1 APPENDICES

APPENDIX 1: SCOPE FOR THE DEVELOPMENT OF THE CLINICAL GUIDELINE

1 GUIDELINE TITLE

Self-harm: the longer term management of self-harm

1.1 Short title

Self-harm (longer term management)

2 THE REMIT

The Department of Health has asked NICE: 'To prepare a clinical guideline on the management of self-harm (intentional self-poisoning or self-injury, irrespective of the apparent purpose of the act) to include the role of mental health professionals in ensuring service users who have self-harmed receive appropriate treatment for underlying problems that may have led to the act of self-harm.' It will cover the longer term management of self-harm in a variety of settings.
This guideline follows on from 'Self-harm: The short-term physical and psychological management and secondary prevention of self-harm in primary and secondary care' (NICE clinical guideline 16).

3 CLINICAL NEED FOR THE GUIDELINE

3.1 Epidemiology

The prevalence of self-harm is difficult to estimate. A national interview survey in 1999 suggested between 4.6% and 6.6% of people in the UK have self-harmed. A more recent international survey of young people aged 15–16 found the prevalence of self-harm (in the past year) in the UK was 3.2% in boys and 11.1% in girls. The lifetime prevalence for self-harm in the UK was 4.8% in boys and 16.7% in girls.

a. A survey of general hospitals in Oxford, Manchester and Leeds found 7344 people presented with a total of 10,498 episodes of self-harm. Most episodes (80%) were due to self-poisoning and the rest to self-injury (mainly self-cutting). Although most research to date has been hospital-based, it is likely that many self-harm episodes do not come to the attention of health services.
b. A recent systematic review in the UK found that there was a higher prevalence of self-harm in South Asian women than in either South Asian men or white women.

3.2 Current practice

c. Self-harm is usually managed in secondary care. This includes hospital medical care and mental health services. About half of the people who

present to an accident and emergency (A&E) department after self-harming are assessed by a mental health professional. Treatments include psychosocial interventions, pharmacological interventions and harm minimisation.

d. People who self-harm often also have contact with primary care. About half of the people who attend an emergency department after self-harming will have visited their GP in the previous month. A similar proportion will visit their GP within 2 months of attending an A&E department after self-harming.

4 THE GUIDELINE

The guideline development process is described in detail on the NICE website (see section 6, 'Further information').

This scope defines what the guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health.

The areas that will be addressed by the guideline are described in the following sections.

4.1 Population

4.1.1 Groups that will be covered

a. All people aged 8 years or older who self-harm.

4.1.2 Groups that will not be covered

a. Children younger than 8 years.

b. People with a neurodevelopmental disorder with repetitive stereotypical self-injurious behaviour (SIB), for example head-banging in people with a significant learning disability.

4.2 Healthcare setting

a. Care received in primary, secondary, tertiary and community healthcare settings from healthcare professionals who have direct contact with people who self-harm, and who make decisions about risk assessment, needs assessment, treatment and management of care for people who self-harm.

b. The guideline will not provide specific recommendations for A&E departments, paramedic services, prison medical services, the police and those who work in the criminal justice, social care and education sectors, but the guideline will be relevant to their work.

4.3 Clinical management

4.3.1 Key clinical issues that will be covered

a. Medium and longer term care management of people who self-harm.

b. Ongoing psychosocial assessment for the longer term management of people who have self-harmed. This will include an assessment of needs and risk and how these are integrated.
c. Psychosocial interventions for the specific treatment of self-harm compared with control groups and other active interventions. For example, but not exclusively, self-help, problem-solving therapy, mentalisation-based treatment, cognitive behavioural therapy, dialectical behaviour therapy, cognitive analytic therapy, psychodynamic psychotherapy and family therapy.
d. Pharmacological interventions for the specific treatment of self-harm compared with control groups and psychological interventions. For example, antidepressants, anxiolytics and antipsychotics when used as a specific treatment for self-harm.
e. Safe prescribing for people with a history of self-harm.
f. Treatment of groups who may have specific care needs. For example, those from black and minority ethnic groups, people who self-injure, young people and older adults.
g. Harm minimisation and other strategies aimed at reducing the risks and/or harm associated with self-harm. For example, advice on safer cutting, distraction techniques and exploring alternatives to self-harm.
h. Possible adverse effects associated with treating self-harm.
i. Training for healthcare professionals treating people who self-harm.
j. When to refer to other NICE guidelines for the treatment and management of any accompanying or underlying mental health problems.

4.3.2 Clinical issues that will not be covered

a. Acute physical, psychiatric and psychological care of people who have just self-harmed. For the immediate care of people who have self-harmed, please see 'Self-harm: The short-term physical and psychological management and secondary prevention of self-harm in primary and secondary care' (NICE clinical guideline 16).
b. The treatment and management of any mental health problem or substance use disorder that may accompany, underlie or be associated with self-harm. However, the guideline will refer to other relevant NICE guidance (see section 5.1.2).
c. Longer-term management of the physical consequences of self-harm, such as reconstructive surgery, pain management and infection arising from injuries.

4.4 Main outcomes

d. Self-harm and self-harm repetition (for example, self-poisoning or self-cutting).
e. Suicide.
f. Quality of life.
g. Service user determined outcomes.

h. Secondary outcomes such as social and psychological functioning, other causes of mortality, and resource use.

4.5 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 'The guidelines manual' (see 'Further information').

4.6 Status

4.6.1 Scope

This is the final scope.

4.6.2 Timing

The development of the guideline recommendations will begin in November 2009.

5 RELATED NICE GUIDANCE

5.1 Published guidance

5.1.1 NICE guidance to be updated

When reviewing the evidence for this guideline a need maybe identified to update the section on Psychological, pharmacological and psychosocial interventions for the management of self-harm in Self-harm: NICE clinical guideline 16 (2004). Available from www.nice.org.uk/CG16

5.1.2 Other related NICE guidance

- Schizophrenia (update). NICE clinical guideline 82 (2009). Available from www.nice.org.uk/CG82
- Borderline personality disorder. NICE clinical guideline 78 (2009). Available from www.nice.org.uk/CG78
- Antisocial personality disorder. NICE clinical guideline 77 (2009). Available from www.nice.org.uk/CG77
- Bipolar disorder. NICE clinical guideline 38 (2006). Available from www.nice.org.uk/CG38
- Obsessive compulsive disorder (OCD) and body dismorphic disorder (BDD). NICE clinical guideline 31 (2005). Available from www.nice.org.uk/CG31
- Depression in children and young people. NICE clinical guideline 28 (2005). Available from www.nice.org.uk/CG28

- Post-traumatic stress disorder. NICE clinical guideline 26 (2005). www.nice.org.uk/CG26
- Violence. NICE clinical guideline 25 (2005). Available from www.nice.org.uk/CG25
- Depression (amended). NICE clinical guideline 23 (amended 2007). Available from www.nice.org.uk/CG23
- Anxiety (amended). NICE clinical guideline 22 (amended 2007). Available from www.nice.org.uk/CG22
- Eating disorders. NICE clinical guideline 9 (2004). Available from www.nice.org.uk/CG9

5.1.3 Guidance under development

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

- Depression in adults (update). NICE clinical guideline. Publication expected October 2009.
- Depression in adults with a chronic physical health problem. NICE clinical guideline. Publication expected October 2009.

6 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'.

These are available from the NICE website (www.nice.org.uk/guidelinesmanual). Information on the progress of the guideline will also be available from the NICE website (www.nice.org.uk).

APPENDIX 2: DECLARATIONS OF INTERESTS BY GDG MEMBERS

With a range of practical experience relevant to the treatment and management of psychosis in conjunction with substance misuse in the GDG, members were appointed because of their understanding and expertise in healthcare for people with psychosis and substance misuse and support for their families/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 and substance misuse and their families/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 and substance misuse 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

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 individuals with psychosis and substance misuse problems, holding office in a professional organisation or advocacy group with a direct interest in psychosis and substance misuse, other reputational risks relevant to psychosis and substance misuse.

Guideline Development Group - Declarations of interest	
Professor Navneet Kapur - Chair, Guideline Development Group	
Employment	Professor of Psychiatry and Population Health (University of Manchester) Honorary Consultant Psychiatrist (Manchester Mental Health and Social Care Trust)
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	I am an academic and researcher in the field of suicidal behaviour. I am currently an investigator on several large research grants provided by the Department of Health, the National Patient Safety Agency, and the National Institute of Health Research. As part of my work, I apply for research funding from government and charitable organizations.
Personal non-pecuniary interest	I am an academic and researcher in the field of suicidal behaviour. I have published and presented widely in this area, expressing views on a number of diverse issues related to self-harm service provision.
Professor Tim Kendall - Facilitator	
Employment	Director, NCCMH Medical Director, Sheffield Health and Social Care Trust Consultant Adult Psychiatrist Visiting Professor, Research Department of Clinical, Educational and Health Psychology, University College London
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	Grant holder for £1.44 million per year (approx) from NICE for guidelines work. Work with NICE International.

	Undertake some research into mental health, and the mental health workforce for DH, Royal College of Psychiatrists and the academy of medical royal colleges.
Personal non-pecuniary interest	None
Mr Gareth Allen	
Employment	Service User/Carer representative
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Mr Simon Baston	
Employment	Lead Nurse Liaison Psychiatry, Sheffield Health and Social Care NHS Foundation Trust
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Mr Andrew Briggs	
Employment	Consultant Child and Adolescent Psychotherapist, Kent & Medway NHS and Social Care Partnership Trust
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Professor Stephen Briggs	
Employment	Consultant Social Worker, Tavistock And Portman NHS Foundation Trust Professor Of Social Work, University Of East London
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	Co-editor of a book, "Relating to self-harm and suicide; psychoanalytic perspectives on practice, theory and prevention" (published by Routledge, 2008)
Personal non-pecuniary	Clinician in a mental health service for young

interest	people and deliver a 10 week training on working with suicidal and self harming young people. Have undertaken research and written on suicidal and self-harming young people, evaluated a respite centre (Maytree) and currently lead on a research project on self-harm in an emergency department.
Ms Julia Britton	
Employment	Child and Adolescent Psychotherapist and Head of Services, Open Door Young People's Consultation Service
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Mr Anthony Cox	
Employment	PAPYRUS – Prevention of Young Suicide Service User/Carer representative
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	Coordinator for PAPYRUS Prevention of Young Suicide, a national charity which operates a telephone helpline and works to improve services for young people who may self-harm or attempt suicide. We give support and practical advice to young people worried about themselves or to anyone concerned about a young person they know.
Dr Jonathan Evans	
Employment	Consultant Senior Lecturer, University of Bristol
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Dr Paul Gill	
Employment	Consultant in Liaison Psychiatry, Sheffield Health and Social Care Chair, Faculty of Liaison Psychiatry, Royal

	College of Psychiatrists
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Ms Kate Hunt	
Employment	Lead Professional Consultant Clinical Psychologist- Acute & Crisis Services, Sussex Partnership NHS Foundation Trust
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	Led an audit of levels of self-harm within the Women's Secure & Forensic Services which led me to believe that the positive risk taking approach we used pointed to it being an effective intervention in reducing the frequency and severity of self-harming behaviours. We are planning to publish the results of this audit. However, this approach is recommended in the Mainstreaming Gender & Women's Mental Health Implementation Guidance (2003).
Dr Suzanne Kearney	
Employment	GP Registrar
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Professor Rory O'Connor	
Employment	Professor of Psychology, University of Stirling
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Mr Richard Pacitti	
Employment	Chief Executive, Mind in Croydon

	Service User/Carer representative
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Dr Michaela Swales	
Employment	Consultant Clinical Psychologist, North Wales Adolescent Service & Senior Lecturer, School of Psychology, Bangor University
Personal pecuniary interest	Under contract to write a book about problem-solving in the context of Dialectical Behaviour Therapy.
Personal family interest	My husband is the managing director of, and major share holder in, Integral Business Support Ltd, a company that is the sole UK provider of training in Dialectical Behaviour Therapy (DBT) a treatment considered by the self-harm guideline.
Non-personal pecuniary interest	Director of the British Isles Training Team that provides training in DBT to mental health professionals and healthcare organisations throughout the UK and Eire. I fulfil this role as part of my University appointment within the School of Psychology, University of Wales, Bangor. The School of Psychology receives the income from my training in Dialectical Behaviour Therapy. This income funds my secretary at the University, training for clinicians in my local NHS Trust (North Wales NHS Trust) and at times part-funds a psychology assistant post in the clinical service in which I am employed (also North Wales NHS Trust). The School of Psychology was also in receipt of a grant from the ESRC, under the Knowledge Transfer Programme (KTP), to further develop training in DBT and increase dissemination of the treatment. The grant was awarded to the School of Psychology working jointly with Integral Business Support Ltd (see section above on Personal Family Interests). The grant from the ESRC was worth £104, 707 over three years (ended September 2010). The

	company partner will contributed £50 760 to the project over the three year period. I have written a book on DBT from which I will receive royalties.
Personal non-pecuniary interest	Director of the British Isles DBT Training Team which is responsible for delivering all training in DBT in the UK and is in possession of a license to deliver the training from the American Training Company, BTech LLC. I regularly present at conferences and deliver training in DBT.
Dr Alison Wood	
Employment	Consultant in Adolescent Psychiatry, Cheshire and Mersey Regional Tier 4 Adolescent Service
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
NCCMH team	
Mr Benedict Anigbogu	
Employment	Health Economist, NCCMH (from October 2010)
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Ms Henna Bhatti	
Employment	Research Assistant, NCCMH
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Ms Melissa Chan	
Employment	Systematic Reviewer, NCCMH
Personal pecuniary interest	None
Personal family interest	None

Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Mr Matthew Dyer	
Employment	Health Economist, NCCMH (until September 2010)
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Ms Naomi Glover	
Employment	Research Assistant, NCCMH
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Ms Marie Halton	
Employment	Research Assistant, NCCMH
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Ms Katherine Leggett	
Employment	Project Manager, NCCMH
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Mr Nick Meader	
Employment	Systematic Reviewer, NCCMH
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None

Ms Sarah Stockton	
Employment	Senior Information Scientist, NCCMH
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Dr Clare Taylor	
Employment	Editor, NCCMH
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None

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APPENDIX 3: SPECIAL ADVISORS TO THE GUIDELINE DEVELOPMENT GROUP

Professor Richard Jones, Consultant, Morgan Cole LLP

Professor Keith Hawton, Professor of Psychiatry, Oxford University/ Consultant Psychiatrist, Oxfordshire and Buckinghamshire Mental Health NHS Foundation Trust

APPENDIX 4: STAKEHOLDERS WHO RESPONDED TO EARLY REQUESTS FOR EVIDENCE

None

APPENDIX 5: STAKEHOLDERS AND EXPERTS WHO SUBMITTED COMMENTS IN RESPONSE TO THE CONSULTATION DRAFT OF THE GUIDELINE

Stakeholders

To be inserted after consultation

Experts

To be inserted after consultation

APPENDIX 6: RESEARCHERS CONTACTED TO REQUEST INFORMATION ABOUT UNPUBLISHED OR SOON-TO-BE PUBLISHED STUDIES

Ms Cheryl Hunter, Post-Graduate, The University of Manchester.

Ms Kerry Gutridge, Research Associate, Bristol University.

