaffective disorder or psychosis. If data are available, sub-analyses will be conducted for UK/Europe studies.

6. Intensive Case Management

Review question(s)	For adults with psychosis and schizophrenia, what are the benefits and/or potential harms of intensive case management

	interventions compared to non-intensive case management or standard treatment?
Chapter	Chapter 12
Objectives	To evaluate the clinical effectiveness of intensive case management in the treatment of psychosis and schizophrenia
Criteria for considering studies for the review	
Population	***Included*** Adults (18+) with schizophrenia (including schizophrenia-related disorders such as schizoaffective disorder and delusional disorder) or psychosis. *Include papers with a service user population of **AT LEAST**:* 66% Schizophrenia or 66% (Schizophrenia + Bipolar disorder) or 66% (Schizophrenia + "Mood disorders") or 66% Undefined severe mental illness or 66% Bipolar disorder or 66% (Bipolar disorder + "Mood disorders") Those with an established diagnosis of schizophrenia (with onset before age 60) who require treatment beyond age 60. ***Excluded*** Interventions *specifically* for people with bipolar disorder Very late onset schizophrenia (onset from age 60 onwards) Children and young people (unless they are being treated in early intervention services) People with transient psychotic symptoms
• **Intervention**	Intensive case management (caseload ≤ 20)
• **Comparison**	Non-intensive case management (caseload > 20) or standard treatment (not following ACT or CM models)

• **Critical outcomes**	• Service use
	  ○ Hospitalisation: mean number of days per month in hospital
	  ○ Not remaining in contact with psychiatric services
	  ○ Use of services outside of mental health provision (i.e. emergency services)
	• Quality of life
	• Satisfaction
	  ○ User satisfaction (validated measures only)
	  ○ Carer satisfaction (validated measures only)
	Functional disability

Important but not critical	• Service use

outcomes	○ Admitted to hospital ○ Hospital admission rate • Global state ○ Leaving the study early (lost to follow-up) ○ Relapse (as defined in study) ○ Not improved to a clinically meaningful extent (as defined in study) ○ Compliance with medication • Adverse effects ○ Death - all causes and suicide • Social functioning ○ Employment status (number unemployed at end of study) ○ Accommodation status (number homeless or not living independently during or at the end of the study, mean days homeless and mean days in stable accommodation per month in study) • Mental state ○ General symptoms ▪ Not improved to a clinically meaningful extent (as defined in study) ○ Specific symptoms ▪ Positive symptoms (delusions, hallucinations, disordered thinking) • Not improved to a clinically meaningful extent (as defined in study) ▪ Negative symptoms (poor volition, poor self-care, blunted affect) • Not improve to a clinically meaningful extent ▪ Mood depression • Behaviour ○ General behaviour ○ Specific behaviour (self-harm, violent acts etc.) • Carer-focused outcomes ○ Quality of life ○ Depression ○ Burden of care (validated measures only) • Employment/ Income
Study design	• Systematic review of RCTs ○ Primary RCTs
Include unpublished data?	Yes but only where: • the evidence was accompanied by a study report containing sufficient detail to properly assess the quality of the data

	• the evidence was submitted with the understanding that data from the study and a summary of the study's characteristics will be published in the full guideline. Therefore, the GDG should not accept evidence submitted as commercial in confidence. However, the GDG should recognise that unpublished evidence submitted by investigators, might later be retracted by those investigators if the inclusion of such data would jeopardise publication of their research.
Restriction by date	RCT: database inception to June 2013 Systematic review: 1995 to June 2013
Minimum sample size	N=10 per arm (ITT) • Exclude studies with > 50% attrition from both arms of study (unless adequate statistical methodology has been applied to account for missing data).
Study setting	Primary, secondary and tertiary healthcare services that are relevant to the NHS. The guideline will also be relevant to, but not cover the practice of, A&E departments, paramedic services, prison medical services, the police and those who work in the criminal justice system.
Databases searched	Core: CDSR, CENTRAL, DARE, Embase, HTA, MEDLINE, PreMedline Topic specific: CINAHL, PsycINFO
Searching other resources	Hand-reference searching of retrieved literature
Search filters used	Quantitative SR, RCT
The review strategy	**If reviews are found, the GDG will assess their quality, completeness, and applicability to the NHS and to the scope of the guideline. If the GDG identify a systematic review appropriate to the review question, we will search for RCTs conducted or published since the review was conducted, and the GDG will assess if any additional studies could affect the conclusions of the previous review. If new studies could change the conclusions, we will update the review and conduct a new analysis. If new studies could not change the conclusions of an existing review, the GDG will use the existing review to inform their recommendations.** In no reviews are found, we plan to compare all eligible interventions using pairwise meta-analyses. Data will be included in analyses if >66% of the sample have a primary diagnosis as defined in the protocol above. If data are available, sub-analyses will be conducted of studies with >75% of the sample described as having a primary diagnosis of schizophrenia/ schizoaffective disorder or psychosis. If data are available, sub-analyses will be conducted for UK/Europe studies.

7. Early Intervention Services

Review question(s)	For adults with psychosis and schizophrenia, what are the benefits and/or potential harms of early intervention services compared to treatment as usual or another intervention?
Chapter	Chapter 12
Objectives	To evaluate the clinical effectiveness of early intervention services in the treatment of psychosis and schizophrenia
Criteria for considering studies for the review	
Population	***Included*** Adults (18+) with schizophrenia (including schizophrenia-related disorders such as schizoaffective disorder and delusional disorder) or psychosis. *Include papers with a service user population of **AT LEAST**:* 66% Schizophrenia or 66% (Schizophrenia + Bipolar disorder) or 66% (Schizophrenia + "Mood disorders") or 66% Undefined severe mental illness or 66% Bipolar disorder or 66% (Bipolar disorder + "Mood disorders") People in early intervention services, which may include people 14 years and older. However, the guideline will not make recommendations about the specific treatment of people under 18 years of age. ***Excluded*** Interventions *specifically* for people with bipolar disorder Very late onset schizophrenia (onset from age 60 onwards) Children and young people (unless they are being treated in early intervention services) People with transient psychotic symptoms
• Intervention	Early intervention services
• Comparison	Any alternative management strategy

• Critical outcomes	• Adverse events
	  ○ Suicide
	• Functioning disability
	• Service use
	  ○ Hospitalisation (admissions, days)

	○ In contact with services • Response / Relapse • Symptoms of psychosis ○ Total symptoms ○ Positive symptoms ○ Negative symptoms • Employment and Education ○ Competitive employment ○ Occupation (any) ○ Attendance at school/college • Duration of untreated psychosis • Carer satisfaction (validated measures only)
Important but not critical outcomes	• Adverse effects ○ Mortality, all cause ○ Self-harm ○ Violent acts • Service use ○ GP visits ○ A&E visits • Empowerment/ Recovery • Insight • Adherence • User satisfaction (validated measures only) • Accommodation ○ Homelessness ○ Stable accommodation • Leaving the study early • Anxiety and Depression • Quality of life • Carer-focused outcomes ○ Quality of life ○ Depression ○ Burden of care (validated measures only) • Employment/ Income
Study design	• Systematic reviews of RCTs

	○ Primary RCTs
• Include unpublished data?	Yes but only where: • the evidence was accompanied by a study report containing sufficient detail to properly assess the quality of the data • the evidence was submitted with the understanding that data from the study and a summary of the study's characteristics will be published in the full guideline. Therefore, the GDG should not accept evidence submitted as commercial in confidence. However, the GDG should recognise that unpublished evidence submitted by investigators, might later be retracted by those investigators if the inclusion of such data would jeopardise publication of their research.
• Restriction by date	Systematic review, RCT: 2002 to June 2013
• Minimum sample size	N=10 per arm (ITT) • Exclude studies with > 50% attrition from either arm of study (unless adequate statistical methodology has been applied to account for missing data).
• Study setting	Primary, secondary and tertiary healthcare services that are relevant to the NHS. The guideline will also be relevant to, but not cover the practice of, A&E departments, paramedic services, prison medical services, the police and those who work in the criminal justice system.
Databases searched	Core: CDSR, CENTRAL, DARE, Embase, HTA, MEDLINE, PreMedline Topic specific: CINAHL, PsycINFO
Other resources searched	Hand-reference searching of retrieved literature
Search filter used	Quantitative SR, RCT
The review strategy	**If reviews are found, the GDG will assess their quality, completeness, and applicability to the NHS and to the scope of the guideline. If the GDG identify a systematic review appropriate to the review question, we will search for RCTs conducted or published since the review was conducted, and the GDG will assess if any additional studies could affect the conclusions of the previous review. If new studies could change the conclusions, we will update the review and conduct a new analysis. If new studies could not change the conclusions of an existing review, the GDG will use the existing review to inform their recommendations.** In no reviews are found, we plan to compare all eligible interventions using pairwise meta-analyses. Data will be included in analyses if >66% of the sample have a primary diagnosis as defined in the protocol above. If data are available, sub-analyses will be conducted of studies with >75% of the sample described as having a primary diagnosis of schizophrenia/ schizoaffective disorder or psychosis. If data are available, sub-analyses will be conducted for UK/Europe studies.

8. Crisis Interventions

Review question(s)	For adults with psychosis and schizophrenia, what are the benefits and/or potential harms of Crisis Interventions compared to treatment as usual or another intervention?
Chapter	Chapter 12
Sub-questions	i. Crisis Resolution and Home Treatment teams (CRHTs) ii. Crisis Houses (also called Recovery Houses)
Objectives	To evaluate the clinical effectiveness of crisis interventions in the treatment of psychosis and schizophrenia
Criteria for considering studies for the review	
• Population	***Included*** Adults (18+) with schizophrenia (including schizophrenia-related disorders such as schizoaffective disorder and delusional disorder) or psychosis. *Include papers with a service user population of **AT LEAST**:* 66% Schizophrenia or 66% (Schizophrenia + Bipolar disorder) or 66% (Schizophrenia + "Mood disorders") or 66% Undefined severe mental illness or 66% Bipolar disorder or 66% (Bipolar disorder + "Mood disorders") ***Excluded*** Interventions *specifically* for people with bipolar disorder Very late onset schizophrenia (onset from age 60 onwards) Children and young people (unless they are being treated in early intervention services) People with transient psychotic symptoms
• Intervention	Crisis Resolution and Home Treatment teams Crisis houses
• Comparison	Any alternative management strategy
Critical outcomes	• Service use

	○ Admission/ Readmission to hospital ○ Number of days in hospital ○ Number of staff/user contacts • Satisfaction ○ **User satisfaction (validated measures only)** ○ Carer satisfaction (validated measures only) • Mental health act use
Important but not critical outcomes	• Service use ○ Not remaining in contact with psychiatric services ○ Use of services outside of mental health provision (i.e. emergency services) • Global state ○ Leaving the study early (lost to follow-up) ○ Relapse (as defined in study) ○ Not improved to a clinically meaningful extent (as defined in study) ○ Compliance with medication • Adverse effects ○ Death - all causes and suicide • Quality of life • Social functioning ○ Employment status (number unemployed at end of study) ○ Accommodation status (number homeless or not living independently during or at the end of the study, mean days homeless and mean days in stable accommodation per month in study) • Mental state ○ General symptoms ○ Not improved to a clinically meaningful extent (as defined in study) ○ Specific symptoms ○ Positive symptoms (delusions, hallucinations, disordered thinking) ...1. Not improved to a clinically meaningful extent (as defined in study) ○ Negative symptoms (poor volition, poor self-care, blunted affect) ...1. Not improve to a clinically meaningful extent ○ Mood depression • Behaviour ○ General behaviour ○ Specific behaviour (self-harm, violent acts etc.) • Carer-focused outcomes

	○ Quality of life ○ Depression ○ Burden of care (validated measures only) ○ Employment/ Income
• Study design	• Systematic reviews of RCTs • Primary RCTs
• Include unpublished data?	Yes but only where: • the evidence was accompanied by a study report containing sufficient detail to properly assess the quality of the data • the evidence was submitted with the understanding that data from the study and a summary of the study's characteristics will be published in the full guideline. Therefore, the GDG should not accept evidence submitted as commercial in confidence. However, the GDG should recognise that unpublished evidence submitted by investigators, might later be retracted by those investigators if the inclusion of such data would jeopardise publication of their research.
• Restriction by date?	Systematic review, RCT: 2002 to June 2013
• Minimum sample size	N=10 per arm (ITT) Exclude studies with > 50% attrition from either arm of study (unless adequate statistical methodology has been applied to account for missing data).
• Study setting	Primary, secondary and tertiary healthcare services that are relevant to the NHS. The guideline will also be relevant to, but not cover the practice of, A&E departments, paramedic services, prison medical services, the police and those who work in the criminal justice system.
Databases searched	Core: CDSR, CENTRAL, DARE, Embase, HTA, MEDLINE, PreMedline Topic specific: CINAHL, PsycINFO
Other resources searched	Hand-reference searching of retrieved literature
Search filter used	Quantitative SR, RCT
The review strategy	**If reviews are found, the GDG will assess their quality, completeness, and applicability to the NHS and to the scope of the guideline. If the GDG identify a systematic review appropriate to the review question, we will search for RCTs conducted or published since the review was conducted, and the GDG will assess if any additional studies could affect the conclusions of the previous review. If new studies could change the conclusions, we will update the review and conduct a new analysis. If new studies could not change the conclusions of an existing review, the GDG will use the existing review to inform their recommendations.** In no reviews are found, we plan to compare all eligible interventions using pairwise meta-analyses. Data will be included in analyses if >66% of the sample have a primary diagnosis as defined in the protocol above.