Professor Keith Hawton, Consultant Psychiatrist with Oxfordshire and Buckinghamshire Mental Health NHS Foundation Trust.

Ms Sue Waterhouse, National Deputy Equality Lead, National Mental Health Development Unit.

Dr Agnes Hultén, National Swedish and Stockholm County Centre for Suicide Research and Prevention of Mental Ill-health, Stockholm, Sweden,

Dr Prathiba Chitsabesan, Lead Consultant, Child Psychiatrist for Stockport CAMHS.

Professor Sunita Stewart, Department of Psychiatry, UT Southwestern Medical Center, Dallas.

Professor Ian Colman, Assistant Professor, School of Public Health, University of Alberta.

Dr Mari A Bjornaas, Department of Acute Medicine, Oslo University Hospital, Norway.

Dr Alison Wood, Consultant in Adolescent Psychiatry, Cheshire and Mersey Regional Tier 4 Adolescent Service.

APPENDIX 7: ANALYTIC FRAMEWORK AND CLINICAL QUESTIONS

For the following clinical questions, separate analyses will be conducted (where data is available) for groups identified in the scope that have specific care needs:

Young people and older adults
BME groups

1. **Assessments**

1.1. For people who self-harm, does formal risk assessment, needs assessment and psychosocial assessment improve outcomes?

(Note: Impact of setting/organizational context and content of assessment to be taken into account if data is available)

1.2. What are the risk and protective factors (internal and external) amongst people who self harm that predict outcomes (eg. Suicide, non-fatal repetition, other psychological outcomes)?

2. **Psychosocial interventions**

2.1. For people who self-harm, do psychosocial interventions (compared with no treatment or other interventions) improve outcomes? What are the associated adverse effects?

- Interventions: Problem-solving, interpersonal therapy, cognitive behavioural therapy, peer support groups, self help, computer-based interventions, dialectical behaviour therapy, counselling, psychodynamic interventions, family interventions, group therapy, postcards, assertive outreach, multi-systemic therapy, respite care, crisis management (refer to BPD guideline)

2.2. For people who self-harm, do psychosocial interventions in combination with pharmacological interventions (compared with psychosocial or pharmacological interventions alone) improve outcomes? What are the associated adverse effects?

3. **Pharmacological Interventions**

3.1. For people who self-harm, do drug treatments improve outcomes? What are the associated adverse effects?

- Interventions: Antidepressants, antipsychotics, lithium, anticonvulsants (e.g. valproate, carbamazepine, lamotrigine), benzodiazepines, analgesics

3.2. For people who self-harm, what are the key principles underlying safer prescribing?

Consider:

- prescribing frequency – weekly, monthly
- toxicity of drug

4. Self management and Harm minimisation

4.1. For people who self-harm, does the provision of self management and/or harm minimisation strategies, compared with no treatment or treatment as usual, improve outcomes?

Interventions include: replacement therapy, positive emotion technique

5. Training

5.1. Does the provision of staff training (knowledge, skills based) improve outcomes (eg. Staff attitudes, user satisfaction, user engagement with services)?

Note: Impact of setting and content of training to be taken into account if data is available

1 APPENDIX 8: REVIEW PROTOCOLS

2 Appendix 8A: Risk and needs assessment

Topic	[Risk and needs assessment]
Review question(s)	Q#1.1 For people who self-harm, does formal risk assessment, needs assessment and psychosocial assessment improve outcomes? (Note: Impact of setting/organizational context and content of assessment to be taken into account if data available)
Sub-question(s)	Are self-harm or suicide prediction scales clinically useful in predicting a repetition of self harm?
Chapter	5 – Psychosocial assessment
Sub-section	Section 5.3 Risk assessment scales Section 5.4 Needs assessment Section 5.5 Psychosocial assessment
Topic Group	Jonathan Evans (Editor) Rory O'Connor/ Kate Hunt/ Simon Baston/ Suzanne Kearney/ Michaela Swales
Sub-section lead	Jonathan Evans and Rory O'Connor
Objectives	See sub-question
Criteria for considering studies for the review	
• Intervention	N/A
• Comparator	N/A
• Types of participants	People who experience self-harm (or suicide ideation, where the study clearly reports a history of self-harm). This includes all types of self-harm, irrespective of motive.
• Critical outcomes	Prediction of repeated self-harm or suicide measured by sensitivity and specificity values.
• Important, but not critical outcomes	N/A
• Other outcomes	N/A
• Study design	Prospective cohort or case control studies
• Include unpublished data?	No
• Restriction by date?	No
• Dosage	N/A
• Minimum sample size	N/A
• Study setting	Inpatient and outpatient (as long as participants had history of previous self-harm)
Search strategy	**Databases:** EMBASE, MEDLINE, PsycINFO **New search:** CINAHL
Searching other resources	GDG members identified if any key studies were missed.
Existing reviews	
• **Updated**	**N/A**
• **Not updated**	N/A
General search filter used	See search strategy in Appendix
Question specific search filter	See search strategy in Appendix

Amendments to filter/ search strategy	See search strategy in Appendix
The review strategy	The studies could not be meta analysed. Each study was narratively summarised. The studies which look at risk assessment scales were divided into sub-sections of those that predict a fatal and those that predict a non fatal outcome.
Additional assessments	1. Exclude retrospective studies design; 2. Exclude general population (without history of previous self harm) 3. Exclude studies that use another scale as a reference standard to measure repetition of self harm.

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1 Appendix 8b: Risk and protective factors

Topic	[Risk and protective factors]
Review question(s)	Q#1.2 What are the risk and protective factors (internal and external) amongst people who self harm that predict outcomes (eg. Suicide, non-fatal repetition, other psychological outcomes)?
Sub-question(s)	N/A
Chapter	6 – Psychosocial assessment
Sub-section	Section 6.2 Risk and protective factors
Topic Group	Jonathan Evans (Editor) Kate Hunt/ Simon Baston/ Suzanne Kearney/ Michaela Swales
Sub-section lead	Kate Hunt
Objectives	To explore the risk and protective factors associated with a repetition of self-harming behaviour
Criteria for considering studies for the review	
• Intervention	N/A
• Comparator	N/A
• Types of participants	Participants (aged 8 years old or above) admitted to hospital for treatment of index episode of self harm) Self-endorsed self-harming behaviour are also included.
• Critical outcomes	Repetition (fatal and non-fatal outcome)
• Important, but not critical outcomes	N/A
• Other outcomes	N/A
• Study design	Prospective cohort studies
• Include unpublished data?	No
• Restriction by date?	No
• Dosage	N/A
• Minimum sample size	N/A
• Study setting	Inpatient and outpatient (as long as participants had history of previous self-harm)
Search strategy	**Databases:** CINAHL, EMBASE, MEDLINE, PSYCINFO, HMIC, PsycEXTRA, PsycBOOKS **New search:**
Searching other resources	Experts in the field were contacted to identify if any key studies were missed.
Existing reviews	
• **Updated**	**N/A**
• **Not updated**	N/A
General search filter used	See search strategy in Appendix
Question specific search filter	See search strategy in Appendix
Amendments to filter/ search strategy	See search strategy in Appendix

The review strategy	2 independent reviewers reviewed the studies for its eligibility according to the inclusion criteria. Studies that meet eligibility will be examined to see if they could be meta-analysed. The criteria for inclusion in meta-analysis are the report of effects measure and its confidence interval. Studies that do not report effects measure and its confidence interval will be reviewed in a narrative manner.
Additional assessments	1. Exclude retrospective studies design; 2. Exclude general population (without history of previous self harm)

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1 Appendix 8c: Psychological Interventions

Topic	[Psychological Interventions]
Review question(s)	Q#2 For people who self-harm, do psychosocial interventions (compared with no treatment or other interventions) improve outcomes? What are the associated adverse effects?
Sub-question(s)	2.2 For people who self-harm, do psychosocial interventions in combination with pharmacological interventions (compared with either interventions alone) improve outcomes? What are the associated adverse effects?
Chapter	7 – Psychosocial interventions
Sub-section	
Topic Group	7 – Rory O'Connor, Paul Gill, Stephen Briggs, Andrew Briggs, Alison Wood
Sub-section lead	N/A
Objectives	To review the effectiveness of interventions for the management of repetition of self-harm behaviour
Criteria for considering studies for the review	
• Intervention	Chapter 7 - Problem-solving, interpersonal therapy, cognitive behavioural therapy, peer support groups, self help, computer-based interventions, dialectical behaviour therapy, counselling, psychodynamic interventions, family interventions, group therapy, postcards, assertive outreach, multi-systemic therapy, respite care, crisis management (refer to BPD guideline)
• Comparator	Treatment as usual
• Types of participants	Participants (aged 8 years old or above) admitted to hospital for treatment of index episode of self harm) Self-endorsed self-harming behaviour are also included.
• Critical outcomes	Repetition (fatal outcome: completed suicide; non-fatal repetition)
• Important, but not critical outcomes	Depression, hopelessness, suicide ideation scores
• Other outcomes	N/A
• Study design	Randomized controlled trials
• Include unpublished data?	No
• Restriction by date?	No
• Dosage	N/A
• Minimum sample size	10 in each treatment arm
• Study setting	Inpatient and outpatient (as long as participants had history of previous self-harm)
Search strategy	**Databases:** CINAHL, EMBASE, MEDLINE, PSYCINFO, HMIC, PsycEXTRA, PsycBOOKS

	New search:
Searching other resources	Experts in the field were contacted to identify if any key studies were missed.
Existing reviews	
• **Updated**	Hawton 2011 Updated Cochrane review for self-harm interventions
• **Not updated**	N/A
General search filter used	See search strategy in Appendix
Question specific search filter	See search strategy in Appendix
Amendments to filter/ search strategy	See search strategy in Appendix
The review strategy	Data from the Cochrane review update will be used for meta-analysis. Studies will be checked for our inclusion criteria.
Additional assessments	1. Exclude non-randomized studies 2. Exclude studies that were designed for people with borderline personality disorder (refer to relevant NICE guideline)

1

1 Appendix 8d: Pharmacological Interventions

Topic	[Pharmacological Interventions]
Review question(s)	Q#3 For people who self-harm, do pharmacological interventions (compared with no treatment or other interventions) improve outcomes? What are the associated adverse effects?
Sub-question(s)	3.2 For people who self-harm, what are the key principles underlying safer prescribing?
Chapter	8 - Pharmacological interventions
Sub-section	
Topic Group	8 – Suzanne Kearney, Alison Wood, Paul Gill
Sub-section lead	N/A
Objectives	To review the effectiveness of interventions for the management of repetition of self-harm behaviour
Criteria for considering studies for the review	
• Intervention	Chapter 8 - Antidepressants, antipsychotics, lithium, anticonvulsants (e.g. valproate, carbamazepine, lamotrigine), benzodiazepines, analgesics
• Comparator	Treatment as usual or placebo
• Types of participants	Participants (aged 8 years old or above) admitted to hospital for treatment of index episode of self harm) Self-endorsed self-harming behaviour are also included.
• Critical outcomes	Repetition (fatal outcome: completed suicide; non-fatal repetition)
• Important, but not critical outcomes	Depression, hopelessness, suicide ideation scores
• Other outcomes	N/A
• Study design	Randomized controlled trials
• Include unpublished data?	No
• Restriction by date?	No
• Dosage	N/A
• Minimum sample size	10 in each treatment arm
• Study setting	Inpatient and outpatient (as long as participants had history of previous self-harm)
Search strategy	**Databases:** CINAHL, EMBASE, MEDLINE, PSYCINFO, HMIC, PsycEXTRA, PsycBOOKS **New search:**
Searching other resources	Experts in the field were contacted to identify if any key studies were missed.
Existing reviews	
• **Updated**	Hawton 2011 Updated Cochrane review for self-harm interventions
• **Not updated**	N/A

General search filter used	See search strategy in Appendix
Question specific search filter	See search strategy in Appendix
Amendments to filter/ search strategy	See search strategy in Appendix
The review strategy	Data from the Cochrane review update will be used for meta-analysis. Studies will be checked for our inclusion criteria.
Additional assessments	1. Exclude non-randomized studies 2. Exclude studies that were designed for people with borderline personality disorder (refer to relevant NICE guideline)

1

1 Appendix 8e: Harm reduction

Topic	[Harm reduction]
Review question(s)	Q#4. For people who self-harm, does the provision of self management and/or harm minimisation/reduction strategies, compared with no treatment or treatment as usual, improve outcomes?
Sub-question(s)	N/A
Chapter	7 – Psychosocial interventions
Sub-section	7.3 Harm reduction
Topic Group	7 – Rory O'Connor, Paul Gill, Stephen Briggs, Andrew Briggs, Alison Wood 8 – Suzanne Kearney, Alison Wood, Paul Gill
Sub-section lead	N/A
Objectives	To review the evidence around harm minimisation/reduction techniques
Criteria for considering studies for the review	
• Intervention	replacement therapy, positive emotion technique
• Comparator	Treatment as usual
• Types of participants	Participants (aged 8 years old or above) admitted to hospital for treatment of index episode of self harm) Self-endorsed self-harming behaviour are also included.
• Critical outcomes	Repetition (fatal outcome: completed suicide; non-fatal repetition) Reduction in frequency or severity
• Important, but not critical outcomes	Depression, hopelessness, suicide ideation scores
• Other outcomes	N/A
• Study design	Any study designs (the GDG acknowledged the very limited evidence base in this area, therefore they decide to loosen the normal criteria)
• Include unpublished data?	Will be discussed if there are relevant materials
• Restriction by date?	No
• Dosage	N/A
• Minimum sample size	N/A
• Study setting	Inpatient and outpatient (as long as participants had history of previous self-harm)
Search strategy	**Databases:** CINAHL, EMBASE, MEDLINE, PSYCINFO, HMIC, PsycEXTRA, PsycBOOKS
Searching other resources	Experts in the field were contacted to identify if any key studies were missed.
Existing reviews	
• **Updated**	N/A
• **Not updated**	N/A
General search filter used	See search strategy in Appendix

Question specific search filter	See search strategy in Appendix
Amendments to filter/ search strategy	See search strategy in Appendix
The review strategy	N/A
Additional assessments	N/A

1

1 Appendix 8f: Training

Topic	[Training]
Review question(s)	Q5.1 Does the provision of staff training (knowledge, skills based) improve outcomes (eg. Staff attitudes, user satisfaction, user engagement with services)?
Sub-question(s)	N/A
Chapter	5 – Training
Sub-section	N/A
Topic Group	N/A
Sub-section lead	N/A
Objectives	To review the evidence around effectiveness of training
Criteria for considering studies for the review	
• Intervention	Any knowledge, skills based training
• Comparator	Treatment as usual
• Types of participants	Healthcare professionals
• Critical outcomes	Staff attitudes, staff knowledge, service users' satisfaction, and service users' engagement with services
• Important, but not critical outcomes	N/A
• Other outcomes	N/A
• Study design	RCTs preferably
• Include unpublished data?	Will be discussed if there are relevant materials
• Restriction by date?	No
• Dosage	N/A
• Minimum sample size	N/A
• Study setting	N/A
Search strategy	**Databases:** CINAHL, EMBASE, MEDLINE, PSYCINFO, HMIC, PsycEXTRA, PsycBOOKS
Searching other resources	Keith Hawton's review on staff attitudes
Existing reviews	
• **Updated**	N/A
• **Not updated**	N/A
General search filter used	See search strategy in Appendix
Question specific search filter	See search strategy in Appendix

Amendments to filter/ search strategy	See search strategy in Appendix
The review strategy	N/A
Additional assessments	N/A

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APPENDIX 9: SEARCH STRATEGIES FOR THE IDENTIFICATION OF CLINICAL STUDIES

Search strategies

The search strategies should be referred to in conjunction with information set out in Section 3.5. Each search was constructed using the groups of terms as set out in Box 1. The full set of terms for each search in Medline are documented below.

1

Box 1: Summary of systematic search strategies

Chapter: Experience of care				
Review area	**Search type**	**Search construction (applicable to each review area)**	**Study design**	**Databases / date range**
Experience of care	Update (Taylor *et al.*, 2009)	[(Self-harm terms) AND (Experience of care terms) AND (Qualitative/ survey lit terms)] *[(Self-harm terms) AND (SR filter)]	Qualitative studies, quantitative studies [survey literature] Systematic reviews	CINAHL, EMBASE, MEDLINE, PsycINFO, HMIC, IBSS, PsycBOOKS, PsycEXTRA [01.01.2006 up to 25 January 2011] CINAHL, EMBASE, MEDLINE, PsycINFO, CDSR, DARE [01.01.1995 up to 25 January 2011]
** Generic search for systematic reviews conducted for evidence relating to all clinical questions*				
Chapter: Training				
Review area	**Search type**	**Search construction (applicable to each review area)**	**Study design**	**Databases / date range**
Staff training	New	[(Self-harm terms) AND (Staff training terms) AND (RCT filter)] *[(Self-harm terms) AND (SR filter)]	Randomised controlled trials Systematic reviews	CINAHL, EMBASE, MEDLINE, PsycINFO, CENTRAL [Inception of databases up to 25 January 2011] CINAHL, EMBASE, MEDLINE, PsycINFO, CDSR, DARE [01.01.1995 up to 25 January 2011]
** Generic search for systematic reviews conducted for evidence relating to all clinical questions*				
Chapter: Psychosocial assessment				

Review area	Search type	Search construction (applicable to each review area)	Study design	Databases / date range
Risk and protective factors	New	[(Self-harm terms) AND (Risk and protective factor terms) AND (Observational filter)]	Observational studies	CINAHL, EMBASE, MEDLINE, PsycINFO [Inception of databases up to 25 January 2011]
		*[(Self-harm terms) AND (SR filter)]	Systematic reviews	CINAHL, EMBASE, MEDLINE, PsycINFO, CDSR, DARE [01.01.1995 up to 25 January 2011]
Formal risk assessment, needs assessment and psychosocial assessment	New	[(Self-harm terms) AND (Risk assessment, needs assessment, psychosocial assessment terms) AND (Observational filter)]	Observational studies	CINAHL, EMBASE, MEDLINE, PsycINFO [Inception of databases up to 25 January 2011]
		*[(Self-harm terms) AND (SR filter)]	Systematic reviews	CINAHL, EMBASE, MEDLINE, PsycINFO, CDSR, DARE [01.01.1995 up to 25 January 2011]
** Generic search for systematic reviews conducted for evidence relating to all clinical questions*				
Chapter: Psychosocial interventions				

Review area	Search type	Search construction (applicable to each review area)	Study design	Databases / date range
Self management and/or harm reduction strategies	New	[(Self-harm terms) and (Self management and/or harm reduction strategy terms)]	Pieced [most relevant terms, all studies; less relevant terms, randomised controlled trials and observational studies]	CINAHL, EMBASE, MEDLINE, PsycINFO [Inception of databases up to 25 January 2011]
		*[(Self-harm terms) AND (SR filter)]	Systematic reviews	CINAHL, EMBASE, MEDLINE, PsycINFO, CDSR, DARE [01.01.1995 up to 25 January 2011]
Psychosocial interventions	Update, generic (Hawton *et al.*, 2011)	[(Self-harm terms) and (RCT filter)]	Randomised controlled trials	Embase; Medline; CINAHL; PsycINFO; CENTRAL.[01.01.2010 up to 25 January 2011]
		*[(Self-harm terms) AND (SR filter)]	Systematic reviews	CINAHL, EMBASE, MEDLINE, PsycINFO, CDSR, DARE [01.01.1995 up to 25 January 2011]
** Generic search for systematic reviews conducted for evidence relating to all clinical questions*				
Chapter: Pharmacological interventions				

Review area	Search type	Search construction (applicable to each review area)	Study design	Databases / date range
Pharmacological interventions	Update, generic(Hawton *et al.*, 2011)	[(Self harm terms) AND (RCT filter)]	Randomised controlled trials	Embase; Medline; CINAHL; PsycINFO; CENTRAL [01.01.2010 up to 25 January 2011]
		*[(Self-harm terms) AND (SR filter)]	Systematic reviews	CINAHL, EMBASE, MEDLINE, PsycINFO, CDSR, DARE [01.01.1995 up to 25 January 2011]
Safer prescribing	New	[(Self harm terms) AND (Safer prescribing terms) AND (OS filter)]	Observational studies	Embase; Medline; CINAHL; PsycINFO. [Inception of databases up to 25 January 2011]
		*[(Self-harm terms) AND (SR filter)]	Systematic reviews	CINAHL, EMBASE, MEDLINE, PsycINFO, CDSR, DARE [01.01.1995 up to 25 January 2011]
** Generic search for systematic reviews conducted for evidence relating to all clinical questions*				

Population Search terms

a) Self harm - population search terms

Medline – Ovid SP interface

1. overdose/ or self-injurious behavior/ or self mutilation/ or suicidal ideation/ or suicide/ or suicide, attempted/
2. (autoaggress$ or auto aggress$ or automutilat$ or auto mutilat$ or cutt$ or overdose$ or (self adj2 cut$) or selfdestruct$ or self destruct$ or selfharm$ or self harm$ or selfimmolat$ or self immolat$ or selfinflict$ or self inflict$ or selfinjur$ or self injur$ or selfmutilat$ or self mutilat$ or selfpoison$ or self poison$ or suicid$).ti,ab.
3. or/1-2

Question specific search strategies

a) Experience of care [search update]

i) For people who self-harm, what are their experiences of having self-harmed, of access to services and of treatment?; ii) For families and carers of people who self-harm, what are their experiences of caring for people with self-harm and what support is available for families and carers?; iii) For health care professional who work with people who self-harm, what are their experiences of working with people who self-harm and what training needs are specified by this group?

Medline – Ovid SP interface

1. anthropology, cultural/ or ethnology/ or focus groups/ or life change events/ or nursing methodology research/ or observation/ or qualitative research/
2. (constant comp$ or ((content or discourse) adj analysis) or emic or ethnograph$ or ethnon$ or etic or focus group$ or grounded theory or group interview$ or inside$ perspective$ or ((live or lived) adj experience) or ((narrative or thematic) adj analysis) or participant obser$ or phenomolog$ or (qualitative adj (approach or analysis or method$ or research or stud$)) or semi-structured or social constructi$).ti,ab.
3. ((client$ or consumer$ or inpatient$ or patient or user) adj experience$).ti,ab.
4. or/1-3
5. exp *health surveys/ or *health care surveys/
6. (survey$ or question$).ti,ab.
7. or/5-6
8. *attitude to health/ or *attitude/ or exp patient attitude/
9. (experien$ or attitude$).ti,ab.

10. or/8-9
11. 4 or (7 and 10)

b) Staff training

Medline – Ovid SP interface

Does the provision of staff training (knowledge, skills based) improve outcomes (eg. Staff attitudes, user satisfaction, user engagement with services)?

1. educational, premedical/ or exp education, professional/ or faculty/ or faculty, medical/ or faculty, nursing/ or exp inservice training/ or exp professional competence/ or exp schools, health occupations/
2. accreditation/ or certification/ or competency based education/ or credentialing/ or exp curriculum/ or education/ or knowledge/ or learning/ or mentors/ or teaching/ or ed.fs.
3. (competen$ or course$1 or cpd$1 or curricul$ or educat$ or information or instruct$ or knowledge or learn$ or module$ or posttrain$ or pretrain$ or ((clinical or professional) adj2 (develop$ or improv$ or practice)) or skill$ or teach$ or train$ or workshop$ or work shop$).ti,ab.
4. "attitude of health personnel"/ or exp health personnel/ or exp professional role/ or specialization/ or exp medicine/ or exp nursing/ or exp pharmacy/ or exp psychology/ or exp physicians/ or exp psychiatry/
5. (analyst$ or clinician$ or consultant$1 or counsel?or$ or cpe or doctor$ or employee or gp$1 or health visitor$ or medical expert$ or nurs$ or personnel or pharmacist$ or physician$ or practitioner$ or professional$ or psychiatrist$ or psychoanalyst$ or psychologist$ or psychotherapist$ or specialist$ or staff$ or therapist$ or worker$1).ti,ab.
6. (or/2-3 and or/4-5)
7. exp health personnel/ed
8. or/1,6,7

c) Risk and protective factors

Medline – Ovid SP interface

What are the risk and protective factors (internal and external) amongst people who self harm that predict outcomes?

1. risk factors/
2. (risk$ adj2 relative).ti,ab.
3. ((predict$ or protect$ or risk$) adj2 (associat$ or attribute$ or correlate$ or determinant$ or factor$ or variable$)).ti,ab.
4. or/1-3

5. ((predict$ or risk$) adj2 (ongoing or recur$ or re cur$ or reattempt$ or re attempt$ or recur$ or repeat$ or repetit$)).ti,ab.
6. prospective repetit$.ti,ab.
7. ((associat$ or attribute$ or correlate$ or determinant$ or factor$ or variable$) adj8 (ongoing or recur$ or re cur$ or reattempt$ or re attempt$ or recur$ or repeat$ or repetit$) adj8 (autoaggress$ or aggress$ or automutilat$ or cutt$ or destruct$ or dsh or episode$ or harm$ or immolat$ or inflict$ or injur$ or mutilat$ or overdose$ or (self adj2 cut$) or poison$ or selfdestruct$ or selfharm$ or selfimmolat$ or selfinflict$ or selfinjur$ or selfmutilat$ or selfpoison$ or sh or suicid$)).ti,ab.
8. or/5-7
9. resilience, psychological/
10. (buffer$ or cope$ or recovery or resilien$).ti,ab.
11. or/9-10
12. or/4,8,11

d) Formal risk assessment, needs assessment and psychosocial assessment

Medline – Ovid SP interface

For people who self-harm, does formal risk assessment, needs assessment and psychosocial assessment improve outcomes?

1. (checklist/ or geriatric assessment/ or interview/ or interview, psychological/ or mass screening/ or nursing assessment/ or "outcome and process assessment (health care)"/ or "outcome assessment (health care)"/ or exp personality assessment/ or exp psychiatric status rating scales/ or exp psychological tests/ or questionnaires/)
2. (form$1 or checklist$ or check list$ or index$ or indices or interview$ or instrument$ or inventor$ or item$1 or measure$ or psychometric$ or psycho metric$ or question$ or scale$ or score$ or scoring or self report$ or subscale$ or test$ or tool$).ti,ab.
3. 1 or 2
4. "predictive value of tests"/ or recurrence/ or risk$.hw.
5. (predict$ or ongoing or recur$ or re cur$ or reattempt$ or re attempt$ or recur$ or repeat$ or repetit$ or risk$).ti,ab.
6. 4 or 5
7. area under curve/ or exp sensitivity and specificity/
8. ((area under adj2 curve) or auc or (diagnostic adj2 odds ratio$) or ((false or true) adj negative) or ((false or true) adj positive) or (likelihood adj3 ratio$) or ((pretest or pre test or posttest or post test) adj2 probabilit$) or (predict$ adj3 value$) or receiver operating characteristic or (roc adj2 (analy$ or curv$ or plot$)) or sensititiv$ or specificit$).tw.

9. 7 or 8
10. and/3,6,9
11. needs assessment/ or risk assessment/
12. ((client$ or clinical$ or consumer$ or need$ or patient$ or psychiatric or psychological or psychosocial or psycho social or risk or service user$ or therapeutic) adj2 (assess$ or evaluat$)).ti,ab.
13. (((assess$ or predict$ or risk$) adj2 (form$1 or checklist$ or check list$ or index$ or indices or interview$ or instrument$ or inventor$ or item$1 or measure$ or psychometric$ or question$ or scale$ or score$ or scoring or self report$ or subscale$ or test$ or tool$)) or (comprehensive adj (assessment$ or evaluation$))).ti,ab.
14. (adult suicidal ideation questionnaire or asiq or (beck depression inventory or bdi) or (beck hopelessness scale or bhs) or ((beck scale adj2 suicide ideation) or bsi) or ((brief reasons adj2 living inventory) or brfl) or (brief symptom inventory or bsi) or ((college student reasons adj2 living inventory) or csrli or csr li) or ((edinburgh risk adj2 repetition scale) or errs) or (firestone assessment adj2 self-destructive thoughts) or ((global clinical assessment) or gca) or ((hamilton depression rating scale) or hdrs) or ((hamilton rating scale adj2 depression) or hamd or ham d or hrsd or hrs d) or ((intersept scale adj2 suicidal thinking) or isst) or lethality scale$ or (life satisfaction scale or ls scale) or lifetime parasuicide count or ((linehan reasons adj2 living inventory) or lrfl) or ((manchester self harm rule) or mshr) or ((modified scale adj2 suicide ideation) or mssi) or (parasuicide history interview or phi) or ((quiz adj2 depression adj2 suicide adj2 later life) or qdsll) or (reasons adj2 living inventory) or ((reasons adj2 living scale adj2 older adult questionnaire) or rfloa or rfl oa) or ((reasons adj2 living scale adj2 younger adult questionnaire) or rflya or rfl ya) or risk rescue rating or ((scale adj2 suicide ideation) or ssi) or (self-inflicted injury severity form or siisf or sii sf) or (self-monitoring suicide ideation scale or smsis of sms is) or (suicidal behaviors interview or sbi) or (suicidal ideation questionnaire or siq) or (suicidal ideation screening questionnaire or sisq or sis q) or (suicidal intent scale or sis) or ((suicide assessment scale) or suas) or (suicide behaviors questionnaire or sbq) or (suicide intervention response inventory or siri) or (suicide opinion questionnaire or soq) or (suicide potential rating scale or suicide lethality scale or spls or spl s) or (suicide probability scale or sps) or (suicide status form or ssf) or ((symptom driven diagnostic system adj2 primary care) or sddspc or sdds pc) or ((positive adj2 negative suicide ideation inventory) or pansi)).ti,ab.
15. or/11-14
16. or/10,15

e) Self management and/or harm minimisation

Medline – Ovid SP interface

For people who self-harm, does the provision of self management and/or harm minimisation strategies, compared with no treatment or treatment as usual, improve outcomes?