	If data are available, sub-analyses will be conducted of studies with >75% of the sample described as having a primary diagnosis of schizophrenia/ schizoaffective disorder or psychosis. If data are available, sub-analyses will be conducted for UK/Europe studies.

9. Community Mental Health Teams (CMHTs)

Review question(s)	For adults with psychosis and schizophrenia, what are the benefits and/or potential harms of CMHTs compared to treatment as usual or another intervention?
Sub-question(s)	
Chapter	Chapter 12
Objectives	To evaluate the clinical effectiveness of community mental health teams in the treatment of psychosis and schizophrenia
Criteria for considering studies for the review	
• Population	***Included*** Adults (18+) with schizophrenia (including schizophrenia-related disorders such as schizoaffective disorder and delusional disorder) or psychosis. *Include papers with a service user population of **AT LEAST**:* 66% Schizophrenia or 66% (Schizophrenia + Bipolar disorder) or 66% (Schizophrenia + "Mood disorders") or 66% Undefined severe mental illness or 66% Bipolar disorder or 66% (Bipolar disorder + "Mood disorders") ***Excluded*** Interventions *specifically* for people with bipolar disorder Very late onset schizophrenia (onset from age 60 onwards) Children and young people (unless they are being treated in early intervention services) People with transient psychotic symptoms
• Intervention	Community mental health teams

• Comparison	Any alternative management strategy

Critical outcomes	• Service use
	  o Hospitalisation: mean number of days per month in hospital
	  o Not remaining in contact with psychiatric services
	  o Use of services outside of mental health provision (i.e. emergency services)
	• Social functioning
	  o Employment status (number unemployed at end of study)
	  o Accommodation status (number homeless or not living independently during or at the end of the study, mean days homeless and mean days in stable accommodation per month in study)
	• Quality of life
	• Mental state
	  o General symptoms
	  o Total symptoms
	  o Positive symptoms (delusions, hallucinations, disordered thinking)
	  o Negative symptoms (poor volition, poor self-care, blunted affect)
	• Satisfaction
	  o User satisfaction (validated measures only)
	  o Carer satisfaction (validated measures only)

Important but not critical outcomes	• Service use
	  o Admitted to hospital
	  o Hospital admission rate
	• Global state
	  o Leaving the study early (lost to follow-up)
	  o Relapse (as defined in study)
	  o Not improved to a clinically meaningful extent (as defined in study)
	  o Compliance with medication
	• Adverse effects
	  o Death - all causes and suicide
	• Mental state
	  o Mood depression
	• Behaviour
	  o General behaviour
	  o Specific behaviour (self-harm, violent acts etc.)
	• Carer-focused outcomes

	○ Quality of life ○ Depression ○ Burden of care (validated measures only) ○ Employment/ Income
• Study design	• Systematic reviews of RCTs • Primary RCTs
• Include unpublished data?	Yes but only where: • the evidence was accompanied by a study report containing sufficient detail to properly assess the quality of the data • the evidence was submitted with the understanding that data from the study and a summary of the study's characteristics will be published in the full guideline. Therefore, the GDG should not accept evidence submitted as commercial in confidence. However, the GDG should recognise that unpublished evidence submitted by investigators, might later be retracted by those investigators if the inclusion of such data would jeopardise publication of their research.
• Restriction by date?	Systematic review, RCT: 2002 to June 2013
• Minimum sample size	N=10 per arm (ITT) Exclude studies with > 50% attrition from either arm of study (unless adequate statistical methodology has been applied to account for missing data).
• Study setting	Primary, secondary and tertiary healthcare services that are relevant to the NHS. The guideline will also be relevant to, but not cover the practice of, A&E departments, paramedic services, prison medical services, the police and those who work in the criminal justice system.
Databases searched	Core: CDSR, CENTRAL, DARE, Embase, HTA, MEDLINE, PreMedline Topic specific: CINAHL, PsycINFO
Other resources searched	Hand-reference searching of retrieved literature
Search filter used	Quantitative SR, RCT
The review strategy	**If reviews are found, the GDG will assess their quality, completeness, and applicability to the NHS and to the scope of the guideline. If the GDG identify a systematic review appropriate to the review question, we will search for RCTs conducted or published since the review was conducted, and the GDG will assess if any additional studies could affect the conclusions of the previous review. If new studies could change the conclusions, we will update the review and conduct a new analysis. If new studies could not change the conclusions of an existing review, the GDG will use the existing review to inform their recommendations.** In no reviews are found, we plan to compare all eligible interventions using pairwise meta-analyses.

	Data will be included in analyses if >66% of the sample have a primary diagnosis as defined in the protocol above. If data are available, sub-analyses will be conducted of studies with >75% of the sample described as having a primary diagnosis of schizophrenia/ schizoaffective disorder or psychosis. If data are available, sub-analyses will be conducted for UK/Europe studies.

10. Acute day hospitals

Review question(s)	For adults with psychosis and schizophrenia, what are the benefits and/or potential harms of acute day hospitals compared to treatment as usual or another intervention?
Sub-question(s)	
Chapter	Chapter 12
Objectives	To evaluate the clinical effectiveness of acute day hospitals in the treatment of psychosis and schizophrenia
Criteria for considering studies for the review	
• Population	***Included*** Adults (18+) with schizophrenia (including schizophrenia-related disorders such as schizoaffective disorder and delusional disorder) or psychosis. *Include papers with a service user population of **AT LEAST**:* 66% Schizophrenia or 66% (Schizophrenia + Bipolar disorder) or 66% (Schizophrenia + "Mood disorders") or 66% Undefined severe mental illness or 66% Bipolar disorder or 66% (Bipolar disorder + "Mood disorders") ***Excluded*** Interventions *specifically* for people with bipolar disorder Very late onset schizophrenia (onset from age 60 onwards) Children and young people (unless they are being treated in early intervention services) People with transient psychotic symptoms

• Intervention	Acute day hospitals
• Comparison	Any alternative management strategy

Critical outcomes	• Service use
	  o Hospitalisation: mean number of days per month in hospital
	  o Not remaining in contact with psychiatric services
	  o Use of services outside of mental health provision (i.e. emergency services)
	• Satisfaction
	  o User satisfaction (validated measures only)
	  o Carer satisfaction (validated measures only)
	• Mental health act use

Important but not critical outcomes	• Service use
	  o Admitted to hospital
	  o 2.2 Hospital admission rate
	• Global state
	  o Leaving the study early (lost to follow-up)
	  o Relapse (as defined in study)
	  o Not improved to a clinically meaningful extent (as defined in study)
	  o Compliance with medication
	• Adverse effects
	  o Death - all causes and suicide
	• Quality of life
	• Social functioning
	  o Employment status (number unemployed at end of study)
	  o Accommodation status (number homeless or not living independently during or at the end of the study, mean days homeless and mean days in stable accommodation per month in study)
	• Mental state
	  o General symptoms
	  ▪ Not improved to a clinically meaningful extent (as defined in study)
	  o Specific symptoms
	  ▪ Positive symptoms (delusions, hallucinations, disordered thinking)
	  • Not improved to a clinically meaningful extent (as defined in study)
	  ▪ Negative symptoms (poor volition, poor self-care, blunted affect)
	  • Not improve to a clinically meaningful extent
	  ▪ Mood depression

	• Behaviour
	  o General behaviour
	  o Specific behaviour (self-harm, violent acts etc.)
	• Carer-focused outcomes
	  o Quality of life
	  o Depression
	  o Burden of care (validated measures only)
	  o Employment/ Income

• Study design	• Systematic reviews of RCTs • Primary RCTs
• Include unpublished data?	Yes but only where: • the evidence was accompanied by a study report containing sufficient detail to properly assess the quality of the data • the evidence was submitted with the understanding that data from the study and a summary of the study's characteristics will be published in the full guideline. Therefore, the GDG should not accept evidence submitted as commercial in confidence. However, the GDG should recognise that unpublished evidence submitted by investigators, might later be retracted by those investigators if the inclusion of such data would jeopardise publication of their research.
• Restriction by date?	Systematic review, RCT: 2002 to June 2013
• Minimum sample size	N=10 per arm (ITT) Exclude studies with > 50% attrition from either arm of study (unless adequate statistical methodology has been applied to account for missing data).
• Study setting	Primary, secondary and tertiary healthcare services that are relevant to the NHS. The guideline will also be relevant to, but not cover the practice of, A&E departments, paramedic services, prison medical services, the police and those who work in the criminal justice system.
Databases searched	Core: CDSR, CENTRAL, DARE, Embase, HTA, MEDLINE, PreMedline Topic specific: CINAHL, PsycINFO
Other resources searched	Hand-reference searching of retrieved literature
Search filter used	Quantitative SR, RCT
The review strategy	**If reviews are found, the GDG will assess their quality, completeness, and applicability to the NHS and to the scope of the guideline. If the GDG identify a systematic review appropriate to the review question, we will search for RCTs conducted or published since the review was conducted, and the GDG will assess if any additional studies could affect the conclusions of the previous review. If new studies could change the conclusions, we will update the review and conduct a**

	new analysis. If new studies could not change the conclusions of an existing review, the GDG will use the existing review to inform their recommendations. In no reviews are found, we plan to compare all eligible interventions using pairwise meta-analyses. Data will be included in analyses if >66% of the sample have a primary diagnosis as defined in the protocol above. If data are available, sub-analyses will be conducted of studies with >75% of the sample described as having a primary diagnosis of schizophrenia/ schizoaffective disorder or psychosis. If data are available, sub-analyses will be conducted for UK/Europe studies.