1. self care/
2. ((self adj (care or instruct$ or manag$ or monitor$ or regulat$ or reinforc$ or re inforc$)) or selfcare or selfinstruct$ or selfmanag$ or selfmonitor$ or selfregulat$ or (minimal adj (contact or guidance)) or (mutual adj (help or aid or support$))).ti,ab.
3. harm reduction/ or risk management/ or risk reduction behavior/
4. ((autoaggress$ or auto aggress$ or automutilat$ or mutilat$ or cutt$ or overdose$ or (self adj2 cut$) or selfdestruct$ or destruct$ or selfharm$ or harm$ or selfimmolat$ or immolat$ or selfinflict$ or inflict$ or selfinjur$ or injur$ or selfmutilat$ or mutilat$ or selfpoison$ or poison$ or suicid$) adj2 (minimi$ or reduc$)).ti,ab.
5. ((autoaggress$ or auto aggress$ or automutilat$ or mutilat$ or cutt$ or overdose$ or (self adj2 cut$) or selfdestruct$ or destruct$ or selfharm$ or harm$ or selfimmolat$ or immolat$ or selfinflict$ or inflict$ or selfinjur$ or injur$ or selfmutilat$ or mutilat$ or selfpoison$ or poison$ or suicid$) adj4 (((decreas$ or diminish$ or fall$ or fell or less$ or limit$ or low or lower$) adj2 risk$) or minimi$ or reduc$) adj8 (approach$ or communicat$ or counsel$ or educat$ or instruct$ or interven$ or learn$ or manag$ or module$ or network$ or program$ or psychoanaly$ or psychotherap$ or rehab$ or skill$ or strateg$ or support$ or taught or teach$ or technique$ or therap$ or train$ or treat$ or workshop$ or work shop$)).ti,ab.
6. ((advice$ or advis$ or deal$ or instruct$ or educat$ or learn$ or taught or teach$) adj8 (injur$ or scar$ or wound$)).ti,ab.
7. (((advice$ or instruct$ or educat$ or learn$ or taught$ or teach$) adj3 risk$)) or ((advice$ or advis$ or discuss$ or educat$ or learn$ or taught$ or teach$) adj8 risk$ adj8 (autoaggress$ or auto aggress$ or automutilat$ or mutilat$ or cutt$ or overdose$ or (self adj2 cut$) or selfdestruct$ or destruct$ or selfharm$ or harm$ or selfimmolat$ or immolat$ or selfinflict$ or inflict$ or selfinjur$ or injur$ or selfmutilat$ or mutilat$ or selfpoison$ or poison$ or suicid$))).ti,ab.
8. hotlines.sh.
9. (call in or callline$ or call line$ or help line$ or helpline$ or hotline$ or hot line$ or phone in or phonein or (caller$1 adj3 (interven$ or program$ or therap$ or treat$)) or (talk$ adj2 friend$) or ((phone$ or telephone$) adj2 support$)).ti,ab.
10. relaxation/ or relaxation therapy/
11. (relaxation or ((autogen$ or relax$) adj5 (apply or applied or approach$ or assist$ or coach$ or educat$ or help$ or imagery or instruct$ or interven$ or learn$ or manag$ or modif$ or program$ or seminar$ or

strateg$ or support$ or teach$ or technique$ or therap$ or train$ or treat$ or workshop$ or work shop$)) or relaxed state or ((breath$ or movement or respirat$ or relax$) adj2 (exercis$ or interven$ or physiotherap$ or technique$ or therap$ or train$)) or ((control?ed or deep) adj breathing)).ti,ab.

12. ((replacement$ or substitut$) adj3 (approach$ or educat$ or instruct$ or interven$ or learn$ or manag$ or network$ or program$ or promot$ or rehab$ or strateg$ or taught or teach$ or technique$ or therap$ or train$ or treat$ or workshop$ or work shop$)).ti,ab.
13. (giggl$ or humo?r or laugh or laughter).ti,ab.
14. ((positive$ adj2 (emotion$ or therap$ or think$ or psycho$)) or (emotion$ adj2 (cope or coping or psychotherap$ or therap$))).ti,ab.
15. (damag$ adj2 limit$).ti,ab.
16. (manag$ risk$ or (positive$ adj2 risk$ adj2 tak$) or (relation$ adj2 secur$)).ti,ab.
17. (comforts or distractions or (((divert adj2 attention) or distract$) adj5 (automutilat$ or mutilat$ or cutt$ or overdose$ or (self adj2 cut$) or selfdestruct$ or destruct$ or selfharm$ or harm$ or selfimmolat$ or immolat$ or selfinflict$ or inflict$ or selfinjur$ or injur$ or selfmutilat$ or mutilat$ or selfpoison$ or poison$ or suicid$))).ti,ab.
18. (ice or icecube$ or marker pen$ or pillow$1 or pinch or pinching or ((elastic or rubber) adj band$) or toothbrush$ or tooth brush$ or (tak$ adj2 (bath$ or shower$)) or ((clean or sterile) adj2 (cutt$ or instrument))).ti,ab.
19. (goal$ adj2 set$).ti,ab.
20. (diary or diaries).ti,ab.
21. therapeutic contract.ti,ab.
22. ((cope$ or coping) adj3 (approach$ or assist$ or coach$ or educat$ or help$ or imagery or instruct$ or interven$ or learn$ or manag$ or modif$ or program$ or seminar$ or strateg$ or support$ or teach$ or technique$ or therap$ or train$ or treat$ or workshop$ or work shop$)).ti,ab.
23. (risk$ adj2 (minimi$ or reduc$)).ti,ab.
24. creativeness/ or exercise/ or exp recreation/
25. (active living or bicycling or (cycling not rapid cycling) or gardening or ((a?robic$ or physical$) adj (activit$ or agil$ or educat$ or fitness$)) or hobby or hobbies or kinesiotherap$ or kinesitherap$ or recreation$ or running or sport$ or swimming or tidying or walking or yoga).ti,ab.
26. community networks/ or friends/ or group processes/ or peer group/ or self help groups/
27. ((support$ adj (based or cent$ or focus?ed)) or (support$ adj2 (approach$ or educat$ or friend$ or family or instruct$ or interven$ or learn$ or module$ or network$ or peer$1 or program$ or strateg$ or technique$ or therap$ or train$ or treat$ or workshop$ or work shop$)) or ((community or emotion$ or network$ or organi?ation$ or peer$)

adj2 support$) or (network$ adj2 (discuss$ or exchang$ or interact$ or meeting$))).ti,ab.
28. exp consumer health information/ or "patient education as topic"/
29. ((health adj2 (educat$ or informat$ or promot$)) or ((adult$ or client$ or consumer$ or inpatient$ or outpatient$ or participant$ or patient$ or people or user$) adj4 (educat$ or knowledge or information$ or promot$))).ti,ab.
30. or/1-5
31. or/6-29 [ANDed with RCT and OS filter]
32. or/30,31

f) Psychosocial interventions [search update]

For people who self-harm, do psychosocial interventions (compared with no treatment or other interventions) improve outcomes? What are the associated adverse effects?

[Generic search – self harm terms ANDed with RCT filter]

g) Pharmacological interventions [search update]

For people who self-harm, do drug treatments improve outcomes? What are the associated adverse effects?

[Generic search – self harm terms ANDed with RCT filter]

h) Safer prescribing

Medline – Ovid SP interface

For people who self-harm, what are the key principles underlying safer prescribing?

1. exp analgesics/or exp salicylic acids/ or (ana?lges$ or salicyl$).ti,ab.
2. (acetylsalicylic acid or 2 acetoxybenzoate or acenterine or acesal or acetan or acetard or aceticyl or acetilum or acetonyl or acetophen or acetosal or acetosalicylic acid or acetosalin or acetosalum or acetyl salicylate or acetyl salicylic acid or acetylic salicylic acid or acetylin or acetylo or acetylon or acetylosalicylic acid or acetylsal or acetylsalicyclic acid or acetylsalicyl or acetylsalicylate or acetylsalicylate strontium or acetylsalicylic acid or acetylsalycic acid or acetylsalycylic acid or acetysal or acidulatum or acidum acetyl salicylicum or acidum acetylosalicylicum or acidum acetylsalicylicum or acylpyrin or acylpyrine or acytosal or adiro or alabukun or alasil or alka seltzer or alkaspirin or aloxiprimum or anopyrin or arthralgyl or asaflow or asaphen or aspergum or aspirgran or aspirin or aspirina or

aspirine or aspirinine or aspisol or aspro or asrivo or asteric or astrix or bebesan or biprin or boxazin or breoprin or bufferin or cafenol or catalgine or catalgix or cemerit or cemirit or claradin or claragine or colfarit or colfarit or contrheuma or contrheuma retard or daga or darosal or depot aspirin or dispirin or dispril or dolean or easprin or ecotrin or egalgic or emocin or empirin or encaprin or endosprin or endosprin or entericin or enterosarine or enterospirine or entrophen or euthermine or extren or genasprin or godamed or gotosan or helicon or infatabs a or istopirin or istopyrine or ivepirine or juvepirine or kilios or kinderaspirin or magnecyl or measurin or mejoral or micristin or micristin or micropyrin or mikristin or miniasal or mycristin or nu seal or nuseals or ortho acetoxybenzoate or ortho acetoxybenzoic acid or ortho acetyloxybenzoate or ortho acetyloxybenzoic acid or ostoprin or pancemol or para acetylsalicylic acid or paracin or paynocil or pengo or polopirin or polopiryna or polopiryna or premaspin or primaspan or pyronoval or reumyl or rhodine or rhonal or salacetin or salacetogen or saletin or sargepirine or slow release aspirin or sodium acetylsalicylate or sodium bicarbonate acetyl salicylate or sodium bicarbonate acetylsalicylate or soldral or solprin or solpyron or solucetyl or solupsa or solupsan or super tru or tapal or temagin or treupahlin or treuphalin or turivital or verin or vitalink or xaxa or zorprin).ti,ab.

3. alfentanil/or (alfentanil or alfenta or alfentanil or alfentanil hydrochloride or alfentanyl or alfentanyl or fanaxal or limifen or rapifen).ti,ab.
4. (almotriptan or almogran or almotriptan malate or axert).ti,ab.
5. (buprenorphin$ or buprenex or buprex or finibron or lepetan or prefin or suboxone or subutex or temgesic or transtec).ti,ab.
6. caffeine/or caffeine$.ti,ab.
7. cannabis/or (cannabis or cannabi or cannabis or ganja or ganjas or hemp or hemps or marihuana or marihuanas or marijuana or marijuanas or opiate).ti,ab.
8. (cocodamol or acetaminophen plus codeine phosphate or empracet or hypertussin or lindilane or nedolon or panadeine or paracodal or percogesic with codeine or talvosilen or treuphadol plus).ti,ab.
9. (codeine phosphate or ardinex or codein phosphate or codeine or codeine phosphate or codicompren retard or colrex compound or galcodine or isocodeine or kodein or n methylmorphine or tricodein or tussipect).ti,ab.
10. (codydramol or codidramol).ti,ab.
11. cyclizine/or (cyclizine or collox or cyclizine or marazine or marezine or marzine or neo devomit or valoid).ti,ab.
12. dextromoramide/or (dextromoramide or d moramide or dextro moramide or dextromoramide or dextromoramine or dimorlin or d-moramide or jetrium or moramide or palfium or palfium or palphium or pyrrolamidol or pyrrolamidole or pyrroloamidol).ti,ab.

13. dextropropoxyphene/or (co proxamol or coproxamol or cosalgesic or d propoxyphene or darvon or dextropropoxyphene or diantalvic or distalgesic or d-propoxyphene or dystalgesic or paradex or propoxyphene).ti,ab.
14. (dihydrocodeine or cis dihydrocodeine or codhydrin or codhydrine or codicontin or cohydrin or dehacodin or dh codeine or didrate or dihydrin or dihydroneopine or drocode or hydrocodeine or hydrocodin or nadein or nadeine or napacodin or novicodin or paracodein or paracodin or paramol or parzone or rapacodin or remedacen or tiamon mono or trans dihydrocodeine).ti,ab.
15. (dipipanone or pipadone or piperidyl amidone).ti,ab.
16. eletriptan.ti,ab.
17. ergotamine/ or (ergate or ergomar or ergostat or ergotamine tartrate or ergotaminetartras or exmigra or femergin or gynergen or lingraine or medihaler ergotamine or relpax or virdex or wigrettes).ti,ab.
18. fentanyl/or (fentanyl$ or duragesic or duragesic or durogesic or fentamyl or fentanest or fentanil or fentora or fetnanyl or ionsys or leptanal or phentanyl or sublimaze or transfenta).ti,ab.
19. (frovatriptan allegro or frova or migard or miguard).ti,ab.
20. (heroin$1 or acetomorphine or diacephine or diacetyl morphine or diacetylmorphine or diagesil or diamorf or diamorphine or diaphorin or morphacetin).ti,ab.
21. (hydromorphone or biomorphyl or cofalaudid or dihydromorphinone or dihydromorphone or dilaudid or dimorphone or hydromorphinone hydrochloride hydromorphon or hydromorphone or hymorphan or laudacon or laudaconum or novolaudon or palladon or palladone or palladone or semcox or sophidone).ti,ab.
22. isometheptene mucate.ti,ab.
23. ketorolac$.sh. or (droal or isometheptenemucate or isometheptine mucate or ketocol or ketorolac or midrin or taradyl or toradol or toratex).ti,ab.
24. meptazinol/ or (meptazinol or meptazinol or meptid).ti,ab.
25. exp methadone/ or (methadone$ or adanon or adanon hydrochloride or algidon or algolysin or algoxale or althose or amidon or amidone or amidosan or anadon or biodone or butalgin or deamin or depridol or diaminon or dianone or dolafin or dolamid or dolesone or dolophine or dolophine hydrochloride or dorex or dorexol or fenadon or heptadon or heptanon or ketalgin or mecodin or mepecton or mephenon or metadol or metasedin or methaddict or methadose or methex or miadone or moheptan or phenadon$1 or phymet or physepton or physeptone or pinadone or polamidon or polamivet or polamivit or sinalgin or symoron).ti,ab.
26. methysergide/or (methysergide$ or deseril or desernil sandoz or desril or dimethylergometrin or dimethylergometrine or dimethylergonovine or methisergid or methisergide or methyl sergide or