11. Vocational Rehabilitation

Review question(s)	For adults with psychosis and schizophrenia, what are the benefits and/or potential harms of vocational rehabilitation interventions compared to treatment as usual or other interventions?
Sub-question(s)	
	i. Supported employment ii. Pre-vocational training (including individual placement support, volunteering, training) iii. Modifications of above (paid work or additional psychological therapy) iv. Cognitive remediation with vocational rehabilitation
Chapter	Chapter 13
Objectives	To evaluate the effectiveness of vocational rehabilitation interventions for people with psychosis and schizophrenia
Criteria for considering studies for the review	
• Population	***Included*** Adults (18+) with schizophrenia (including schizophrenia-related disorders such as schizoaffective disorder and delusional disorder) or psychosis. *Include papers with at least:* 66% Schizophrenia or

	66% (Schizophrenia + Bipolar disorder) or 66% (Schizophrenia + "Mood disorders") or 66% Undefined severe mental illness ***Excluded*** Papers with >66% bipolar sample diagnosis Papers with >66% bipolar + mood disorder diagnosis Interventions *specifically* for people with bipolar disorder Very late onset schizophrenia (onset from age 60 onwards) Children and young people (unless they are being treated in early intervention services) People with transient psychotic symptoms
• Intervention	Vocational rehabilitation interventions
• Comparison	Any alternative management strategy
• **Outcomes**	

Critical outcomes	• Employment and Education
	  o Competitive employment
	  o Occupation (any)
	  o Attendance at school/college
	• Quality of life
	• Functional disability

Important but not critical outcomes	• Adverse effects
	  o Suicide
	  o Mortality, all cause
	  o Self-harm
	  o Violent acts
	• Anxiety and depression
	• Accommodation
	  o Homelessness
	  o Stable accommodation
	• Empowerment/ Recovery
	• User satisfaction (validated measures only)
	• Response / Relapse
	  o Relapse (as defined in study)
	  o Response (improvement in symptoms)
	• Symptoms of psychosis

	○ Total symptoms ○ Positive symptoms ○ Negative symptoms • Duration of untreated psychosis • Service use ○ Hospitalisation (admissions, days) ○ GP visits ○ A&E visits • Dropout ○ Withdrawal due to adverse event ○ Loss to follow-up, any reason • Carer-focused outcomes ○ Quality of life ○ Depression ○ Burden of care (validated measures only) ○ Employment/ Income
• Study design	• Systematic reviews of RCTs • Primary RCTs
• Include unpublished data?	Yes but only where: • the evidence was accompanied by a study report containing sufficient detail to properly assess the quality of the data • the evidence was submitted with the understanding that data from the study and a summary of the study's characteristics will be published in the full guideline. Therefore, the GDG should not accept evidence submitted as commercial in confidence. However, the GDG should recognise that unpublished evidence submitted by investigators, might later be retracted by those investigators if the inclusion of such data would jeopardise publication of their research.
• Restriction by date?	**Sub questions i,ii,iii**: Systematic review, RCT: 2002 to June 2013 **Sub question iv**: RCT: database inception to June 2013 Systematic review: 1995 to June 2013 NB: Vocational rehabilitation with cognitive remediation was not reviewed in the previous guideline. Therefore, an additional

	search for SRs/RCTs was run from an earlier date.
• Minimum sample size	N=10 per arm (ITT) Exclude studies with > 50% attrition from either arm of study (unless adequate statistical methodology has been applied to account for missing data).
• Study setting	Primary, secondary and tertiary healthcare services that are relevant to the NHS. The guideline will also be relevant to, but not cover the practice of, A&E departments, paramedic services, prison medical services, the police and those who work in the criminal justice system.
Databases searched	Core: CDSR, CENTRAL, DARE, Embase, HTA, MEDLINE, PreMedline Topic specific: CINAHL, PsycINFO
Other resources searched	Hand-reference searching of retrieved literature
Search filters used	Quantitative SR, RCT
The review strategy	**If reviews are found, the GDG will assess their quality, completeness, and applicability to the NHS and to the scope of the guideline. If the GDG identify a systematic review appropriate to the review question, we will search for RCTs conducted or published since the review was conducted, and the GDG will assess if any additional studies could affect the conclusions of the previous review. If new studies could change the conclusions, we will update the review and conduct a new analysis. If new studies could not change the conclusions of an existing review, the GDG will use the existing review to inform their recommendations.** In no reviews are found, we plan to compare all eligible interventions using pairwise meta-analyses. Data will be included in analyses if >66% of the sample have a primary diagnosis as defined in the protocol above. If data are available, sub-analyses will be conducted of studies with >75% of the sample described as having a primary diagnosis of schizophrenia/ schizoaffective disorder or psychosis. If data are available, sub-analyses will be conducted for UK/Europe studies.

12. Trauma in psychosis and schizophrenia

Review question(s)	For adults with psychosis and schizophrenia, what are the benefits and/or potential harms of psychological management strategies for previous trauma compared to treatment as usual or another intervention?
Chapter	Chapter 9
Objectives	To evaluate the benefits and harms of psychological interventions for trauma for adults with psychosis and schizophrenia.

Criteria for considering studies for the review	
Population	*Included* Adults (18+) with schizophrenia (including schizophrenia-related disorders such as schizoaffective disorder and delusional disorder) or psychosis. *Include papers with at least:* 66% Schizophrenia or 66% (Schizophrenia + Bipolar disorder) or 66% (Schizophrenia + "Mood disorders") or 66% Undefined severe mental illness Those with an established diagnosis of schizophrenia (with onset before age 60) who require treatment beyond age 60. People in early intervention services, which may include people 14 years and older. However, the guideline will not make recommendations about the specific treatment of people under 18 years of age. *Excluded* Papers with >66% bipolar sample diagnosis Papers with >66% bipolar + mood disorder diagnosis Interventions *specifically* for people with bipolar disorder Very late onset schizophrenia (onset from age 60 onwards) Children and young people (unless they are being treated in early intervention services) People with transient psychotic symptoms
Intervention	Trauma-focused interventions
Comparison	Any other management strategy
Outcomes	
Critical outcomes	Anxiety symptoms (including PTSD) Symptoms of psychosis Total symptoms Positive symptoms Negative symptoms Response / Relapse Relapse (as defined in study) Response (improvement in symptoms) Depression symptoms

	Dropout (proxy measure for acceptability) Withdrawal due to adverse event Loss to follow-up, any reason
Important but not critical outcomes	
Other outcomes	
Study design	Systematic reviews of RCTs Primary RCTs
Include unpublished data?	Yes but only where: the evidence was accompanied by a study report containing sufficient detail to properly assess the quality of the data the evidence was submitted with the understanding that data from the study and a summary of the study's characteristics will be published in the full guideline. Therefore, the GDG should not accept evidence submitted as commercial in confidence. However, the GDG should recognise that unpublished evidence submitted by investigators, might later be retracted by those investigators if the inclusion of such data would jeopardise publication of their research.
Restriction by date?	Systematic review: 1995 to June 2013 RCT: inception of databases to June 2013
Minimum sample size	N=10 per arm (ITT) Exclude studies with > 50% attrition from either arm of study (unless adequate statistical methodology has been applied to account for missing data).
Study setting	Primary, secondary and tertiary healthcare services that are relevant to the NHS. The guideline will also be relevant to, but not cover the practice of, A&E departments, paramedic services, prison medical services, the police and those who work in the criminal justice system.
Databases searched	Core: CDSR, CENTRAL, DARE, Embase, HTA, MEDLINE, PreMedline Topic specific: CINAHL, PsycINFO
Other resources searched	Hand-reference searching of retrieved literature
Search filter used	Quantitative SR, RCT
The review strategy	If reviews are found, the GDG will assess their quality, completeness, and applicability to the NHS and to the scope of the guideline. If the GDG identify a systematic review appropriate to the review question, we will search for RCTs conducted or published since the review was conducted, and the GDG will assess if any additional studies could affect the conclusions of the previous review. If new studies could change the conclusions, we will update the review and conduct a new analysis. If new studies could not change the conclusions of an existing review, the GDG will use the existing review to inform their recommendations. In no reviews are found, we plan to compare all eligible interventions using pairwise meta-analyses.

	Data will be included in analyses if >66% of the sample have a primary diagnosis as defined in the protocol above. If data are available, sub-analyses will be conducted of studies with >75% of the sample described as having a primary diagnosis of schizophrenia/ schizoaffective disorder or psychosis. If data are available, sub-analyses will be conducted for UK/Europe studies.

APPENDIX 7: DATA EXTRACTION FORMS

An Excel-based data extraction tool, developed by NCCMH staff, was adapted for use in the current context to extract RCT evidence. The following screen grabs provide an example of the study characteristics extracted for each study and the methodology checklist. Further information was extracted about funding, publication status, comparisons and study results (not shown). Review Manager 5.1 (The Cochrane Collaboration, 2011) was used to extract data for the review of case identification instruments. Word-based forms were used to extract evidence about access to services and the experience of care.

Study characteristics

	B	D	H	I	J	K	L	M	N	O	P	Q	S	T	U
1	Study_ID	INTERVENTION	Year	Locality	Country	Recruit_Loc	Recruit_Q	N_Rand	Diagnostic_Intrvw	Diagnosis	Diagnosis_Q	Inclusion_criteria Q	Age	Sex	Race
2	Aberg-Wistedt-Sweden	B) Intensive Case management	1995	Stockholm	Sweden	Mixed referral	Patients were recruited for participation in the	40	Not reported	Schiz Spectrum	DSM-III-R schizophreni	i. recently admitted to ward or currently in	37.65	0.35	Not reported
3	ACIL2008	A) Physical activity	2008	Central Anatolia	TU	Mental Health Outpatient	patients who had hospitalized upon the	30	Not reported	Schizophrenia	schizophreni a diagnoses	i. discharged from the hospital	32.36	0.4	Not reported
4	ALVAREZ2006	A) Healthy eating and physical activity	1996	Cantabria	ES	Mixed referral	Referrals were considered for participant and were	61	Structured Clinical Interview -	SMI (unspecified)	DSM-IV criteria for	i. lived in the catchment area	26.8	0.246	Not reported
5	ANZAI2002	A) Self-management, professional led	2002	Tokyo	JA	Mental Health Inpatient	inpatients	32	Not reported	Schizophrenia	inpatients meeting ICD-	i. volunteered and who gave written informed	46.8	0.25	0
6	ATTUX2013	A) Healthy eating and physical activity	2013	São Paulo	BR	Mental Health Outpatient	Participants were already enrolled in the outpatient	160	Structured Clinical Interview - Patient	Schizophrenia	diagnosis on the	i. aged between 18 and 65 years old; ii.	37.236875	0.4	0.7375
7	Audini-UK	B) Intensive Case management	1994	London	UK	Mental Health Outpatient	Patients had entered the trial at month 0 when	66	Not reported	SMI (unspecified)	serious mental	i. completed at least 18 months in ACT	37	0.55	0.65
8	BARBIC2009	A) Peer Support	2009	Ontario	CA	Mental Health Outpatient	Managers from two ACT teams screened 140	33	Not reported	SMI (including bipolar)	met DSM-IV diagnostic	i. used ACT services for more than six consecutive	44.635	0.3333	Not reported
9	BAUER2006	A) Self-management, professional led	2006	Multiple	US	Mental Health Outpatient	all patients with suspected bipolar	330	Structured Clinical Interview -	Bipolar	Diagnosis of bipolar	i. Index episode of manic, major depressive, or mixed	46.6	0.0915	Not reported
10	BEARD1963	C) Vocational Rehabilitation	1963	New York	US	Mental Health Outpatient	Recently released psychiatric patients	352	Not reported	SMI (unspecified)	psychiatric patients	i. Undergone psychiatric hospitalisation for at least	Not reported	0.4	0.88
11	BECKER1967	C) Vocational Rehabilitation	1967	Texas	US	Mental Health Inpatient	This is one of two Federal hospitals. Within	50	Not reported	SMI (unspecified)	general psychiatric	i. Hospitalised for more than two years in the last	46	Not reported	Not reported
12	BEEBE2010	A) Physical activity	2010	Knoxville	US	Mental Health Outpatient	Participants were recruited from a	97	Not reported	Schiz Spectrum	a chart diagnosis of	i. English speaking; ii. medical clearance for	46.9	0.474	0.546
13	BELL1993	C) Vocational Rehabilitation	1996	West Haven,	US	Mixed referral	psychiatry service of the VA medical center. (N=	150	Structured Clinical Interview (SCID)	Schiz Spectrum	DSM-III-R (American	i. relatively stable phase of disorder, operationally	43.2514493	0.03623	0.6884