methylmethylergonovine or methylsergide or methysergid or methysergide or sansert).ti,ab.
27. exp morphine/ or morphinans/or (morphine or astramorph or avinza or depodur or depomorphine or dolcontin or duramorph or duramorple or kadian or kapanol or moraxen or morphia or morphinesulfate or moscontin or ms contin or mst continus or mst mundipharma or noceptin or oblioser or oramorph or roxanol or sevredol or skenan lp).ti,ab.
28. exp naloxone/or (naloxone or maloxone or nalaxone or nalone or nalonee or narcan or narcanti or narcon or narvcam).ti,ab.
29. (naratriptan or amerge or naramig).ti,ab.
30. nefopam/ or (nefopam or acupan or ajan or fenazoxine or lenipan or nocipan).ti,ab.
31. opiate alkaloids/or opium/ or (opiate$ or opioid$ or opium).ti,ab.
32. (oxycodone or bionine or bionone or bolodorm or broncodal or bucodal or cafacodal or cardanon or codenon or dihydrohydroxydodeinone or dihydrone or dinarkon or endone or eubine or eucodal or eucodale or eudin or eukdin or eukodal or eumorphal or eurodamine or eutagen or hydrocodal or hydroxycodeinoma or hydroxycodeinon or ludonal or medicodal or narcobasina or narcobasine or narcosin or nargenol or narodal or nucodan or opton or ossicodone or oxanest or oxicone or oxiconum or oxikon or oxycodeinon or oxycodeinonhydrochloride or oxycodone or oxycodonhydrochlorid or oxycodyl or oxycone or oxycontin or oxygesic or oxykon or oxynorm or pancodine or pavinal or pronarcin or remoxy or roxicodone or roxycodone or sinthiodal or stupenal or tebodal or tekodin or thecodin or theocodin).ti,ab.
33. acetaminophen/or (paracetamol or acetaminophen or acamol or acephen or acetaco or acetamidophenol or acetominophen or algotropyl or anacin 3 or anacin3 or apap or datril or hydroxyacetanilide or p-acetamidophenol or panadol or tylenol).ti,ab.
34. pentazocine/or (pentazocine or dolapent or fortal or fortalgesic or fortral or fortraline or fortwin or lexir or liticon or peltazon or pentacozine or pentafen or pentagin or pentalgina or pentazocin or pentozocine or perutagin or sosegon or sosigon or talioin or talwin).ti,ab.
35. exp meperidine/ or (pethidine or algil or alodan or centralgin or centralgine or demerol or dispadol or dolanquifa or dolantal or dolantin or dolantine or dolargan or dolcontral or dolenal or dolestin or dolin or dolocontral or doloneurin or doloneurotrat or dolor or dolosa or dolosal or dolosan or dolsin or dolvanol or endolate or isonipecain or isonipecaine or l pethidine or lidol or lydol or mefedina or mepadin or meperiden or meperidin or meperidine or mephedine or mepiridine or mialgin or pantalgin or petadin or petantin or petantina or pethanol or pethedine or pethidin or pethidine or petidin or

phetidine or piridosal or sauteralgyl or simesalgina or supplosal or synlaudine).ti,ab.
36. (pizotifen or mosegor or sanmigran or sanomigran).ti,ab.
37. (rizatriptan or maxalt).ti,ab.
38. sumatriptan/ or (sumatriptan succinate or imigran or imiject or imitrex or sumadol or sumigrene).ti,ab.
39. (tolfenamic acid or clotam or clotan or rociclyne or tolfedine or tolfenamate).ti,ab.
40. tramadol/or (tramadol or adolonta or amadol or biodalgic or biokanol or contramal or dolzam or jutadol or kontram xl or melanate or mtwtramadol or nobligan or prontofort or ranitidin 1a pharma or takadol or theradol or tiral or topalgic or tradol or tradolpuren or tradonal or tralgiol or trama abz or trama dorsch or trama kd or tramabeta or tramadin or tramadoc or tramadoldolgit or tramadolhameln or tramadolium chloride or tramadolor or tramadolratiopharm or tramadorsch or tramadura or tramagetic or tramagit or tramake or tramal or tramex or tramundin or trasedal or trodon or trondon or ultram or xymel 50 or zamudol or zumalgic or zydol or zytram).ti,ab.
41. (zolmitriptan or ascotop or zomig or zomigon).ti,ab.
42. (zopiclone or amoban or imovance or imovane or ximovan or zimovane or zoplicon).ti,ab.
43. or/1-42
44. exp benzodiazepines/ or (benzo$1 or benzodiazepin$).ti,ab.
45. (alprazolam or alprox or apo alpraz or apoalpraz or aprazolam$1 or cassadan$1 or esparon$1 or helex or kalma or novo alprazol$1 or novoalprazol$1 or nu alpraz or nualpraz or ralozam or solanax or tafil$1 or trankimazin$1 or valeans or xanax or xanor).ti,ab.
46. (bromazepam or anxyrex or bartul or bromalich or bromaz pharma or bromazanil$1 or bromazep von ct or durazanil$ or lectopam$1 or lexamil$1 or lexatin$1 or lexaurin$1 or lexilium or lexomil$1 or lexotan$1 or lexotanil$1 or lexotanil$1 or normoc or sintrogel$1).ti,ab.
47. (chlordiazepoxid$1 or methaminodiazepoxid$1 or elenium$1 or librium$1 or chlozepid$1 or ansiacal$1 or benzodiapin$1 or cebrum$1 or chlordiazepoxyd$1 or chlorodiazepoxid$1 or clopoxid$1 or contol$1 or decacil$1 or defobin$1 or disarim$1 or dizepin$1 or dopoxid$1 or droxol$1 or eden psich or elenium$1 or elenum$1 or equibral$1 or kalmocaps or labican$1 or librelease or libritabs or librium or lipoxide or mesural$1 or metaminodiazepoxid$1 or methaminodiazepoxid$1 or mildmen$1 or mitran$1 or multum$1 or murcil$1 or napoton$1 or napoton$1 or novosed$1 or psichial$1 or psicosan$1 or psicoterin$1 or radepur or reliberan$1 or reposans or risolid or seren vita or servium or silibrin$1 or sk lygen or sonimen$1 or timosin$1 or viansin$1 or viopsicol$1).ti,ab.
48. (clobazam or chlorepin$1 or clobazepam or clorepin$1 or frisium or noiafren$1 or urbadan$1 or urbanil$1 or urbanyl).ti,ab.

49. (clonazepam or antelepsin$1 or clonopin$1 or iktorivil$1 or klonazepam or klonopin$1 or landsen$1 or rivotril$1).ti,ab.
50. (clorazepat$1 or carboxylic acid or chlorazepat$1 or chloroazepat$1 or clorazepic acid or tranxen$1 or tranxilium).ti,ab.
51. (delorazepam or briantum$1 or chlordemethyldiazepam or chlordesmethyldiazepam or chloro n demethyldiazepam or chlorodemethyldiazepam or chlorodesmethyldiazepam or chloronordiazepam).ti,ab.
52. (diazepam or alupram or ansiolin$1 or antenex or apaurin$1 or apaurin$1 or apozepam or assival$1 or audium$1 or bialzepam or bialzepan$1 or calmpos$1 or cercin$1 or cersin$1 or chlordiazepam or dialar or diastat or diazelium or diazemuls or diazidem or ducen$1 or duxen$1 or eridan or eurosan$1 or evacalm$1 or fanstan$1 or faustan$1 or gewacalm$1 or lamra or lembrol$1 or lipodiazepam or lorinon$1 or methyldiazepinon$1 or methyldiazepinon$1 or morosan$1 or neocalm$1 or neurolytril$1 or noan or novazam or paceum or plidan or psychopax or relanium or 1 rimapam or sedapam or seduxen$1 or serendin$1 or setonil$1 or sibazon$1 or sonacon$1 or stesolid$1 or stesolin$1 or tanquo tablinen$ or tensium or tranimul$1 or tranquo puren or umbrium$1 or valaxon$1 or valclair or valiquid$1 or valium or valpam or valreleas$ or vatran$1 or vival$1 or vivol or zetran$1).ti,ab.
53. (flunitrazepam or flurazepam or fluridrazepam or darken$1 or fluni 1a pharma or flunibeta or flunimerck or fluninoc or flunipam or flunita or flunitrax or flunizep von ct or hypnodorm$1 or hypnosedon$1 or inervon$1 or narcozep or parnox or rohipnol$1 or rohypnol$1 or roipnol$1 or silece or valsera).ti,ab.
54. (flurazepam or benozil$1 or dalmadorm$1 or dalman$1 or dalmate or dormodor$1 or lunipax or staurodorm$1 or dalman$1 or dormodor$1 or dalmadorm$1).ti,ab.
55. (flutoprazepam or restas).ti,ab.
56. loprazolam.ti,ab.
57. (lorazepam or almazin$1 or alzapam or apolorazepam or ativan or bonatranquan$1 or donix or duralozam or durazolam or idalprem or kendol$1 or laubeel or lorabenz or loranas$1 or loranaz$1 or lorans or lorax or lorazep von ct or loridem$1 or lorivan$1 or mesmerin$1 or novo lorazem$1 or novolorazem$1 or novo lorazem$1 or nu loraz or nuloraz or orfidal or orifadal$1 or pro dorm or quait or securit or sedicepan$1 or sinestron$1 or somagerol$1 or tavor or temesta or tolid or wypax).ti,ab.
58. (lormetazepam or loramet or (lorazepam adj2 methyl) or methyllorazepam or minians or minias or noctamid$1 or pronoctan$1).ti,ab.
59. (mexazolam or melex or sedoxil$1).ti,ab.
60. (midazolam or dormicum or dormonid$1 or hypnoval$1 or hypnovel$1 or hypnoyvel$1 or versed).ti,ab.

61. (nitrazepam or alodorm or atempol$1 or benzalin$1 or dormalon$1 or dormo puren or dumolid or eatan or eunoctin$1 or hypnotex or imadorm or imeson$1 or insomin$1 or mogadan$1 or mogadon$1 or nelbon$1 or nirven$1 or nitra zepam or nitrados or nitravet or nitrazadon$1 or nitrazep or nitrodiazepam or novanox or pacisyn or radedorm$1 or remnos or restorem$1 or sedamon$1 or serenade or somnased$1 or somnibel$1 n or somnit$1).ti,ab.
62. (oxazepam or abboxapam or adumbran$1 or alopam or anxiolit$1 or azutranquil$1 or durazepam or expidet$1 or hilong or isodin$1 or linbial$1 or noctazepam or oxapuren$1 or oxepam or praxiten$1 or serax or serenid$1 or serepax or seresta or serpax or sigacalm$1 or sobril$1 or tazepam$1 or uskan).ti,ab.
63. (prazepam or centrax or demetrin$1 or lysanxia or mono demetrin$1 or monodemetrin$1 or reapam or sedapran$1 or verstran).ti,ab.
64. (temazepam or apo temazepam or dasuen or euhypnos or hydroxydiazepam or levanxol$1 or methyloxazepam or nocturne$1 or norkotral tema or normison$1 or normitab or nortem or oxydiazepam or planum or pronervon t or remestan$1 or restoril$1 or signopam or temaz$1 or temazep von ct or temazepax or temtabs or tenox or texapam).ti,ab.
65. or/44-64
66. exp antidepressive agents, tricyclic/ or (tca$1 or tricyclic$).ti,ab.
67. (amitriptyl$1 or amitryptil$1 or amitryptin$1 or amitryptylin$1 or amytriptil$1 or amytriptyl$1 or amytryptil$1 or adepress or adepril$1 or ambivalon$1 or amineurin$1 or amitid$1 or amitril$1 or amitrip or amitrol$1 or anapsique or antitriptylin$1 or apoamitriptylin$1 or damilen$1 or damylen$1 or domical$1 or elatrol$1 or elavil$1 or endep or enovil$1 or etafon$1 or etafron$1 or euplit$1 or lantron$1 or laroxal$1 or laroxyl$1 or lentizol$1 or novoprotect or proheptadien$1 or redomex or sarboten retard 75 or saroten$1 or sarotex or stelminal$1 or sylvemid$1 or syneudon$1 or teperin$1 or terepin$1 or triptafen$1 or triptanol$1 or triptizol$1 or triptyl or triptylin$1 or tryptanol$1 or tryptin$1 or tryptizol$1).ti,ab.
68. (chlomipramin$1 or chlorimipramin$1 or chloroimipramin$1 or clomipramin$1 or anafranil$1 or anafranilin$1 or anafranyl or domipramin$1 or hydiphen$1 or monochlor imipramin$1 or monochlorimipramin$1 or monochloroimipramin$1).ti,ab.
69. (dothiepin$1 or dosulepin$1 or altapin$1 or depresym$1 or dopress or dothep or idom or prothiaden$1 or prothiadien$1 or prothiadin$1 or protiaden$1 or thaden).ti,ab.
70. (doxepin$1 or adapin$1 or apodoxepin$1 or aponal$1 or co dox or curatin$1 or deptran$1 or desidox or doneurin$1 or doxepia or espadox or mareen or prudoxin$1 or quitaxon$1 or silenor or sinepin or sinequan$1 or sinquan$1 or xepin$1 or zonalon$1).ti,ab.
71. (imipramin$1 or antideprin$1 or berkomin$1 or chrytemin$1 or deprimin or deprinol$1 or depsonil or dynaprin or eupramin or ia

pram or imavate or imidobenzyl$1 or imidol$1 or imipramid$1 or imipramil or imiprex or imiprin$1 or imizin$1 or irmin or janimin$1 or melipramin$1 or norchlorimipramin$1 or norpramin$1 or novopramin$1 or presamin$1 or pryleugan$1 or psychoforin$1 or psychoforin$1 or servipramin$1 or sk pramin$1 or surplix or tofranil$1 or trofanil$1).ti,ab.

72. (lofepramin$1 or lopramin$1 or amplit$1 or deftan$1 or feprapax or gamanil$1 or gamonil$1 or lomont or lopramin$1 or tymelyt).ti,ab.
73. (mianserin$1 or athymil$1 or bolvidon$1 or investig or lantanon$1 or lanthanon$1 or lerivon$1 or miaxan$1 or norval or serelan$1 or tetramid$1 or tolvin$1 or tolvon$1).ti,ab.
74. (nortriptylin$1 or acetexa or allegron$1 or altilev or atilev or avantyl or aventyl or desitriptylin$1 or desmethylamitriptylin$1 or martimil$1 or noramitriptylin$1 or norfenazin$1 or noritren$1 or norpress or nortrilen$1 or nortryptilin$1 or nortryptylin$1 or pamelor or paxtibi or propylamin$1 or psychostyl or sens?val).ti,ab.
75. opipramol/or (opipramol$1 or dinsidon$1 or ensidon$1 or eusidon$1 or insidon$1 or nisidan$1 or oprimol or pramolan$1).ti,ab.
76. (trazodon$1 or beneficat or deprax or desirel or desyrel$1 or molipaxin$1 or pesyrel$1 or rpragazon$1 or pragmarel$1 or pragmazon$1 or thombran$1 or thrombin$1 or thrombran$1 or tombran$1 or trasodon$1 or trazolan$1 or trazorel or trazon$1 or trialodine or trittico).ti,ab.
77. (trimepramin$1 or trimeprimin$1 or trimepropimin$1 or trimidura or trimineurin$1 maleate or trimipramin$1 or trimoprimin$1 or eldoral$1 or herphonal$1 or trimineurin$1 or novo tripramin$1 or novotripramin$1 or nutrimipramin$1 or rhotrimin$1 or stangyl or surmontil$1 or apo trimip or apotrimip or herphonal$1 or stangyl or surmontil$1).ti,ab.
78. exp serotonin uptake inhibitors/ or (((serotonin or 5 ht or 5 hydroxytryptamine) adj (uptake or reuptake or re uptake) adj inhibit$) or ssri$).ti,ab.
79. (citalopram or celexa or cipramil$1 or cytalopram or elopram or escitalopram or lexapro or nitalapram or sepram or seropram).ti,ab.
80. (escitalopram or cipralex or lexapro or seroplex).ti,ab.
81. (fluoxetin$1 or fluctin$1 or flunirin$1 or fluoxifar or prosac or prozac or prozamin or sarafem or symbyax).ti,ab.
82. (fluvoxamin$1 or depromel$1 or desiflu or dumirox or faverin$1 or fevarin$1 or floxyfral$1 or fluoxamin$1 or fluroxamin$1 or fluvoxadura or luvox).ti,ab.
83. (nefazadon$1 or dutonin or nefadar or reseril$1 or serzon$1).ti,ab.
84. (paroxetin$1 or aropax or deroxat or motivan$1 or paxil or pexeva or seroxat or tagonis).ti,ab.
85. (sertralin$1 or altrulin$1 or aremis or besitran$1 or gladem or lustral$1 or naphthylamin$1 or sealdin$1 or serad or serlain$1 or tresleen or zoloft).ti,ab.