	B	D	V	W	X	Y	Z	AA	AB	AC	AD	AE	AF	AG	AH
1	Study_ID	INTERVENTION	Diagnosis_Q	Schiz_Spec	Psychosis	Bipolar	Mood Disorder	Personality	AgeOnset	Hospitalised	Admissions	PrevHospital_Q	CurrMed	Med_Q	OtherDemo
2	Aberg-Wistedt-Sweden	B) Intensive Case management	Diagnosis: schizophrenic	1	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	N/A	1	(E.I.F.A: 'Currently	N/A
3	ACIL2008	A) Physical activity	schizophrenia diagnoses made	1	Not reported	Not reported	Not reported	Not reported	22.095	Not reported	Not reported	N/A	1	All of participant	N/A
4	ALVAREZ2006	A) Healthy eating and physical activity	DSM-IV criteria (APA, 1994) for a	1	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	N/A	0.032	At baseline,	The mean self-
5	ANZAI2002	A) Self-management, professional led	32 inpatients meeting ICD-10	1	Not reported	0	0	0.03125	26.2	1	4.28	The mean±SD duration of the	1	(E.I.F.A: Currently	N/A
6	ATTUX2013	A) Healthy eating and physical activity	Schizophrenia= 88% ; other	0.88	0.09375	Not reported	Not reported	Not reported	23	Not reported	Not reported	N/A	0.9875	N/A	N/A
7	Audini-UK	B) Intensive Case management	Diagnosis: serious mental	0.3	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	0.17	first admission rates= 70%;	Not reported	N/A	N/A
8	BARBIC2009	A) Peer Support	Schizophrenia and related	0.7879	Not reported	0.2121	0.2121	Not reported	26.595	Not reported	10.77	Number of psychiatric	Not reported	N/A	Parent= 21.21%;
9	BAUER2006	A) Self-management, professional led	Bipolar type I= 265/ 306; Type	Not reported	0.33	1	1	Not reported	21	1	5.3	Hospitalisation rate(mean±SD	Not reported	N/A	N/A
10	BEARD1963	C) Vocational Rehabilitation	75% have diagnosis of	0.75	0.07	Not reported	0.11	Not reported	Not reported	1	Not reported	Undergone psychiatric	0.6667	two thirds were	N/A
11	BECKER1967	C) Vocational Rehabilitation	Of the 50 patients, 4	0.78	Not reported	Not reported	Not reported	0.08	33	1	Not reported	The length of hospitalization	Not reported	N/A	Both groups had
12	BEEBE2010	A) Physical activity	Schizoaffective= 69/97;	1	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	N/A	1	The most commonly	Participant weights
13	BELL1993	C) Vocational Rehabilitation	(N= 138) Schizophrenia:	1	Not reported	Not reported	Not reported	Not reported	22.8884058	1	8.609	Lifetime psychiatric	Not reported	N/A	(N= 138) Treatment

Methodology checklist

	B	D	AJ	AK	AL	AM	AN	AO	AP	AQ	AR	AS	AT
1	Study_ID	INTERVENTION	RandMethod	Quotation	ROB	After_Recruit	Impervious	Quotation	ROB	Assess_Out	Assess_Blind	Quotation	ROB
2	Aberg-Wistedt-Sweden	B) Intensive Case management	Random numbers table	randomly assigned. (E.I.F.A: 'The	Low	Yes	No	(E.I.F.A: 'The two people involved in enrolling the	High	No	N/A	(Primary outcome: not available. Secondary	Unclear
3	ACIL2008	A) Physical activity	Unclear	Individuals, which matched all necessary	Unclear	Yes	Unclear	The forms were applied in consecutive order to all	Unclear	Yes	Unclear	(No mention of blinding)	Unclear
4	ALVAREZ2006	A) Healthy eating and physical activity	Computer/Online	first randomly assigned to one of three different anti-	Low	Yes	Yes	Patients who met criteria and gave written informed	Low	Yes	No	Clinical ratings were completed by a	High
5	ANZAI2002	A) Self-management, professional led	Unclear	Patients were randomly assigned to participate in	Unclear	Yes	Unclear	Only patients who volunteered and who	Unclear	Yes	Unclear	(E.I.F.A: '. The PANSS was evaluated by	Low
6	ATTUX2013	A) Healthy eating and physical activity	Computer/Online	randomly assigned using a	Low	Yes	Yes	Participants who agreed to take part in the study	Low	Yes	Yes	Blind investigators	Low
7	Audini-UK	B) Intensive Case management	Unclear	patients were randomised	Unclear	Yes	Unclear	No details.	Unclear	Yes	Unclear	(Primary outcome: clinician/participant	Unclear
8	BARBIC2009	A) Peer Support	Unclear	participants were grouped on the basis of which	Unclear	Yes	Unclear	Study assessments were conducted one week	Unclear	No	N/A	Self report. Three assessors, who were blind	Low
9	BAUER2006	A) Self-management, professional led	Computer/Online	Randomization was accomplished with a	Low	Yes	Yes	Randomization was accomplished with a	Low	Yes	Yes	Blinded clinical and functional measures were	Low
10	BEARD1963	C) Vocational Rehabilitation	Other	to achieve random assignment of research	Low	Unclear	Unclear	N/A	Unclear	No	N/A	(hospital and employment figures)	Low
11	BECKER1967	C) Vocational Rehabilitation	Unclear	25 patients each were selected by lot. The	Unclear	Yes	Unclear	From the resulting population of 149	Unclear	No	N/A	(employment and hospital outcomes)	Low
12	BEEBE2010	A) Physical activity	Computer/Online	We assigned participants to the experimental	Low	Yes	Yes	We assigned participants using a randomization	Low	No	N/A	The SEE and OEES are limited because of their	Low
13	BELL1993	C) Vocational Rehabilitation	Unclear	The randomisation procedure was stratified	Unclear	Yes	Unclear	At the conclusion of intake, subjects were	Unclear	Yes	Unclear	PANSS	Unclear

	B	D	AV	AW	AX	AY	AZ	BA	BB	BC	BE	BF	BG	BH	BI
1	Study_ID	INTERVENTION	DropRate	Mthd_Analy	Quotation	ROB	Registered	Reg_Num	All_Out	Quotation	Quotatio	Stopped_Early	ROB	Funding_Source	Pub_Status
2	Aberg-Wistedt-Sweden	B) Intensive Case management	Yes	Available case	The study did not address this outcome. (E.I.F.A: '3	Unclear	Not Reported	(E.I.F.A: 'The study	No- Paper clearly	(More outcomes of	No details.	No	Low	(E.I.F.A: 'Stockholm	Published paper(s)
3	ACIL2008	A) Physical activity	Not Reported	Available case	(No mention of missing data)	Unclear	Not Reported	N/A	Unclear - But all	N/A	N/A	No	Low	None acknowledged	Published paper(s)
4	ALVAREZ2006	A) Healthy eating and physical activity	Yes	Per protocol	All participants randomised completed	Low	Not Reported	N/A	No- Paper clearly	Assessments with the SAPS	N/A	No	Low	Marques de Valdecilla	Published paper(s)
5	ANZAI2002	A) Self-management, professional led	Yes	Available case	Before training started, two participants in the	Low	Not Reported	(E.I.F.A.:No , we did not	No- Paper clearly	(E.I.F.A: We also	N/A	No	Low	Health and Labor Sciences	Published paper(s)
6	ATTUX2013	A) Healthy eating and physical activity	No	Last Observation	intention-to-treat analysis, with the Last Observation	High	Yes	NCT01368406	Yes - checked	Protocol: Primary	N/A	No	Low	State of São Paulo Funding	Published paper(s)
7	Audini-UK	B) Intensive Case management	Yes	Available case	(Number and reason for attrition reported.	Low	Not Reported	N/A	Unclear - But all	(All listed outcomes are	No details.	No	Low	Wolfson Foundation	Published paper(s)
8	BARBIC2009	A) Peer Support	Not Reported	Other imputation	All statistical analyses were intent-totreat	Unclear	Not Reported	N/A	Unclear - But all	N/A	N/A	No	Low	None acknowledged	Published paper(s)
9	BAUER2006	A) Self-management, professional led	Yes	Other imputation	Analyses were based on intention to treat and used	Low	Not Reported	N/A	No- Paper clearly	(cannot extract FU data)	N/A	No	Low	Department of Veterans	Published paper(s)
10	BEARD1963	C) Vocational Rehabilitation	No	Available case	(>50% dropout; variable N)	High	Not Reported	N/A	Unclear - But all	N/A	the experime	No	Unclear	National Institute of	Published paper(s)
11	BECKER1967	C) Vocational Rehabilitation	Yes	No dropout	(Inpatients)	Low	Not Reported	N/A	Unclear - But all	N/A	N/A	No	Low	None acknowledged	Published paper(s)
12	BEEBE2010	A) Physical activity	No	Other imputation	data were analyzed using a mixed model (proc MIX).	High	Not Reported	N/A	No- Paper clearly	(Outcomes reported are	N/A	No	Low	National Institutes of	Published paper(s)
13	BELL1993	C) Vocational Rehabilitation	Yes	Available case	Of the 150 subjects initially randomized,	Low	No	(E.I.F.A: 'clinical trial	No- Paper clearly	No significant between-	Six subjects	No	Low	Department of Veterans	Published paper(s)

APPENDIX 8: METHODOLOGY CHECK LIST TEMPLATE FOR CLINICAL STUDIES AND REVIEWS

Methodology checklist for randomised controlled trials

Study identification Include author, title, reference, year of publication	
Guideline topic:	**Review question no:**
Checklist completed by:	
	Circle one option for each question

A. Selection bias (systematic differences between the comparison groups)		
A1	An appropriate method of randomisation was used to allocate participants to treatment groups (which would have balanced any confounding factors equally across groups)	Yes No Unclear N/A
A2	There was adequate concealment of allocation (such that investigators, clinicians and participants cannot influence enrolment or treatment allocation)	Yes No Unclear N/A
A3	The groups were comparable at baseline, including all major confounding and prognostic factors	Yes No Unclear N/A
Based on your answers to the above, in your opinion was selection bias present? If so, what is the likely direction of its effect?		
Low risk of bias	Unclear/unknown risk	High risk of bias
Likely direction of effect:		
B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)		
B1	The comparison groups received the same care apart from the intervention(s) studied	Yes No Unclear N/A

B2	Participants receiving care were kept 'blind' to treatment allocation	Yes No Unclear N/A
B3	Individuals administering care were kept 'blind' to treatment allocation	Yes No Unclear N/A
Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?		
Low risk of bias Unclear/unknown risk High risk of bias		
Likely direction of effect:		
C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)		
C1	All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	Yes No Unclear N/A
C2	a. How many participants did not complete treatment in each group?	
	b. The groups were comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment)	Yes No Unclear N/A
C3	a. For how many participants in each group were no outcome data available?	
	b. The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available).	Yes No Unclear N/A
Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?		
Low risk of bias Unclear/unknown risk High risk of bias		
Likely direction of effect:		
D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)		

D1	The study had an appropriate length of follow-up	Yes No Unclear N/A
D2	The study used a precise definition of outcome	Yes No Unclear N/A
D3	A valid and reliable method was used to determine the outcome	Yes No Unclear N/A
D4	Investigators were kept 'blind' to participants' exposure to the intervention	Yes No Unclear N/A
D5	Investigators were kept 'blind' to other important confounding and prognostic factors	Yes No Unclear N/A
Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?		
Low risk of bias Unclear/unknown risk High risk of bias		
Likely direction of effect:		

Methodology checklist: systematic reviews and meta-analyses

Study identification *Include author, title, reference, year of publication*	
Guideline topic:	**Review question no:**
Checklist completed by:	
SCREENING QUESTIONS	
In a well-conducted, relevant systematic review:	***Circle one option for each question***
The review addresses an appropriate and clearly focused question that is relevant to the guideline review question	Yes No Unclear
The review collects the type of studies you consider relevant to the guideline review question	Yes No Unclear

The literature search is sufficiently rigorous to identify all the relevant studies	Yes No Unclear
Study quality is assessed and reported	Yes No Unclear
An adequate description of the methodology used is included, and the methods used are appropriate to the question	Yes No Unclear

APPENDIX 9: METHODOLOGY CHECKLIST TEMPLATE FOR ECONOMIC STUDIES

The methodological quality of each study was evaluated using a NICE checklist (NICE, 2012), reproduced below. For information about how to complete the checklist, see *The Guidelines Manual* [NICE, 2012].