86. or/66-85
87. or/1-86
88. (ae or ct or po or to).fs.
89. exp abnormalities, drug induced/ or exp adverse drug reaction reporting systems/ or exp death/ or exp drug hypersensitivity/ or exp drug-induced liver injury / or drug interactions/ or exp intraoperative complications/ or drug monitoring/ or exp drug tolerance/ or overdose/ or exp poisoning/ or exp postoperative complications/ or exp product surveillance, postmarketing/ or respiration depression/ or risk/ or risk assessment/ or risk factors/ or exp toxemia/
90. (causa$ or ((adverse or negativ$ or side or undesir$ or unwanted) adj2 (effect$ or event$ or outcome$ or reaction$)) or death$ or discontinuation effect$ or (caution$ or complication$ or contraindicat$ or contra indicat$ or harm$ or hazard$ or interaction$1 or intolerab$ or lethal$ or noxious$ or overdos$ or safety or safe or tolerab$ or toxic$ or warning$) or (treatment emergent or adrs)).ti,ab.
91. or/88-90
92. 87 and 91

Search filters

a) Systematic review search filter – adaptated from a filter designed by the Health Information Research Unit of the McMaster University, Ontario.

Medline – Ovid SP interface

1. meta-analysis/or meta-analysis as topic/
2. meta-analysis.pt.
3. ((evidence or quantitative$ or systematic$) adj2 (overview or review)).ti,ab.
4. (((bibliographic or electronic) adj database$) or bids or cochrane or embase or index medicus or isi citation or medline or psyclit or psychlit or pubmed or scisearch or science citation or (web adj2 science)).ti,ab. and review.pt.
5. (metaanal$ or meta anal$ or metasynthes$ or meta synthes$).ti,ab.
6. ((pool$ or combined or combining) adj2 (data or trials or studies or results)).ti,ab.
7. or/1-6

b) RCT search filter – adaptated from a filter designed by the Health Information Research Unit of the McMaster University, Ontario.

Medline – Ovid SP interface

1. exp clinical trial/ or cross over studies/ or double blind method/ or random allocation/ or randomized controlled trials as topic/ or single blind method/
2. (clinical adj2 trial$).ti,ab.
3. (crossover or cross over).ti,ab.
4. (((single$ or doubl$ or trebl$ or tripl$) adj2 blind$) or mask$ or dummy or singleblind$ or doubleblind$ or trebleblind$ or tripleblind$).ti,ab.
5. (placebo$ or random$).mp.
6. (clinical trial$ or controlled clinical trial$ or random$).pt.
7. animals/ not (humans/ or human$.tw.)
8. (or/1-6) not 7

c) Observational study filter – developed in house.

Medline– Ovid SP interface

1. case-control studies/
2. cohort studies/
3. cross-sectional studies/
4. epidemiologic studies/
5. follow-up studies/
6. longitudinal studies/
7. prospective studies/
8. retrospective studies/
9. (cohort$1 or cross section$ or crosssection$ or followup$ or follow up$ or followed or longitudinal$ or prospective$ or retrospective$).ti,ab.
10. (case adj2 (control$ or series)).ti,ab.
11. or/1-10

Search terms for case control studies excluded from filter (where required) as specified in the review protocols.

APPENDIX 10: CLINICAL STUDY DATA EXTRACTION FORM

Intervention studies

Methods	Allocation: Follow-up period: N lost to follow up:
Participants	Setting: Inclusion criteria: Numbers: N participants: N experimental, N control. Profile: N% (n=) female. n% (n=) had diagnosis of X disorder. Source of participants:
Interventions	Experimental: Intervention: Control: Therapist: Type of therapy offered: Experimental: Control: Length of treatment:
Outcomes	Included: Outcome A, B, C etc. Excluded:
Notes	

APPENDIX 11: QUALITY CHECKLISTS FOR CLINICAL STUDIES AND REVIEWS

Methodology checklist: 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:					

Notes on use of Methodology checklist: randomised controlled trials

The studies covered by this checklist are designed to answer questions about the relative effects of interventions such as drugs, psychological therapies, operations or placebos. Such studies can include comparisons of 'test and treat strategies' involving a diagnostic test and subsequent management. The checklist does not cover comparisons of diagnostic test accuracy or questions about prognosis.

This checklist replaces the methodology checklist for randomised controlled trials from 'The guidelines manual' 2007 (appendix C).

Some of the items on this checklist may need to be filled in individually for different outcomes reported by the study. It is therefore important that the systematic reviewer has a clear idea of what the important outcomes are **before** appraising a study. You are likely to need input from the Guideline Development Group in defining the important outcomes.

Checklist items are worded so that a 'yes' response always indicates that the study has been designed/conducted in such a way as to minimise the risk of bias for that item. An 'unclear' response to a question may arise when the item is not reported or not clearly reported. 'N/A' should be used when a randomised controlled trial cannot give an answer of 'yes' no matter how well it has been done.

This checklist is designed to assess the internal validity of the study; that is, whether the study provides an unbiased estimate of what it claims to show. Internal validity implies that the differences observed between groups of participants allocated to different interventions may (apart from the possibility of random error) be attributed to the intervention under investigation. Biases are characteristics that are likely to make estimates of effect differ systematically from the truth.

Recording the presence and direction of bias

The checklist contains four sections (A–D), each of which addresses a potential source of bias relating to internal validity. At the end of each section you are asked to give your opinion on whether bias is present and to estimate the likely direction of this bias – that is, whether you think it will have increased or decreased the effect size reported by the study. It will not always be possible to determine the direction of bias, but thinking this through can help greatly in interpreting results.

A: Selection bias

Selection bias may be introduced into a study when there are systematic differences between the participants in the different treatment groups. As a result, the differences in the outcome observed may be explained by pre-existing differences between the groups rather than because of the treatment itself. For example, if the people in one group are in poorer health, then they are more likely to have a bad outcome than those in the other group, regardless of the effect of the treatment. The treatment groups should be similar at the start of the study – the only difference between the groups should be the intervention received.

Randomisation

There are two aspects to randomisation:

- generation of the random allocation sequence that results in groups that differ only randomly
- allocation concealment, so that both the participant and the investigator are unaware of which group the next participant will be allocated to when entering the study.

A1. An appropriate method of randomisation was used to allocate participants to treatment groups

If an appropriate method of randomisation has been used, each participant should have an equal chance of ending up in any of the treatment groups. Examples of random allocation sequences include random numbers generated by computer, tables of random numbers, and drawing of lots or envelopes. The allocation sequence should not be related to outcome or prognosis, or be predictable, such as date of birth or admission date. There are some more complicated ways of allocating people to treatment groups that minimise the differences between groups, such as block randomisation and minimisation. Although these are not truly random, they are usually considered to be adequate for the purpose. If a study does not report the method of randomisation used, this should be scored as 'unclear'.

A2. There was adequate concealment of allocation

If investigators are aware of the allocation group for the next participant being enrolled in the study, there is potential for participants to be enrolled in an order that results in imbalances in important characteristics. For example, a clinician might feel that participants who are more unwell are likely to do

better on a new, experimental, treatment and be tempted to enrol such participants when they know they will be allocated to that group. This would result in the participants in the intervention group being, on average, more unwell. Concealment of treatment group may not always be feasible (as in, for example, a comparison of a surgical with a medical intervention), but concealment of allocation up until the point of enrolment in the study should always be possible.

The information presented within the paper should provide some assurance that allocations were not known until at least the point of enrolment. Centralised allocation, computerised allocation systems and the use of coded identical containers are all regarded as adequate methods of concealment. Sealed envelopes can be considered as adequate concealment if the envelopes are serially numbered, sealed and opaque, and allocation is performed by a third party. Poor methods of allocation concealment include alternation, or the use of case record numbers, date of birth or day of the week.

If the method of allocation concealment used is regarded as poor, or relatively easy to subvert, the study must be given a lower quality rating. If a study does not report any concealment approach, this should be scored as 'unclear'.

A3. The groups were comparable at baseline, including all major confounding and prognostic factors

Studies may report the distributions of potential prognostic and confounding factors in the comparison groups, or important differences in the distribution of these factors may be noted.

Formal tests comparing the groups are problematic – failure to detect a difference does not mean that a difference does not exist, and multiple comparisons of factors may falsely detect some differences that are not real. Clinical input may be required to determine whether all likely confounders have been considered. Confounding factors may differ according to outcome, so you will need to consider potential confounding factors for all of the outcomes that are of interest to your review.

B: Performance bias

Performance bias refers to systematic differences between the comparison groups in the care provided to the participants, other than the intervention under investigation.

This may consist of additional treatment, advice or counselling, rather than a physical intervention, or even simply a belief about the effects of an intervention. If performance bias is present, it can be difficult to attribute any observed effect to the experimental treatment rather than to the other factors.

B1. The comparison groups received the same care apart from the intervention(s) studied

There should be no differences between the treatment groups apart from the intervention received. If some participants received additional treatment

(known as 'co-intervention'), this treatment is a potential confounding factor that may compromise the results.

Blinding

Blinding (also known as masking) refers to the process of withholding information about treatment allocation or exposure status from those involved in the study who could potentially be influenced by this information. This can include participants, investigators, those administering care and those involved in data collection and analysis. If people are aware of the treatment allocation or exposure status ('unblinded'), this can bias the results of studies, either intentionally or unintentionally, through the use of other effective co-interventions, decisions about withdrawal, differential reporting of symptoms or influencing concordance with treatment. Blinding of those assessing outcomes is covered in section D on detection bias. Blinding of participants and carers is not always possible, particularly in studies of non-drug interventions, and so performance bias may be a particular issue in these studies. It is important to think about the likely size and direction of bias caused by failure to blind.

The terms 'single blind', 'double blind' and even 'triple blind' are sometimes used in studies. Unfortunately, they are not always used consistently. Commonly, when a study is described as 'single blind', only the participants are blind to their group allocation. When both participants and investigators are blind to group allocation, the study is often described as 'double blind'. It is preferable to record exactly who was blinded, if reported, to avoid misunderstanding.

B2. Participants receiving care were kept 'blind' to treatment allocation

The knowledge of assignment to a particular treatment group may affect outcomes, such as a study participant's reporting of symptoms, self-use of other known interventions or even dropping out of the study.

B3. Individuals administering care were kept 'blind' to treatment allocation

If individuals who are administering the intervention and/or other care to the participant are aware of treatment allocation, they may treat participants receiving one treatment differently from those receiving the comparison treatment; for example, by offering additional co-interventions.

C: Attrition bias

Attrition refers to the loss of participants during the course of a study. Attrition bias occurs when there are systematic differences between the comparison groups with respect to participants lost, or differences between participants lost to the study and those who remain. Attrition can occur at any point after participants have been allocated to their treatment groups. As such, it includes participants who are excluded after allocation (and may indicate a violation of eligibility criteria), those who do not complete treatment (whether or not they continue measurement) and those who do not

complete outcome measurement (regardless of whether or not treatment was completed). Consideration should be given to why participants dropped out, as well as how many. Participants who dropped out of a study may differ in some significant way from those who remained as part of the study throughout. Drop-out rates and reasons for dropping out should be similar across all treatment groups. The proportion of participants excluded after allocation should be stated in the study report, and the possibility of attrition bias considered within the analysis; however, these are not always reported.

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)

If the comparison groups are followed for different lengths of time, then more events are likely to occur in the group followed up for longer, distorting the comparison. This may be overcome by adjusting the denominator to take the time into account; for example by using person-years.

C2a. How many participants did not complete treatment in each group?

A very high number of participants dropping out of a study should give concern. The drop-out rate may be expected to be higher in studies conducted over a longer period of time. The drop-out rate includes people who did not even start treatment; that is, they were excluded from the study after allocation to treatment groups.

C2b. 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)

If there are systematic differences between groups in terms of those who did not complete treatment, consider both why participants dropped out and whether any systematic differences in those who dropped out may be related to the outcome under study, such as potential confounders. Systematic differences between groups in terms of those who dropped out may also result in treatment groups that are no longer comparable with respect to potential confounding factors.

C3a. For how many participants in each group were no outcome data available?

A very high number of participants for whom no outcome data were available should give concern.

C3b. 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)

If there are systematic differences between groups in terms of those for whom no outcome data were available, consider both why the outcome data were

not available and whether there are any systematic differences between participants for whom outcome data were and were not available.

D: Detection bias (this section should be completed individually for each important relevant outcome)

The way outcomes are assessed needs to be standardised for the comparison groups; failure to 'blind' people who are assessing outcomes can also lead to bias, particularly with subjective outcomes. Most studies report results for more than one outcome, and it is possible that detection bias may be present in a study for some, but not all, outcomes. It is therefore recommended that this section is completed individually for each important outcome that is relevant to the guideline review question under study. To avoid biasing your review, you should identify the relevant outcomes **before** considering the results of the study. Clinical input may be required to identify the most important outcomes for a review.

D1. The study had an appropriate length of follow-up

The follow-up of participants after treatment should be of an adequate length to identify the outcome of interest. This is particularly important when different outcomes of interest occur early and late after an intervention. For example, after surgical interventions there is usually an early harm because of side effects, with benefits apparent later on. A study that is too short will give an unbalanced assessment of the intervention.
For events occurring later, a short study will give an imprecise estimate of the effect, which may or may not also be biased. For example, a late-occurring side effect will not be detected in the treatment arm if the study is too short.

D2. The study used a precise definition of outcome D3. A valid and reliable method was used to determine the outcome

The outcome under study should be well defined. It should be clear how the investigators determined whether participants experienced, or did not experience, the outcome. The same methods for defining and measuring outcomes should be used for all participants in the study. Often there may be more than one way of measuring an outcome (for example, physical or laboratory tests, questionnaire, reporting of symptoms). The method of measurement should be valid (that is, it measures what it claims to measure) and reliable (that is, it measures something consistently).

D4. Investigators were kept 'blind' to participants' exposure to the intervention D5. Investigators were kept 'blind' to other important confounding and prognostic factors

In this context the 'investigators' are the individuals who are involved in making the decision about whether a participant has experienced the outcome under study. This can include those responsible for taking physical measurements and recording symptoms, even if they are not ultimately responsible for determining the outcome. Investigators can introduce bias

through differences in measurement and recording of outcomes, and making biased assessments of a participant's outcome based on the collected data. The degree to which lack of blinding can introduce bias will vary depending on the method of measuring an outcome, but will be greater for more subjective outcomes, such as reporting of pain.

Physical separation of the assessment from the participant (for example, sending samples off to a laboratory) can often be considered as blind if it can be assumed that the laboratory staff are unaware of the treatment assignment.