Study identification *Including author, title, reference, year of publication*			
Guideline topic:			**Question no:**
Checklist completed by:			
Section 1: Applicability (relevance to specific guideline review question(s) and the NICE reference case). This checklist should be used first to filter out irrelevant studies.		**Yes/ Partly/ No/Unclear /NA**	**Comments**
1.1	Is the study population appropriate for the guideline?		
1.2	Are the interventions appropriate for the guideline?		
1.3	Is the healthcare system in which the study was conducted sufficiently similar to the current UK NHS context?		
1.4	Are costs measured from the NHS and personal social services (PSS) perspective?		
1.5	Are non-direct health effects on individuals excluded?		
1.6	Are both costs and health effects discounted at an annual rate of 3.5%?		
1.7	Is the value of health effects expressed in terms of quality-adjusted life years (QALYs)?		
1.8	Are changes in health-related quality of life (HRQoL) reported directly from patients and/or carers?		
1.9	Is the valuation of changes in HRQoL (utilities) obtained from a representative sample of the general public?		
1.10	Overall judgement: Directly applicable/Partially applicable/Not applicable There is no need to use section 2 of the checklist if the study is considered 'not applicable'.		

Other comments:

Section 2: Study limitations (the level of methodological quality) This checklist should be used once it has been decided that the study is sufficiently applicable to the context of the clinical guideline.		**Yes/ Partly /No/ Unclear/ NA**	**Comments**
2.1	Does the model structure adequately reflect the nature of the health condition under evaluation?		
2.2	Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?		
2.3	Are all important and relevant health outcomes included?		
2.4	Are the estimates of baseline health outcomes from the best available source?		
2.5	Are the estimates of relative treatment effects from the best available source?		
2.6	Are all important and relevant costs included?		
2.7	Are the estimates of resource use from the best available source?		
2.8	Are the unit costs of resources from the best available source?		
2.9	Is an appropriate incremental analysis presented or can it be calculated from the data?		
2.10	Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?		
2.11	Is there no potential conflict of interest?		
2.12	Overall assessment: Minor limitations/Potentially serious limitations/Very serious limitations		
Other comments:			

APPENDIX 10: RESEARCH RECOMMENDATIONS

The Guideline Development Group has made the following recommendations for research, based on its review of evidence, to improve NICE guidance and patient care in the future.

1. Peer support interventions

What is the clinical and cost effectiveness of peer support interventions in people with psychosis and schizophrenia?

Why this is important

Service users have strongly supported the development of peer support interventions, which have recently proliferated in the UK, but current evidence for these interventions in people with psychotic disorders is not strong and the studies are mainly of very low quality. Moreover the content of the programmes has varied considerably, some using structured interventions, others providing more informal support. There is therefore an urgent need for high-quality evidence in this area. The programme of research would be in several stages. First, there should be development work to establish what specifically service users want from peer support workers, as opposed to what they want from professionals; and what are the conditions for optimal delivery of the intervention? This development work should be co-produced by exploring the views of service users, experienced peer support workers and developers of peer support interventions, and suitable outcome measures should be identified reflecting the aims of peer support. Second, the intervention, delivered as far as possible under the optimal conditions, should be tested in a high-quality trial. Further research should test structured and manualised formats versus unstructured formats (in which service user and peer decide together what to cover in the session). Benefits and adverse effects experienced by peer support workers should also be measured.

2. People who choose not to take antipsychotic medication

What is the clinical and cost effectiveness of psychological intervention alone, compared with treatment as usual, in people with psychosis or schizophrenia who choose not to take antipsychotic medication?

Why this is important

The development of alternative treatment strategies is important for the high proportion of people with psychosis and schizophrenia who choose not to take antipsychotic medication, or discontinue it due to adverse effects or lack of efficacy. There is evidence that psychological interventions (CBT and family intervention) as an adjunct to antipsychotic medication are effective in the treatment of psychosis and schizophrenia and are cost saving. However, there is little evidence for family intervention or CBT alone, without antipsychotic medication.

The programme of research should compare the clinical and cost effectiveness of psychological intervention alone (CBT and/or family intervention) with treatment as usual for people with psychosis or schizophrenia who choose not to take antipsychotic medication, using an adequately powered study with a randomised controlled design. Key outcomes should include symptoms, relapse rates, quality of life, treatment acceptability, social functioning and the cost effectiveness of the interventions.

3. The benefits and risks of discontinuing antipsychotic medication

What are the short- and long-term benefits and risks of guided medication discontinuation and/or reduction in first episode psychosis and can this be achieved without risk of serious relapse?

Why this is important

There is growing concern about the long-term health risks, increased mortality and cortical grey matter loss linked to cumulative neuroleptic exposure in people with psychosis. The majority of young adults discontinue their medication in an unplanned way due to these risks. A Dutch moderately-sized open trial has reported successful discontinuation of medication in 20% of people without serious relapse; at 7-year follow-up there was continuous benefit for guided reduction in terms of side effects, functioning and employment, with no long-term risks. If replicated, this would mark a significant breakthrough in reducing the long-term health risks associated with antipsychotic treatment and improving outcomes.

The programme of research should use an adequately powered, multicentre, double-blind, randomised controlled design to test the benefits, risks and costs of discontinuing or reducing antipsychotic medication among young adults with first episode psychosis who have achieved remission. The primary outcome should be quality of life; secondary outcomes should include side effects, such as metabolic disorders and weight gain, serious relapse, acceptability and user preference.

4. Maintaining the benefits of early intervention in psychosis services after discharge

How can the benefits of early intervention in psychosis services be maintained once service users are discharged after 3 years?

Why this is important

Early intervention in psychosis services deliver evidence-based interventions in a positive, youth-friendly setting, improve outcomes, are cost effective and have high service user acceptability and engagement. Once people are transferred to primary care or community mental health services these gains are diminished. The guideline recommends that trusts consider extending these services. However, the extent to which gains would be maintained and who would benefit most is not known. The successful element of early intervention in psychosis services might be incorporated

into mainstream services for psychosis, but how this would function, and its cost effectiveness, needs to be determined.

The suggested programme of research should use an adequately powered, multi-centre randomised trial comparing extending early intervention in psychosis services (for example, for 2 years) versus providing augmented (step-down) care in community mental health services versus treatment as usual to determine whether the gains of early intervention can be maintained and which service users would benefit most under each condition. The primary outcome should be treatment/service engagement and secondary outcomes should include relapse, readmission, functioning and user preference.

5. Interventions for PTSD symptoms in people with psychosis and schizophrenia

What is the benefit of a CBT-based trauma reprocessing intervention on PTSD symptoms in people with psychosis and schizophrenia?

Why this is important

PTSD symptoms have been documented in approximately one-third of people with psychosis and schizophrenia. PTSD in this context predicts worse mental health outcomes, greater service use, and poorer service and life satisfaction. Two-thirds of the traumatic intrusions, observed in first episode and established psychosis, relate to symptoms of psychosis and its treatment (including detention). One study has demonstrated proof-of-principle in first episode psychosis for trauma reprocessing, focusing on psychosis-related intrusions. Replication of the study will fill a major gap in treatment for this population and may have other benefits on psychotic symptoms and service use.

The suggested programme of research would use an adequately powered, multi-centre randomised trial to test whether a CBT-based trauma reprocessing intervention can reduce PTSD symptoms and related distress in people with psychosis and schizophrenia. The trial should be targeted at those with high levels of PTSD symptoms, particularly traumatic intrusions, following first episode psychosis. The follow-up should be up to 2 years and the intervention should include 'booster' elements and a health economic evaluation.

APPENDIX 11: SCHIZOPHRENIA IN ADULTS (2009) METHODS CHAPTER

3 METHODS USED TO UPDATE THIS GUIDELINE

3.1 OVERVIEW

The update of this guideline drew upon methods outlined by NICE (The Guidelines Manual [NICE, 2007]). A team of healthcare professionals, lay representatives and technical experts known as the Guideline Development Group (GDG), with support from the NCCMH staff, undertook the update of a patient-centred evidence-based guideline. There are six basic steps in the process of updating a guideline:

- define the scope, which sets the parameters of the update and provides a focus and steer for the development work
- update the clinical questions developed for the previous guideline
- develop criteria for updating the literature search and conduct the search
- design validated protocols for systematic review and apply to evidence recovered by search
- synthesise and (meta-) analyse data retrieved, guided by the clinical questions, and produce evidence summaries (for both the clinical and health economic evidence)
- decide if there is sufficient new evidence to change existing recommendations, and develop new recommendations where necessary.

The update will provide recommendations for good practice that are based on the best available evidence of clinical and cost effectiveness. In addition, to ensure a service user and carer focus, the concerns of service users and carers regarding health and social care have been highlighted and addressed by recommendations agreed by the whole GDG.

3.2 THE SCOPE

NICE commissioned the NCCMH to review recent evidence on the management of schizophrenia and to update the existing guideline 'Schizophrenia: full national clinical guideline on core interventions in primary and secondary care' (NCCMH, 2003). The NCCMH developed a scope for the guideline update (see Appendix 1). The scope for the update of the guideline also included updating the NICE technology appraisal on the use of a typical antipsychotics (NICE, 2002), which had been incorporated into the previous guideline.
The purpose of the scope is to:

- provide an overview of what the guideline will include and exclude
- identify the key aspects of care that must be included

- set the boundaries of the development work and provide a clear framework to enable work to stay within the priorities agreed by NICE and the NCC, and the remit from the Department of Health/Welsh Assembly Government
- inform the development of updated clinical questions and search strategy
- inform professionals and the public about expected content of the guideline
- keep the guideline to a reasonable size to ensure that its development can be carried out within the allocated period.

The draft scope was subject to consultation with registered stakeholders over a 4-week period. During the consultation period, the scope was posted on the NICE website (www.nice.org.uk). Comments were invited from stakeholder organisations and Guideline Review Panel (GRP). Further information about the GRP can also be found on the NICE website. The NCCMH and NICE reviewed the scope in light of comments received, and the revised scope was signed off by the GRP.

3.3 THE GUIDELINE DEVELOPMENT GROUP

The GDG consisted of: professionals in psychiatry, psychiatric pharmacy, clinical psychology, nursing, arts therapies and general practice; academic experts in psychiatry and psychology; and service users and a carer. The guideline development process was supported by staff from the NCCMH, who undertook the clinical and health economics literature searches, reviewed and presented the evidence to the GDG, managed the process, and contributed to drafting the guideline.

3.3.1 Guideline Development Group meetings

Fourteen GDG meetings were held between June 2007 and December 2008. During each day-long GDG meeting, clinical questions and clinical and economic evidence were reviewed and assessed in a plenary session, and recommendations formulated. At each meeting, all GDG members declared any potential conflicts of interest, and service user and carer concerns were routinely discussed as part of a standing agenda.

3.3.2 Topic groups

The GDG divided its workload along clinically relevant lines to simplify the guideline development process, and GDG members formed smaller topic groups to undertake guideline work in that area of clinical practice. Four topic groups were formed to cover: (1) pharmacology interventions, (2) psychological and psychosocial interventions, (3) access and engagement with services and (4) primary and physical healthcare. These groups were designed to efficiently manage the large volume of evidence appraisal prior to presenting it to the GDG as a whole. Each topic group was chaired by a GDG member with expert knowledge of the topic area (one of the

health- care professionals). Topic groups refined the clinical questions, refined the clinical definitions of treatment interventions, reviewed and prepared the evidence with the systematic reviewer before presenting it to the GDG as a whole, and helped the GDG to identify further expertise in the topic. Topic group leaders reported the status of the group's work as part of the standing agenda. They also introduced and led the GDG discussion of the evidence review for that topic and assisted the GDG Chair in drafting the section of the guideline relevant to the work of each topic group.