Methodology checklist: cohort studies

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	The method of allocation to treatment groups was unrelated to potential confounding factors (that is, the reason for participant allocation to treatment groups is not expected to affect the outcome(s) under study)	Yes	No	Unclear	N/A
A2	Were any attempts made within the design or analysis to balance the comparison groups for potential confounders?	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/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:					

1

Notes on use of Methodology checklist: cohort studies

Cohort studies are designed to answer questions about the relative effects of interventions, such as drugs, psychological therapies, operations or placebos. Such studies can include comparisons of 'test and treat strategies' involving a diagnostic test and subsequent management. This checklist does not cover comparisons of diagnostic test accuracy or questions about prognosis.

This checklist replaces the methodology checklist for cohort studies from 'The guidelines manual 2007' (appendix D).

Some of the items on this checklist may need to be filled in individually for different outcomes reported by the study. It is therefore important that the systematic reviewer has a clear idea of what the important outcomes are **before** appraising a study. You are likely to need input from the Guideline Development Group in defining the important outcomes.

Checklist items are worded so that a 'yes' response always indicates that the study has been designed/conducted in such a way as to minimise the risk of bias for that item. An 'unclear' response to a question may arise when the item is not reported or is not reported clearly. 'N/A' should be used when a cohort study cannot give an answer of 'yes' no matter how well it has been done.

This checklist is designed to assess the internal validity of the study; that is, whether the study provides an unbiased estimate of what it claims to show. Internal validity implies that the differences observed between groups of participants allocated to different interventions may (apart from the possibility of random error) be attributed to the intervention under investigation. Biases are characteristics that are likely to make estimates of effect differ systematically from the truth.

Recording the presence and direction of bias

This checklist contains four sections (A–D), each of which addresses a potential source of bias relating to internal validity. At the end of each section you are asked to give your opinion on whether bias is present, and to estimate the likely direction of this bias – whether you think it will have increased or decreased the effect size reported by the study. It will not always be possible to determine the direction of bias, but thinking this through can help greatly in interpreting results.

A: Selection bias

Selection bias can be introduced into a study when there are systematic differences between the participants in the different treatment groups. As a result, the differences in the outcome observed may be explained by pre-existing differences between the groups rather than because of the treatment itself. For example, if the people in one group are in poorer health, then they are more likely to have a bad outcome than those in the other group, regardless of the effect of the treatment. The treatment groups should be

similar at the start of the study – the only difference between the groups should be in terms of the intervention received.

The main difference between randomised trials and non-randomised studies is the potential susceptibility of the latter to selection bias. Randomisation should ensure that, apart from the intervention received, the treatment groups differ only because of random variation. However, care needs to be taken in the design and analysis of non-randomised studies to take account of potential confounding factors. There are two main ways of accounting for potential confounding factors within non-randomised studies. Firstly, participants can be allocated to treatment groups to ensure that the groups are equal with respect to the known confounders. Secondly, statistical techniques can be used within the analysis to take into account known differences between groups. Neither of these approaches is able to address unknown or unmeasurable confounding factors, and it is important to remember that measurement of known confounders is subject to error. It can rarely, if ever, be assumed that all important factors relevant to prognosis and responsiveness to treatment are known. Hence, considerable judgement is needed to assess the internal validity of non-randomised studies; clinical input may be needed to identify potential confounding factors that should be taken into consideration.

A1. The method of allocation to treatment groups was unrelated to potential confounding factors

In non-randomised studies, there will usually be a reason why participants are allocated to the treatment groups (often as a result of clinician and/or patient choice). If this reason is linked to the outcome under study, this can result in confounding by indication (where the decision to treat is influenced by some factor that is related in turn to the treatment outcome). For example, if the participants who are the most ill are selected for the treatment, then the treatment group may experience worse outcomes because of this difference between the groups at baseline. It will not always be possible to determine from the report of a study which factors influenced the allocation of participants to treatment groups.

A2. Were any attempts made within the design or analysis to balance the comparison groups for potential confounders?

This represents an attempt when designing the study to ensure that the groups are similar in terms of known confounding or prognostic factors, in order to optimise comparability between the treatment groups. For example, in a matched design, the controls are deliberately chosen to be equivalent to the treatment group for any potential confounding variables, such as age and sex.

An alternative approach is to use statistical techniques to adjust for known confounding factors in the analysis.

A3. The groups were comparable at baseline, including all major confounding and prognostic factors

Studies may report the distributions of potential prognostic and confounding factors in the comparison groups, or important differences in these factors may be noted.

Formal tests comparing the groups are problematic – failure to detect a difference does not that mean a difference does not exist, and multiple comparisons of factors may falsely detect some differences that are not real. Clinical input may be needed to determine whether all likely confounders have been considered. Confounding factors may differ according to outcome, so you will need to consider potential confounding factors for each of the outcomes that are of interest to your review.

B: Performance bias

Performance bias refers to systematic differences in the care provided to the participants in the comparison groups, other than the intervention under investigation.

This may consist of additional treatment, advice or counselling, rather than a physical intervention, or even simply a belief about the effects of an intervention. If performance bias is present, it can be difficult to attribute any observed effect to the experimental treatment rather than to the other factors. Performance bias can be more difficult to determine within non-randomised than within randomised studies, because the latter are likely to have been better planned and executed according to strict treatment protocols that specify standardised interventions and care. It may be particularly difficult to determine performance bias for retrospective studies, where there is usually no control over standardisation.

B1. The comparison groups received the same care apart from the intervention(s) studied

There should be no differences between the treatment groups apart from the intervention received. If some participants received additional treatment (known as 'co-intervention'), this treatment is a potential confounding factor that may compromise the results.

Blinding

Blinding (also known as masking) refers to the process of withholding information about treatment allocation or exposure status from those involved in the study who could potentially be influenced by this information. This can include participants, investigators, those administering care and those involved in data collection and analysis. If people are aware of the treatment allocation or exposure status ('unblinded'), this can bias the results of studies, either intentionally or unintentionally, through the use of other effective co-interventions, decisions about withdrawal, differential

reporting of symptoms or influencing concordance with treatment. Blinding of those assessing outcomes is covered in section D on detection bias. Blinding of participants and carers is not always possible, particularly in studies of non-drug interventions, and so performance bias may be a particular issue in these studies. It is important to think about the likely size and direction of bias caused by failure to blind.

The terms 'single blind', 'double blind' and even 'triple blind' are sometimes used in studies. Unfortunately, they are not always used consistently. Commonly, when a study is described as 'single blind', only the participants are blind to their group allocation. When both participants and investigators are blind to group allocation the study is often described as 'double blind'. It is preferable to record exactly who was blinded, if reported, to avoid misunderstanding.

B2. Participants receiving care were kept 'blind' to treatment allocation

The knowledge of assignment to a particular treatment group may affect outcomes such as a study participant's reporting of symptoms, self-use of other known interventions or even dropping out of the study.

B3. Individuals administering care were kept 'blind' to treatment allocation

If individuals who are administering the intervention and/or other care to the participant are aware of treatment allocation, they may treat participants receiving one treatment differently from those receiving the comparison treatment; for example, by offering additional co-interventions.

C: Attrition bias

Attrition refers to the loss of participants during the course of a study. Attrition bias occurs when there are systematic differences between the comparison groups with respect to participants lost, or differences between the participants lost to the study and those who remain. Attrition can occur at any point after participants have been allocated to their treatment groups. As such, it includes participants who are excluded after allocation (and may indicate a violation of eligibility criteria), those who do not complete treatment (whether or not they continue measurement) and those who do not complete outcome measurement (regardless of whether or not treatment was completed). Consideration should be given to why participants dropped out, as well as how many. Participants who dropped out of a study may differ in some significant way from those who remained as part of the study throughout. Drop-out rates and reasons for dropping out should be similar across all treatment groups. The proportion of participants excluded after allocation should be stated in the study report and the possibility of attrition bias considered within the analysis; however, these are not always reported.

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)

If the comparison groups are followed for different lengths of time, then more events are likely to occur in the group followed up for longer, distorting the comparison. This may be overcome by adjusting the denominator to take the time into account; for example by using person-years.

C2a. How many participants did not complete treatment in each group?

A very high number of participants dropping out of a study should give concern. The drop-out rate may be expected to be higher in studies conducted over a longer period of time. The drop-out rate includes people who did not even start treatment; that is, they were excluded from the study after allocation to treatment groups.

C2b. 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)

If there are systematic differences between groups in terms of those who did not complete treatment, consider both why participants dropped out and whether any systematic differences in those who dropped out may be related to the outcome under study, such as potential confounders. Systematic differences between groups in terms of those who dropped out may also result in treatment groups that are no longer comparable with respect to potential confounding factors.

C3a. For how many participants in each group were no outcome data available?

A very high number of participants for whom no outcome data were available should give concern.

C3b. 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)

If there are systematic differences between groups in terms of those for whom no outcome data were available, consider both why the outcome data were not available and whether there are any systematic differences between participants for whom outcome data were and were not available.

D: Detection bias (this section should be completed individually for each important relevant outcome)

The way outcomes are assessed needs to be standardised for the comparison groups; failure to 'blind' people who are assessing the outcomes can also lead to bias, particularly with subjective outcomes. Most studies report results for more than one outcome, and it is possible that detection bias may be present for some, but not all, outcomes. It is therefore recommended that this section is completed individually for each important outcome that is relevant to the guideline review question under study. To avoid biasing your review, you

should identify the relevant outcomes **before** considering the results of the study. Clinical input may be required to identify the most important outcomes for a review.

D1. The study had an appropriate length of follow-up

The follow-up of participants after treatment should be of an adequate length to identify the outcome of interest. This is particularly important when different outcomes of interest occur early and late after an intervention. For example, after surgical interventions there is usually early harm because of side effects, with benefits apparent later on. A study that is too short will give an unbalanced assessment of the intervention.

For events occurring later, a short study will give an imprecise estimate of the effect, which may or may not also be biased. For example, a late-occurring side effect will not be detected in the treatment arm if the study is too short.

D2. The study used a precise definition of outcome D3. A valid and reliable method was used to determine the outcome

The outcome under study should be well defined and it should be clear how the investigators determined whether participants experienced, or did not experience, the outcome. The same methods for defining and measuring outcomes should be used for all participants in the study. Often there may be more than one way of measuring an outcome (for example, physical or laboratory tests, questionnaire, reporting of symptoms). The method of measurement should be valid (that is, it measures what it claims to measure) and reliable (that is, it measures something consistently).

D4. Investigators were kept 'blind' to participants' exposure to the intervention D5. Investigators were kept 'blind' to other important confounding and prognostic factors

In this context the 'investigators' are the individuals who are involved in making the decision about whether a participant has experienced the outcome under study. This can include those responsible for taking physical measurements and recording symptoms, even if they are not ultimately responsible for determining the outcome. Investigators can introduce bias through differences in measurement and recording of outcomes, and making biased assessments of a participant's outcome based on the collected data. The degree to which lack of blinding can introduce bias will vary depending on the method of measuring an outcome, but will be greater for more subjective outcomes, such as reporting of pain.

Physical separation of the assessment from the participant (for example, sending samples off to a laboratory) can often be considered as blind if it can be assumed that the laboratory staff are unaware of the treatment assignment.

1 *Methodology checklist: case–control studies*

Study identification Include author, title, reference, year of publication			
Guideline topic:		**Review question no:**	
Checklist completed by:			
Section 1: Internal validity			
		Circle one option for each question	
1.1	The study addresses an appropriate and clearly focused question.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
Selection of participants			
1.2	The cases and controls are taken from comparable populations	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.3	The same exclusion criteria are used for both cases and controls	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.4	What was the participation rate for each group (cases and controls)?	Cases: Controls:	
1.5	Participants and non-participants are compared to establish their similarities or differences	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.6	Cases are clearly defined and differentiated from controls	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.7	It is clearly established that controls are not cases	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
Assessment			
1.8	Measures were taken to prevent knowledge of primary exposure influencing case ascertainment	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable

1.9	Exposure status is measured in a standard, valid and reliable way	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
Confounding factors			
1.10	The main potential confounders are identified and taken into account in the design and analysis	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
Statistical analysis			
1.11	Have confidence intervals been provided?		

1

Section 2: Description of the study **(This information is required for evidence tables to facilitate cross-study comparisons. Please complete all sections for which information is available).** **Please print clearly**		
2.1	How many people participated in the study? *List the numbers of cases and controls separately.*	
2.2	What are the main characteristics of the study population? *Include all characteristics used to identify both cases and controls – for example, age, sex, social class, disease status.*	
2.3	What environmental or prognostic factor is being investigated?	
2.4	What comparisons are made? *Normally only one factor will be compared, but in some cases the extent of exposure may be stratified – for example, non-smokers vs light, moderate or heavy smokers. Note all comparisons here.*	
2.5	For how long are participants followed up? *This is the length of time over which participant histories are tracked in the study.*	
2.6	What outcome measure(s) is/are used? *List all outcomes that are used to assess the impact of the chosen environmental or prognostic factor.*	
2.7	What size of effect is identified? *Effect size should be expressed as an odds ratio. If any other measures are included, note them as well. Include p-values and any confidence intervals that are provided.*	
2.8	How was the study funded? *List all sources of funding quoted in the article, whether government, voluntary sector or industry.*	
2.9	Does this study help to answer your guideline review question? *Summarise the main conclusions of the study and indicate how it relates to the review question.*	

1
2

Notes on use of the Methodology checklist: case–control studies

Case–control studies are designed to answer questions of the type 'What are the factors that caused this event?'. They involve comparison of individuals who have an outcome with other individuals from the same population who do not have the outcome. These studies start after the outcome of an event, and can be used to assess multiple causes of a single event. They are generally used to assess the causes of a new problem but they may also be useful for the evaluation of population-based interventions such as screening.

The questions in **section 1** are aimed at establishing the internal validity of the study under review – that is, making sure that it has been carried out carefully, and that any link between events and outcomes is clearly established. Each question covers an aspect of methodology that has been shown to make a significant difference to the conclusions of a study.

Case–control studies need to be designed very carefully,– the complexity of their design is often not appreciated by investigators, and so many poor-quality studies are conducted. The questions in this checklist are designed to identify the main features that should be present in a well-designed study. There are few criteria that should, alone and unsupported, lead to rejection of a study. However, a study that fails to address or report on more than one or two of the questions in the checklist should almost certainly be rejected.

For each question in this section you should choose one of the following categories to indicate how well it has been addressed in the study:

- well covered
- adequately addressed
- poorly addressed
- not addressed (not mentioned, or this aspect of study design was ignored)
- not reported (mentioned, but with insufficient detail to allow assessment to be made)
- not applicable.

1.1 The study addresses an appropriate and clearly focused question

Unless a clear and well-defined question is specified, it will be difficult to assess how well the study has met its objectives or how relevant it is to the question you are trying to answer.

Selection of participants

1.2 The cases and controls are taken from comparable populations

Study participants may be selected from the target population (all individuals to which the results of the study could be applied), from the source population (a defined subset of the target population from which participants are selected) or from a pool of eligible people (a clearly defined and counted

group selected from the source population). A study that does not include clear definitions of the source population should be rejected.

1.3 The same exclusion criteria are used for both cases and controls

All selection and exclusion criteria should be applied equally to cases and controls. Failure to do so may introduce a significant degree of bias into the results of the study.