3.3.3 Service users and carers

Individuals with direct experience of services gave an integral service-user focus to the GDG and the guideline. The GDG included two service users and a carer. They contributed as full GDG members to writing the clinical questions, helping to ensure that the evidence addressed their views and preferences, highlighting sensitive issues and terminology relevant to the guideline, and bringing service-user research to the attention of the GDG. In drafting the guideline, they contributed to writing the guide- line's introduction and Chapter 4 and identified recommendations from the service user and carer perspective.

3.3.4 Special advisers

Special advisers, who had specific expertise in one or more aspects of treatment and management relevant to the guideline, or provided expertise in methodological aspects of evidence synthesis, assisted the GDG, commenting on specific aspects of the developing guideline and, where necessary, making presentations to the GDG. Appendix 3 lists those who agreed to act as special advisers.

3.3.5 National and international experts

National and international experts in the area under review were identified through the literature search and through the experience of the GDG members. These experts were contacted to recommend unpublished or soon-to-be published studies to ensure up-to-date evidence was included in the development of the guideline. They informed the group about completed trials at the pre-publication stage, systematic reviews in the process of being published, studies relating to the cost effectiveness of treatment and trial data if the GDG could be provided with full access to the complete trial report. Appendix 5 lists researchers who were contacted.

3.4 CLINICAL QUESTIONS

Clinical questions were used to guide the identification and interrogation of the evidence base relevant to the topic of the guideline. Before the first GDG meeting, an

analytic framework (see Appendix 6) was prepared by NCCMH staff based on the scope and the clinical questions developed for the previous guideline. The framework was used to provide a structure from which the clinical questions were drafted. Both the analytic framework and the draft clinical questions were then discussed by the GDG at the first few meetings and amended as necessary. Where appropriate, the framework and questions were refined once the evidence had been searched and, where necessary, sub-questions were generated. Questions submitted by stakeholders were also discussed by the GDG and included where appropriate. For the purposes of the systematic review of clinical evidence, the questions were categorised as primary or secondary. The review focused on providing evidence to answer the primary questions. The final list of clinical questions can be found in Appendix 6.

For questions about interventions, the PICO (patient, intervention, comparison and outcome) framework was used. This structured approach divides each question into four components: the patients (the population under study), the interventions (what is being done), the comparisons (other main treatment options) and the outcomes (the measures of how effective the interventions have been) (see Table 2).
In some situations, the prognosis of a particular condition is of fundamental importance, over and above its general significance in relation to specific interventions. Areas where this is particularly likely to occur relate to assessment of risk, for example in terms of early intervention. In addition, questions related to issues of service delivery are occasionally specified in the remit from the Department of Health/Welsh Assembly Government. In these cases, appropriate clinical questions were developed to be clear and concise.

Table 2: Features of a well-formulated question on effectiveness intervention –the PICO (patient, intervention, comparison and outcome) guide

Patients/ population	Which patients or population of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?
Intervention	Which intervention, treatment or approach should be used?
Comparison	What is/are the main alternative/s to compare with the intervention?
Outcome	What is really important for the patient? Which outcomes should be considered: intermediate or short-term measures; mortality; morbidity and treatment complications; rates of relapse; late morbidity and readmission; return to work, physical and social functioning and other measures, such as quality of life; general health status; costs?

Table 3: Best study design to answer each type of question

Type of question	Best primary study design

Effectiveness or other impact of an intervention	Randomised controlled trial; other studies that may be considered in the absence of a randomised controlled trial are the following: internally/externally controlled before and after trial, interrupted time-series
Accuracy of information (for example risk factor, test, prediction rule)	Comparing the information against a valid gold standard in a randomised trial or inception cohort study
Rates (of disease, patient experience, rare side effects)	Cohort, registry, cross-sectional study
Costs	Naturalistic prospective cost study

To help facilitate the literature review, a note was made of the best study design type to answer each question. There are four main types of clinical question of relevance to NICE guidelines. These are listed in Table 3. For each type of question, the best primary study design varies, where 'best' is interpreted as 'least likely to give misleading answers to the question'.

However, in all cases, a well-conducted systematic review of the appropriate type of study is always likely to yield a better answer than a single study.
Deciding on the best design type to answer a specific clinical or public health question does not mean that studies of different design types addressing the same question were discarded.

3.5 SYSTEMATIC CLINICAL LITERATURE REVIEW

The aim of the clinical literature review was to systematically identify and synthesise relevant evidence from the literature (updating the existing evidence base where appropriate) to answer the specific clinical questions developed by the GDG. Thus, clinical practice recommendations are evidence based where possible and, if evidence is not available, informal consensus methods are used (see Section 3.5.7) and the need for future research is specified.

3.5.1 Methodology

A stepwise, hierarchical approach was taken for locating and presenting evidence to the GDG. The NCCMH developed this process based on methods set out in The Guidelines Manual (NICE, 2007) and after considering recommendations from a range of other sources. These sources included:

- Clinical Policy and Practice Program of the New South Wales Department of

Health (Australia)

- Clinical Evidence online
- The Cochrane Collaboration

- New Zealand Guidelines Group
- NHS Centre for Reviews and Dissemination
- Oxford Centre for Evidence-Based Medicine
- Oxford Systematic Review Development Programme
- Scottish Intercollegiate Guidelines Network (SIGN)
- United States Agency for Healthcare Research and Quality.

3.5.2 The review process

During the development of the scope, a more extensive search was undertaken for systematic reviews and guidelines published since the previous schizophrenia guide- line. These were used to inform the development of review protocols for each topic group. Review protocols included the relevant clinical question(s), the search strategy, the criteria for assessing the eligibility of studies and any additional assessments (see Appendix 7).

The initial approach taken to locating primary-level studies depended on the type of clinical question and potential availability of evidence. Based on the previous guideline and GDG knowledge of the literature, a decision was made about which questions were best addressed by good practice based on expert opinion, which questions were likely to have a good evidence base and which questions were likely to have little or no directly relevant evidence. Recommendations based on good practice were developed by informal consensus of the GDG. For questions with a good evidence base, the review process depended on the type of key question (see below). For questions that were unlikely to have a good evidence base, a brief descriptive review was initially undertaken by a member of the GDG (see Section 3.5.7).

Searches for evidence were updated between 6 and 8 weeks before the guide- line consultation. After this point, studies were included only if they were judged by the GDG to be exceptional (for example, the evidence was likely to change a recommendation).

The search process for questions concerning interventions

For questions related to interventions, the initial evidence base (or updated evidence base) was formed from well-conducted randomised controlled trials (RCTs) that addressed at least one of the clinical questions. Although there are a number of difficulties with the use of RCTs in the evaluation of interventions in mental health, the RCT remains the most important method for establishing treatment efficacy. For other clinical questions, searches were for the appropriate study design (see above).

Standard mental health related bibliographic databases (that is, the Cumulative Index to Nursing and Allied Health Literature [CINAHL], Cochrane Library, Excerpta Medica Database [EMBASE], Medical Literature Analysis and Retrieval

System Online [MEDLINE] and the Psychological Information Database [PsycINFO]) were used for the initial search for all studies potentially relevant to the guideline. Where the evidence base was large, recent high-quality English- language systematic reviews were used primarily as a source of RCTs (see Appendix 9 for quality criteria used to assess systematic reviews). However, in some circumstances existing data sets were utilised. Where this was the case, data were cross-checked for accuracy before use. New RCTs meeting inclusion criteria set by the GDG were incorporated into the existing reviews and fresh analyses performed.

After the initial search results were scanned liberally to exclude irrelevant papers, the review team used EPPI-Reviewer[1], a tool developed by the Evidence for Policy and Practice Information and Co-ordinating Centre (EPPI-Centre) for storing and analysing data for systematic reviews, to manage both the included and the excluded studies (eligibility criteria were developed after consultation with the GDG). Double checking of all excluded studies was not done routinely, but a selection of abstracts was checked to ensure reliability of the sifting. For questions without good-quality evidence (after the initial search), a decision was made by the GDG about whether to (a) repeat the search using subject-specific databases (for example, the Allied and Alternative Medicine Database [AMED], Educational Resources Information Center [ERIC], OpenSIGLE [System for information on Grey Literature in Europe] or Sociological Abstracts), (b) conduct a new search for lower levels of evidence or (c) adopt a consensus process (see Section 3.5.7).

In addition, searches were made of the reference lists of all eligible systematic reviews and included studies. Known experts in the field (see Appendix 5), based both on the references identified in early steps and on advice from GDG members, were sent letters requesting relevant studies that were in the process of being published[2]. In addition, the tables of contents of appropriate journals were periodically checked for relevant studies.

The search process for questions of prognosis

For questions related to prognosis, the search process was the same as described above, except that the initial evidence base was formed from studies with the most appropriate and reliable design to answer the particular question, that is, for cohort studies of representative patients. In situations where it was not possible to identify a substantial body of appropriately designed studies that directly addressed each clinical question, a consensus process was adopted (see Section 3.5.7).

[1] For further information see: http://eppi.ioe.ac.uk/cms/

[2] 4Unpublished full trial reports were also accepted where sufficient information was available to judge eligibility and quality (see section on unpublished evidence).

Search filters
Search filters developed by the review team consisted of a combination of subject heading and free-text phrases. Specific filters were developed for the guideline topic and, where necessary, for each clinical question. In addition, the review team used filters developed for systematic reviews, RCTs and other appropriate research designs (Appendix 8).

Study selection
All primary-level studies included after the first scan of citations were acquired in full and re-evaluated for eligibility (based on the relevant review protocol) at the time they were being entered into EPPI-Reviewer. Eligible systematic reviews and primary- level studies were critically appraised for methodological quality (see Appendix 9 for the quality checklists, and Appendix 15 for characteristics of each study including quality assessment). The eligibility of each study was confirmed by consensus during topic group meetings.
For some clinical questions, it was necessary to prioritise the evidence with respect to the UK context (that is, external validity). To make this process explicit, the topic groups took into account the following factors when assessing the evidence:

- participant factors (for example, gender, age and ethnicity)
- provider factors (for example, model fidelity, the conditions under which the intervention was performed and the availability of experienced staff to undertake the procedure)
- cultural factors (for example, differences in standard care and differences in the welfare system).

It was the responsibility of each topic group to decide which prioritisation factors were relevant to each clinical question in light of the UK context and then decide how they should modify their recommendations.

Unpublished evidence
The GDG used a number of criteria when deciding whether or not to accept unpublished data. First, the evidence must have been accompanied by a trial report containing sufficient detail to properly assess the quality of the research. Second, where evidence was submitted directly to the GDG, it must have been done so with the understanding that details would be published in the full guideline. However, the GDG recognised that unpublished evidence submitted by investigators might later be retracted by those investigators if the inclusion of such data would jeopardise publication of their research.

3.5.3 Data extraction

Outcome data were extracted from all eligible studies, which met the minimum quality criteria, using Review Manager 4.2.10 (The Nordic Cochrane Centre, 2003) or Review Manager 5 (The Nordic Cochrane Centre, 2008).

For each major area reviewed, the GDG distinguished between outcomes that they considered critical and those that were important but not critical for the purposes of

updating the guideline. Only critical outcomes were initially extracted for data analysis (further details about the critical outcomes can be found in the review protocols in each evidence chapter).

In most circumstances, for a given outcome (continuous and dichotomous), where more than 50% of the number randomised to any group were lost to follow up, the data were excluded from the analysis (except for the outcome 'leaving the study early', in which case, the denominator was the number randomised). Where possible, dichotomous efficacy outcomes were calculated on an intention-to-treat basis (that is, a 'once-randomised-always-analyse' basis). Where there was good evidence that those participants who ceased to engage in the study were likely to have an unfavourable outcome, early withdrawals were included in both the numerator and denominator. Adverse events were entered into Review Manager as reported by the study authors because it was usually not possible to determine whether early withdrawals had an unfavourable outcome. Where there was limited data for a particular review, the 50% rule was not applied. In these circumstances the evidence was downgraded because of the risk of bias.

Where necessary, standard deviations (SDs) were calculated from standard errors, confidence intervals or p-values according to standard formulae (see the Cochrane Reviewers' Handbook 4.2.2 [Alderson et al., 2004]). Data were summarised using the generic inverse variance method using Review Manager.

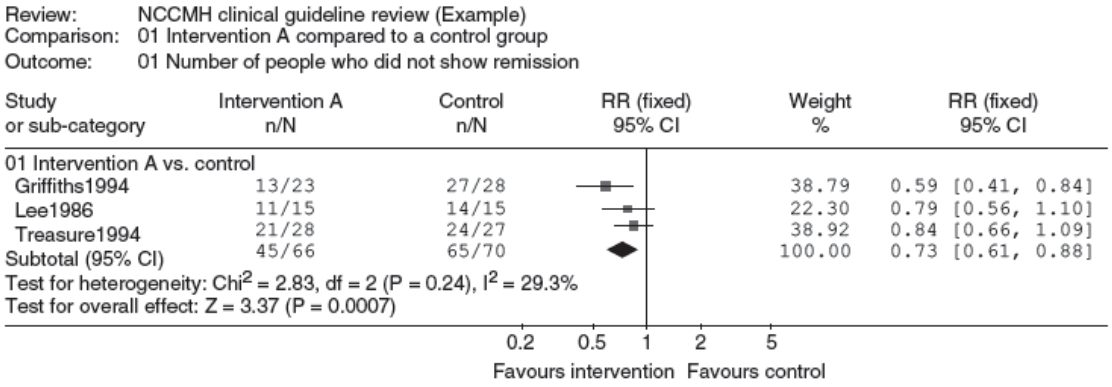
Consultation with another reviewer or members of the GDG was used to over- come difficulties with coding. Data from studies included in existing systematic reviews were extracted independently by one reviewer and cross-checked with the existing data set. Where possible, data extracted by one reviewer were checked by a second reviewer. Disagreements were resolved with discussion. Where consensus could not be reached, a third reviewer or GDG members resolved the disagreement. Masked assessment (that is, blinded to the journal from which the article comes, the authors, the institution and the magnitude of the effect) was not used since it is unclear that doing so reduces bias (Jadad et al., 1996; Berlin, 2001).

3.5.4 Synthesising the evidence

Where possible, meta-analysis was used to synthesise the evidence using Review Manager. If necessary, re-analyses of the data or sub-analyses were used to answer clinical questions not addressed in the original studies or reviews.

Dichotomous outcomes were analysed as relative risks (RR) with the associated 95% confidence interval (CI) (for an example, see Figure 1). A relative risk (also called a risk ratio) is the ratio of the treatment event rate to the control event rate. An RR of 1 indicates no difference between treatment and control. In Figure 1, the overall RR of 0.73 indicates that the event rate (that is, non-remission rate) associated with intervention A is about three quarters of that with the control intervention or, in other words, the relative risk reduction is 27%.

Figure 1: Example of a forest plot displaying dichotomous data

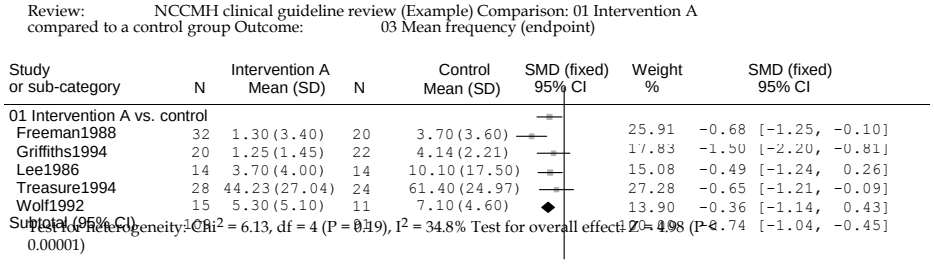


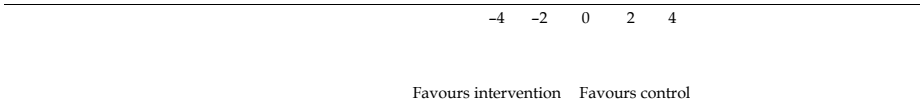
The CI shows with 95% certainty the range within which the true treatment effect should lie and can be used to determine statistical significance. If the CI does not cross the 'line of no effect', the effect is statistically significant.
Continuous outcomes were analysed as weighted mean differences (WMDs) or as a standardised mean difference (SMD) when different measures were used in different studies to estimate the same underlying effect (for an example, see Figure 2). If provided, intention-to-treat data, using a method such as 'last observation carried forward', were preferred over data from completers.

To check for consistency between studies, both the I 2 test of heterogeneity and a visual inspection of the forest plots were used. The I 2 statistic describes the proportion of total variation in study estimates caused by heterogeneity (Higgins & Thompson, 2002). The I 2 statistic was interpreted in the following way:

- >50%: notable heterogeneity (an attempt was made to explain the variation by conducting sub-analyses to examine potential moderators. In addition, studies with effect sizes greater than two SDs from the mean of the remaining studies were excluded using sensitivity analyses. If studies with heterogeneous results were found to be comparable with regard to study and participant characteristics, a random-effects model was used to summarise the results [DerSimonian & Laird,

Figure 2: Example of a forest plot displaying continuous data





1986]. In the random-effects analysis, heterogeneity is accounted for both in the width of CIs and in the estimate of the treatment effect. With decreasing heterogeneity the random-effects approach moves asymptotically towards a fixed-effects model).

- 30 to 50%: moderate heterogeneity (both the chi-squared test of heterogeneity and a visual inspection of the forest plot were used to decide between a fixed and random-effects model).
- <30%: mild heterogeneity (a fixed-effects model was used to synthesise the

results).

3.5.5 Presenting the data to the Guideline Development Group

Study characteristics tables and, where appropriate, forest plots generated with Review Manager were presented to the relevant topic group.

Forest plots

Each forest plot displayed the effect size and CI for each study as well as the overall summary statistic. The graphs were organised so that the display of data in the area to the left of the 'line of no effect' indicated a 'favourable' outcome for the treatment in question.

3.5.6 Forming the clinical summaries and recommendations

After the presentation of evidence, members of the topic group discussed whether there was sufficient evidence to change existing recommendations or drafted new recommendations where necessary. One member of the review team in conjunction with the topic group lead then produced a clinical evidence summary based on the topic group discussion.

3.5.7 Method used to answer a clinical question in the absence of appropriately designed, high-quality research

In the absence of appropriately designed, high-quality research, or where the GDG were of the opinion (on the basis of previous searches or their knowledge of the literature) that there were unlikely to be such evidence, an informal consensus process was adopted. This process focused on those questions that the GDG considered a priority.

Informal consensus

The starting point for the process of informal consensus was that a member of the topic group identified, with help from the systematic reviewer, a narrative review that most directly addressed the clinical question. Where this was not possible, a brief descriptive review of the recent literature was initiated.

This existing narrative review or new review was used as a basis for beginning an iterative process to identify lower levels of evidence relevant to the clinical question and to lead to written statements for the guideline. The process involved a number of steps:

- A description of what is known about the issues concerning the clinical question was written by one of the topic group members.
- Evidence from the existing review or new review was then presented to the GDG and further comments were sought about the evidence and its perceived relevance to the clinical question.
- Based on the feedback from the GDG, additional information was sought and added to the information collected. This might have included studies that did not directly address the clinical question but were thought to contain relevant data.
- If, during the course of preparing the report, a significant body of primary-level studies (of appropriate design to answer the question) were identified, a full systematic review was carried out.
- At this time, possibly subject to further reviews of the evidence, a series of statements that directly addressed the clinical question was developed.
- Following this, on occasion and as deemed appropriate by the development group, the report was sent to appointed experts outside the GDG for peer review and comment. The information from this process was then fed back to the GDG for further discussion of the statements.
- Recommendations were then developed and could also be sent for further external peer review.
- After this final stage of comment, the statements and recommendations were again reviewed and agreed upon by the GDG.

3.6 HEALTH ECONOMICS METHODS

The aim of health economics was to contribute to the guideline's development by providing evidence on the cost effectiveness of interventions for people with schizophrenia covered in the guideline, in areas with likely major resource implications. This was achieved by:

- systematic literature review of existing economic evidence
- economic modelling, where economic evidence was lacking or was considered inadequate to inform decisions.

3.6.1 Key economic issues

Systematic search of the economic literature was undertaken on all areas that were updated since the previous guideline, that is:

- access to and engagement with services, including early intervention services for people with schizophrenia
- pharmacological interventions for people with schizophrenia (excluding rapid tranquillisation)
- psychological interventions for people with schizophrenia.

Moreover, literature on the health-related quality of life of people with schizophrenia was systematically searched to identify studies reporting appropriate utility weights that could be utilised in a cost-utility analysis.

In addition to the systematic review of economic literature, the following economic issues were identified by the GDG in collaboration with the health econo- mist as key priorities for de novo economic modelling in the guideline update:

- cost effectiveness of psychological therapies/psychosocial interventions provided in addition to standard care versus standard care alone; CBT and family intervention were examined
- cost effectiveness of antipsychotic medications for people with schizophrenia that is in remission.

The rest of this section describes the methods adopted in the systematic literature review of economic studies undertaken for this guideline update. The respective methodology adopted in the previous guideline is provided in Appendix 17. Methods employed in *de novo* economic modelling carried out for this guideline update are described in the respective sections of the guideline.

3.6.2 Search strategy

For the systematic review of economic evidence the standard mental-health-related bibliographic databases (EMBASE, MEDLINE, CINAHL and PsycINFO) were searched. For these databases, a health economics search filter adapted from the Centre for Reviews and Dissemination at the University of York was used in combination with a general search strategy for schizophrenia. Additional searches were performed in specific health economics databases (economic evaluation database [NHS EED], Office of Health Economics – Health Economic Evaluations Database [OHE HEED]), as well as in the Health Technology Assessment (HTA) database. For the HTA and NHS EED databases, the general strategy for schizophrenia was used. OHE HEED was searched using a shorter, database-specific strategy. Initial searches were performed in June 2007. The searches were updated regularly, with the final search performed in November 2008. Details of the search strategy for economic studies on interventions for people with schizophrenia are provided in Appendix 10.

In parallel to searches of electronic databases, reference lists of eligible studies and relevant reviews were searched by hand. Studies included in the clinical evidence review were also screened for economic evidence.

The systematic search of the literature identified 10,425 references in total (stage 1). Publications that were clearly not relevant were first excluded (stage 2). The abstracts of all potentially relevant publications were then assessed against a set of selection criteria by the health economist (stage 3). Full texts of the studies potentially meeting the selection criteria (including those for which eligibility was not clear from the abstract) were obtained (stage 4). At this stage, 154 studies had been selected. Studies that did not meet the inclusion criteria, were duplicates, were secondary publications to a previous study, or had been updated in more recent publications were subsequently excluded (stage 5). Finally, 36 papers eligible for inclusion were assessed for internal validity and critically appraised (stage 6). The quality assessment was based on the checklists used by the British Medical Journal to assist referees in appraising full and partial economic analyses (Drummond & Jefferson, 1996) (Appendix 11).

3.6.3 Selection criteria

The following inclusion criteria were applied to select studies identified by the economic searches for further analysis:

- Only papers published in English language were considered.
- Studies published from 1996 onwards were included. This date restriction was imposed to obtain data relevant to current healthcare settings and costs.
- Only studies from Organisation for Economic Co-operation and Development countries were included, as the aim of the review was to identify economic information transferable to the UK context.
- Selection criteria based on types of clinical conditions and patients were identical to the clinical literature review.
- Studies were included provided that sufficient details regarding methods and results were available to enable the methodological quality of the study to be assessed, and provided that the study's data and results were extractable. Poster presentations and abstracts were excluded from the review.
- Full economic evaluations that compared two or more relevant options and considered both costs and consequences (that is, cost-consequence analysis, cost-effectiveness analysis, cost-utility analysis or cost-benefit analysis) were included in the review.
- Studies were included if they used clinical effectiveness data from an RCT, a prospective cohort study, or a systematic review and meta-analysis of clinical studies. Studies were excluded if they had a mirror-image or other retrospective design, or if they utilised efficacy data that were based mainly on assumptions.
- Studies were included only if pharmacological and psychological treatments were clearly described; antipsychotic medications had to be specifically defined so that it was clear which antipsychotic drugs were being compared, the dose and route of administration used, and the duration of treatment. In particular, evaluations in which two or more antipsychotic drugs were treated as a class, and in which comparisons between specific antipsychotic drugs were not provided, were excluded from further consideration. An exception was made in the case of the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS, Lewis et

al., 2006a, 2006b; Jones et al., 2006), two large effectiveness trials conducted in the UK that compared SGAs with FGAs and clozapine with SGAs; it was decided to describe these studies in the systematic economic literature review because their findings and conclusions, although non-informative on the cost effectiveness of specific antipsychotic drugs, were deemed by the GDG to be relevant and useful in decision-making.

- Studies comparing pharmacological interventions with no treatment/placebo were not considered in the review.

- Studies that adopted a very narrow perspective, ignoring major categories of costs to the NHS, were excluded; for example studies were not considered to be informative if they exclusively estimated drug acquisition, psychological intervention or hospitalisation costs.
- Cost effectiveness analyses were included only if their measure of outcome was considered relevant and was recorded in the guideline systematic literature review of clinical evidence; cost utility analyses were included if their measure of outcome was a validated measure, such as quality adjusted life years (QALYs) or DALYs. Health-related quality of life studies were included if they reported preference-based utility weights appropriate to use in a cost utility analysis.

3.6.4 Data extraction

Data were extracted by the health economist using a standard economic data extraction form (Appendix 12).

3.6.5 Presentation of economic evidence

The economic evidence identified by the health economics systematic review is summarised in the respective chapters of the guideline, following presentation of the clinical evidence. The references to included studies and to those potentially eligible that were excluded at stage 5 of the review, as well as the evidence tables with the characteristics and results of economic studies included in the review, are provided in Appendix 14. Methods and results of economic modelling on psychological therapies/ psychosocial interventions are reported in the respective economic sections of Chapter 8. Methods and results of economic modelling on pharmacological interventions aiming at prevention of relapse in people with schizophrenia are presented in Chapter 7.

3.7 STAKEHOLDER CONTRIBUTIONS

Professionals, service users and companies have contributed to and commented on the guideline at key stages in its development. Stakeholders for this guideline include:

- service user/carer stakeholders: the national service user and carer organisations that represent people whose care is described in this guideline
- professional stakeholders: the national organisations that represent healthcare professionals who are providing services to service users
- commercial stakeholders: the companies that manufacture medicines used in the treatment of schizophrenia
- Primary Care Trusts
- Department of Health and Welsh Assembly Government.

Stakeholders have been involved in the guideline's development at the following points:

- commenting on the initial scope of the guideline and attending a briefing meeting held by NICE
- contributing possible clinical questions and lists of evidence to the GDG
- commenting on the draft of the guideline.

3.8 VALIDATION OF THE GUIDELINE

Registered stakeholders had an opportunity to comment on the draft guideline, which was posted on the NICE website during the consultation period. Following the consultation, all comments from stakeholders and others were responded to, and the guideline updated as appropriate. The GRP also reviewed the guideline and checked that stakeholders' comments had been addressed.

Following the consultation period, the GDG finalised the recommendations and the NCCMH produced the final documents. These were then submitted to NICE. NICE then formally approved the guideline and issued its guidance to the NHS in England and Wales.

APPENDIX 12: CHANGES MADE TO THE 2009 GUIDELINE

Chapter number in the 2009 guideline	Title of the chapter in the 2009 guideline	Changes made in the 2014 update
1.	Preface	This has been replaced to explain the changes made in this update, as detailed in the first two paragraphs: The previous 2009 guideline updated most areas of the first (2002) guideline, except for some service-level interventions and the use of rapid tranquillisation. This second update (2014) reviews the areas of service-level interventions that were not updated in the 2009 guideline such as peer support and self-management interventions, vocational rehabilitation and teams and service-level interventions that encompass community-based interventions and alternatives to acute admission. In addition, the second update provides a new review of carers' experience and physical healthcare. Given the change to the title (*Psychosis and Schizophrenia* rather than *Schizophrenia*) this second update also incorporates a review on at risk mental states for psychosis and schizophrenia, and in the updated sections of the guideline, including the recommendations, the term 'psychosis and schizophrenia' is used rather than 'schizophrenia'. The chapter on experience of care in the 2009 guideline has been removed because it was updated by *Service User Experience in Adult Mental Health* (NICE clinical guidance 136, NICE 2011). For a full version of the 2009 guideline see Appendix 27. See Appendix 1 for more details on the scope of this second update. Sections of the guideline where the evidence has not been updated are marked by asterisks (**_**). Sections from the first guideline in

		2002 that have not been updated are marked by asterisks and the date (**2002**-**2002**).
2.	Schizophrenia	This has been replaced and retitled 'Psychosis and schizophrenia' to reflect the new guideline title. The GDG used the 2009 guideline introduction as a starting point, but updated it in line with recent policy and service developments. The introduction also reflects the updated guideline (2014) by including new sections on physical health, inequalities, employment and psychosis.
3.	Methods used to update this guideline	This chapter has been replaced to reflect the most recent guideline methodology. For the 2009 Methods chapter, please see Appendix 11.
4.	Experience of care	This chapter has been removed because service user experience of the treatment and management of psychosis and schizophrenia in adult mental health services has been comprehensively reviewed in other NICE guidance (*Service User Experience in Adult Mental Health* (NICE clinical guidance 136; NICE, 2011)). As a result a new review of carers' experience was undertaken and the introduction states the importance of reading this update in conjunction with *Service User Experience in Adult Mental Health*.
5.	Access and engagement	This chapter has been partially updated, and has been renumbered as Chapter 6 of the 2014 update. The first paragraph has been changed to reflect the amendments made to the chapter: "The review of early intervention has been updated and is now included in chapter 12, Teams and service level interventions. The recommendations from the 2009 guideline for other sections remain but due to the change in population addressed by this guideline the recommendations have been changed to reflect this to say "people with psychosis or

		schizophrenia". Sections of the guideline where the evidence has not be updated since 2009 are marked by asterisks (**_**)." Due to the publication of *Service User Experience in Adult Mental Health* guidance, one recommendation has been removed from the 2009 guideline: 5.3.10.2 When working with people with schizophrenia and their carers: • avoid using clinical language, or keep it to a minimum • ensure that comprehensive written information is available in the appropriate language and in audio format if possible • provide and work proficiently with interpreters if needed • offer a list of local education providers who can provide English language teaching for people who have difficulties speaking and understanding English.
6.	Pharmacological interventions	This chapter has been updated, and has been renumbered as Chapter 10 of the 2014 update. Most sections remain unchanged from the 2009 guideline; however some of the recommendations have been updated to bring them in line with the recommendations from *Psychosis and Schizophrenia in Children and Young People*. This was considered necessary to avoid discrepancies between the child and adult guidelines, particularly regarding early intervention. Consequently new sections have been added to the evidence to recommendations section. In addition some recommendations from the 2009 guideline have been amended to improve the wording and structure with no important changes to the context and meaning of the recommendation. Sections of the guideline where the evidence has not been updated since 2002 are marked as **2002**_**2002** and where the evidence has not be updated since 2009, marked by asterisks (**_**).

		Where in the asterisks (**_**) the sentence relates to the previous guideline, reference is being made to the 2002 guideline; and where the sentence mentions the updated guideline reference is being made to the 2009 guideline.
7.	Economic model of pharmacological interventions	This chapter has not been updated.
8.	Psychological therapy interventions	This chapter has been updated, and renumbered as Chapter 9 in the 2014 update. Most sections remain unchanged from the 2009 guideline; however some of the recommendations have been updated to bring them in line with the recommendations from *Psychosis and Schizophrenia in Children and Young People*. This was considered necessary to avoid discrepancies between the child and adult guidelines, particularly regarding early intervention. Consequently new sections have been added to the evidence to recommendations section. In addition some recommendations from the 2009 guideline have been amended to improve the wording and structure with no important changes to the context and meaning of the recommendation. In addition, a new review was conducted for the psychological management of trauma (section 1.12) because of the inclusion of people with psychosis for this update and the association of trauma with the development of psychosis. Sections of the guideline where the evidence has not been updated since 2002 are marked as **2002**_**2002** and where the evidence has not be updated since 2009, marked by asterisks (**_**).Where in the asterisks (**_**) the sentence relates to the previous guideline, reference is being made to the 2002 guideline; and where the sentence mentions the updated guideline reference is being made to the 2009 guideline.

9.	Service level interventions	This chapter has been entirely replaced by chapter 12, Teams and service-level interventions, in the 2014 update. This chapter fully updates the review of teams and service-level interventions (developed as part of 'community care' in different parts of the world, as well as those specifically developed in the UK) in the first (2002) guideline and the previous (2009) guideline. The GDG recognised that much of the research in this area has followed changes in practice, often led by policy initiatives to move from hospital to community care, with mental health service providers developing different, previously untested, service configurations in the community as an alternative to relatively costly inpatient settings. Sections of the guideline where the narrative has not been updated since 2002 are marked as **2002**_**2002** and where the evidence has not be updated since 2009, marked by asterisks (**_**).Where in the asterisks (**_**) the sentence relates to the previous guideline, reference is being made to the 2002 guideline, unless otherwise specified; and where the sentence mentions the updated guideline reference is being made to the 2009 guideline.
10.	Summary of recommendations	This chapter has been replaced and renumbered as chapter 14, to reflect the most recent recommendations in the 2014 update. This chapter is not included in the draft for consultation, but will be added for the final draft once the recommendations have been finalised.
	Appendix 1: Scope for the development of the clinical guideline	This has been replaced.
	Appendix 2: Declarations of interests by GDG	This has been replaced.

	members	
	Appendix 3: Special advisers to the Guideline Development Group	This has been replaced.
	Appendix 4: Stakeholders and experts who submitted comments in response to the consultation draft of the guideline	This has been replaced.
	Appendix 5: Researchers contacted to request information about unpublished or soon-to-be published studies	This has been replaced.
	Appendix 6: Analytic framework and clinical questions	This has been replaced.
	Appendix 7: Clinical review protocol template	This has been replaced.
	Appendix 8: Search strategies for the identification of clinical studies	This has been replaced.

	Appendix 9: Quality checklists for clinical studies and reviews	This has been replaced.
	Appendix 10: Search strategies for the identification of health economics evidence	Please see Appendix 24 of the 2014 update
	Appendix 11: Quality checklist for economic studies	This has been replaced
	Appendix 12: Data extraction form for economic studies	This has been replaced
	Appendix 13: Winbugs codes used for mixed treatment comparisons in the economic model of pharmacological treatments for relapse prevention	Please see Appendix 25 of the 2014 update
	Appendix 14: Evidence tables for economic studies	Please see Appendix 25 of the 2014 update
	Appendix 15: Study	Please see Appendix 22 of the 2014 update

	characteristics tables	
	Appendix 16: Clinical evidence forest plots and/or data tables	Please see Appendix 23 of the 2014 update
	Appendix 17: Previous guideline methods chapter	This has been replaced

To view the 2009 Schizophrenia guideline and the related appendices please see Appendix 26 in the 2014 update.