1.4 What was the participation rate for each group (cases and controls)?

Differences between the eligible population and the study participants are important because they may influence the validity of the study. A participation rate can be calculated by dividing the number of study participants by the number of people who are eligible to participate. It is more useful if it is calculated separately for cases and controls. If the participation rate is low, or there is a large difference in rate between cases and controls, the study results may be invalid because of differences between participants and non-participants. In these circumstances the study should be downgraded, and rejected if the differences are very large.

1.5 Participants and non-participants are compared to establish their similarities or differences

Even if participation rates are comparable and acceptable, it is still possible that the participants selected to act as cases or controls may differ from other members of the source population in some significant way. A well-conducted case–control study will look at samples of those not participating among the source population to ensure that the participants are a truly representative sample.

1.6 Cases are clearly defined and differentiated from controls

The method of selection of cases is of critical importance to the validity of the study. Investigators have to be certain that cases are truly cases, but must balance this with the need to ensure that the cases admitted into the study are representative of the eligible population. The issues involved in case selection are complex, and should ideally be evaluated by someone with a good understanding of the design of case–control studies. If there is no information on how cases were selected it is probably safest to reject the study as a source of evidence.

1.7 It is clearly established that controls are not cases

Just as it is important to be sure that cases are true cases, it is important to be sure that controls do not have the outcome under investigation. Controls should be chosen so that information on exposure status can be obtained or assessed in a similar way to that used for the selection of cases. If the methods of control selection are not described, the study should be rejected. If different methods of selection are used for cases and controls, the study should be

evaluated by someone with a good understanding of the design of case–control studies.

Assessment

1.8 Measures were taken to prevent knowledge of primary exposure from influencing case ascertainment

If there is a possibility that case ascertainment was influenced by knowledge of exposure status, assessment of any association is likely to be biased. A well-conducted study should take this into account in the design of the study.

1.9 Exposure status is measured in a standard, valid and reliable way

The inclusion of evidence from other sources or previous studies that demonstrate the validity and reliability of the assessment methods, or that the measurement method is a recognised procedure, should increase confidence in study quality.

Confounding factors

1.10 The main potential confounders are identified and taken into account in the design and analysis

Confounding is the distortion of a link between exposure and outcome by another factor that is associated with both exposure and outcome. The possible presence of confounding factors is one of the principal reasons why observational studies are not more highly rated as a source of evidence. The report of the study should indicate which potential confounders have been considered, and how they have been assessed or accounted for in the analysis. Clinical judgement should be used to consider whether all likely confounders have been taken into account. If the measures used to address the potential effects of confounders are considered inadequate, the study should be downgraded or rejected, depending on how serious the risk of confounding is considered to be. A study that does not address the possibility of confounding should be rejected.

Statistical analysis

1.11 Have confidence intervals been provided?

Confidence intervals are the preferred method for indicating the precision of statistical results, and can be used to differentiate between an inconclusive study and a study that shows no effect. Studies that report a single value with no assessment of precision should be treated with caution.

Section 2 of the checklist asks you to summarise key points about the study that will be added to an evidence table (see appendix K) in the next stage of the process.

Methodology checklist: the QUADAS tool for studies of diagnostic test accuracy1

Adapted from: Whiting, P., Rutjes, A.W., Dinnes, J. *et al.* (2004) Development and validation of methods for assessing the quality of diagnostic accuracy studies. Health Technology Assessment, 8, 1–234.

Study identification Including author, title, reference, year of publication				
Guideline topic:		Review question no:		
Checklist completed by:				
		Circle one option for each question		
Was the spectrum of participants representative of the patients who will receive the test in practice?	Yes	No	Unclear	N/A
Were selection criteria clearly described?	Yes	No	Unclear	N/A
Was the reference standard likely to classify the target condition correctly?	Yes	No	Unclear	N/A
Was the period between performance of the reference standard and the index test short enough to be reasonably sure that the target condition did not change between the two tests?	Yes	No	Unclear	N/A
Did the whole sample or a random selection of the sample receive verification using the reference standard?	Yes	No	Unclear	N/A
Did participants receive the same reference standard regardless of the index test result?	Yes	No	Unclear	N/A
Was the reference standard independent of the index test? (that is, the index test did not form part of the reference standard)	Yes	No	Unclear	N/A
Was the execution of the index test described in sufficient detail to permit its replication?	Yes	No	Unclear	N/A
Was the execution of the reference standard described in sufficient detail to permit its replication?	Yes	No	Unclear	N/A
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	No	Unclear	N/A
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes	No	Unclear	N/A
Were the same clinical data available when the test results were interpreted as would be available when the test is used in practice?	Yes	No	Unclear	N/A
Were uninterpretable, indeterminate or intermediate test results reported?	Yes	No	Unclear	N/A
Were withdrawals from the study explained?	Yes	No	Unclear	N/A

Notes on use of Methodology checklist: studies of diagnostic test accuracy
This checklist is designed for the evaluation of studies assessing the accuracy of specific diagnostic tests. It does **not** address questions of the usefulness of the test in practice, or how the test compares with alternatives. Such questions should be assessed using the checklists for studies on interventions (see appendices D, E and F).

The questions in this checklist are aimed at establishing the validity of the study under review – that is, making sure that it has been carried out carefully, and that the conclusions represent an unbiased assessment of the accuracy and reliability of the test being evaluated. Each question covers an aspect of methodology that is thought to make a difference to the reliability of a study.

Checklist items are worded so that a 'yes' response always indicates that the study has been designed and conducted in such a way as to minimise the risk of bias for that item. An 'unclear' response to a question may arise when the answer to an item is not reported, or not reported clearly. 'N/A' should be used when a study of diagnostic test accuracy cannot give an answer of 'yes' no matter how well it has been done.

Was the spectrum of participants representative of the patients who will receive the test in practice?

What is meant by this item

Differences between populations in demographic and clinical features may produce measures of diagnostic accuracy that vary considerably; this is known as spectrum bias. Reported estimates of diagnostic test accuracy may have limited clinical applicability (generalisability) if the spectrum of participants tested is not representative of the patients on whom the test will be used in practice. The spectrum of participants takes into account not only the severity of the underlying target condition but also demographic features and the presence of differential diagnoses and/or comorbidities.
How to score this item
Studies should score 'yes' for this item if you believe, based on the information reported, that the spectrum of participants included in the study was representative of those in whom the test will be used in practice. This judgement should be based on both the method for recruitment and the characteristics of those recruited. Studies that recruited a group of healthy controls and a group known to have the target disorder will be coded as 'no' on this item in nearly all circumstances. Reviewers should pre-specify what spectrum of participants would be acceptable, taking into account factors such as disease prevalence and severity, age and sex. Clinical input may be required from the Guideline Development Group (GDG). If you think that the population studied does not fit into what you specified as acceptable, the

study should be scored as 'no'. If there is insufficient information available to make a judgement, this item should be scored as 'unclear'.

Were selection criteria clearly described?

What is meant by this item

This refers to whether studies have reported criteria for entry into the study.

How to score this item

If you think that all relevant information regarding how participants were selected for inclusion in the study has been provided, then this item should be scored as 'yes'. If study selection criteria are not clearly reported, then this item should be scored as 'no'. In situations where selection criteria are partially reported and you feel that you do not have enough information to score this item as 'yes', then it should be scored as 'unclear'.

Was the reference standard likely to classify the target condition correctly?

What is meant by this item

The reference standard is the method used to determine the presence or absence of the target condition. Indicators of diagnostic test accuracy are calculated by comparing the results of the index test with the results of the reference standard. Estimates of test performance are based on the assumption that the index test is being compared with a reference standard that is 100% sensitive and specific. If there are any disagreements between the reference standard and the index test, it is assumed that the index test is incorrect. Thus the use of an inappropriate reference standard can bias estimation of the diagnostic accuracy of the index test.

How to score this item

Making a judgement about the accuracy of the reference standard may not be straightforward. You may need to consult a member of the GDG to determine whether a test is an appropriate reference standard. If a combination of tests is used, you may have to consider carefully whether these were appropriate. If you believe that the reference standard is likely to classify the target condition correctly, then this item should be scored as 'yes'. If you do not think that the reference standard is likely to have classified the target condition correctly, then this item should be scored as 'no'. If there is insufficient information to make a judgement, then it should be scored as 'unclear'.

Was the period between performance of the reference standard and the index test short enough to be reasonably sure that the target condition did not change between the two tests?

What is meant by this item

Ideally, the results of the index test and the reference standard are collected on the same participants at the same time. If this is not possible and there is a delay, misclassification may occur because of either spontaneous recovery or progression of the disease. This is known as disease progression bias. The length of the period that may cause such bias will vary between conditions. For example, a delay of a few days is unlikely to be a problem for chronic conditions. However, for infectious diseases a delay of only a few days between performance of the index test and the reference standard may be important. This type of bias may also occur in chronic conditions in which the reference standard involves clinical follow-up of several years.
You will have to make judgements about what is considered 'short enough'. You should think about this **before** beginning your review, and define what you consider to be short enough for the specific topic area that you are reviewing. You may need clinical input to decide this.

How to score this item

When to score this item as 'yes' is related to the target condition. For conditions that progress rapidly, a delay of a even few days may be important. For such conditions this item should be scored as 'yes' if the delay between the performance of the index test and the reference standard is very short – a matter of hours or days. However, for chronic conditions, disease status is unlikely to change in a week, a month or even longer. For such conditions, longer delays between performance of the index test and reference standard may be scored as 'yes'. If you think that the period between the performance of the index test and the reference standard was sufficiently long that disease status may have changed between the performance of the two tests, then this item should be scored as 'no'. If insufficient information is provided, it should be scored as 'unclear'.

Did the whole sample or a random selection of the sample receive verification using the reference standard?

What is meant by this item

Partial verification bias (also known as work-up bias, [primary] selection bias or sequential ordering bias) occurs when not all of the study group receive confirmation of the diagnosis by a reference standard. If the results of the index test influence the decision to perform the reference standard, then biased estimates of test performance may arise. If participants are randomly selected to receive the reference standard, the overall diagnostic performance of the test is, in theory, unchanged. However, in most cases this selection is not random, possibly leading to biased estimates of the overall diagnostic accuracy. Partial verification bias generally only occurs in diagnostic cohort studies in which participants are tested using the index test before the reference standard.

How to score this item

If it is clear from the study that all participants (or a random selection) who received the index test went on to receive verification of their disease status using a reference standard, even if this reference standard was not the same for all participants, then this item should be scored as 'yes'. If some of the participants who received the index test did not receive verification of their true disease state (or the selection was not random), then this item should be scored as 'no'. If this information is not reported, this item should be scored as 'unclear'.

Did participants receive the same reference standard regardless of the index test result?

What is meant by this item

Differential verification bias occurs when some of the index test results are verified by a different reference standard. This is a particular problem if these reference standards differ in their definition of the target condition; for example, histopathology of the appendix and natural history for the detection of appendicitis. This usually occurs when participants who test positive on the index test undergo a more accurate, often invasive, reference standard test than those with negative results on the index test. The link (correlation) between a particular (negative) test result and being verified by a less accurate reference standard can lead to biased estimates of test accuracy. Differential verification bias generally only occurs in diagnostic cohort studies in which all participants are tested using the index test before the reference standard is performed.

How to score this item

If it is clear that participants received verification of their true disease status using the same reference standard, then this item should be scored as 'yes'. If some participants received verification using a different reference standard, then this item should be scored as 'no'. If this information is not reported, this item should be scored as 'unclear'.

Was the reference standard independent of the index test? (that is, the index test did not form part of the reference standard)

What is meant by this item

When the result of the index test is used in establishing the final diagnosis, incorporation bias may occur. This incorporation will probably increase the amount of agreement between index test results and the outcome of the reference standard, and hence result in overestimation of the various measures of diagnostic accuracy. For example, a study investigating magnetic resonance imaging (MRI) for the diagnosis of multiple sclerosis could have a reference standard composed of clinical follow-up, cerebrospinal fluid analysis and MRI. In this case, the index test forms part of the reference standard. It is important to note that knowledge of the results of the index test

does not automatically mean that these results are incorporated in the reference standard. This item will only apply when a composite reference standard is used to verify disease status. In such cases it is essential that a full definition of how disease status is verified and which tests form part of the reference standard is provided.

How to score this item

For studies in which a single reference standard is used, this item will not be relevant and should be scored as 'N/A'. If it is clear that the index test did not form part of the reference standard, then this item should be scored as 'yes'. If it appears that the index test formed part of the reference standard, then this item should be scored as 'no'. If this information is not reported, this item should be scored as 'unclear'.

Was the execution of the index test described in sufficient detail to permit its replication? Was the execution of the reference standard described in sufficient detail to permit its replication?

What is meant by these items

A sufficiently detailed description of the execution of the index test and the reference standard is important for two reasons. Firstly, variation in measures of diagnostic accuracy can sometimes be traced back to differences in the execution of index tests and reference standards. Secondly, a clear and detailed description (or references) is needed to implement a certain test in another setting. If tests are executed in different ways then this would be expected to have an impact on test performance. The extent to which this would be expected to affect results depends on the type of test being investigated.

How to score these items

If the study reports sufficient details to permit replication of the index test and the reference standard, then these items should be scored as 'yes'. In other cases these items should be scored as 'no'. In situations where details of test performance are partially reported and you consider that you do not have enough information to score these items as 'yes', then they should be scored as 'unclear'.

Were the index test results interpreted without knowledge of the results of the reference standard? Were the reference standard results interpreted without knowledge of the results of the index test?

What is meant by these items

This issue is similar to the blinding of the people who assess outcomes in intervention studies. Interpretation of the results of the index test may be influenced by knowledge of the results of the reference standard, and vice versa. This is known as review bias, and may lead to inflated measures of

diagnostic test accuracy. The extent to which this can affect test results will be related to the degree of subjectivity in the interpretation of the test result – the more subjective the interpretation, the more likely that the interpreter can be influenced by the results of the index test in interpreting the results of the reference standard, and vice versa. It is therefore important to consider the topic area that you are reviewing and to determine whether interpretation of the results of the index test or the reference standard could be influenced by knowledge of the results of the other test.

How to score these items

If the study clearly states that the test results (index test or reference standard) were interpreted blind to the results of the other test, then these items should be scored as 'yes'. If this does not appear to be the case, then they should be scored as 'no'. If this information is not reported, these items should be scored as 'unclear'. If in the topic area that you are reviewing the index test is always performed first, then interpretation of the results of the index test will usually be done without knowledge of the results of the reference standard. Similarly, if the reference standard is always performed first, then the results will be interpreted without knowledge of the results of the index test. In situations where one form of review bias does not apply, the item should be scored as 'N/A'. If interpretation of test results is entirely objective, then test interpretation is not susceptible to review bias and the item should be scored as 'N/A'. Another situation in which this form of bias may not apply is when test results are interpreted in an independent laboratory. In such situations it is unlikely that the person interpreting the test results will have knowledge of the results of the other test (either index test or reference standard).

Were the same clinical data available when the test results were interpreted as would be available when the test is used in practice?

What is meant by this item

The availability of information on clinical data during the interpretation of test results may affect estimates of test performance. In this context, clinical data are defined broadly to include any information relating to the participant that is obtained by direct observation, such as age, sex and symptoms. The knowledge of such factors can influence the diagnostic test result if the test involves an interpretative component. If clinical data will be available when the test is interpreted in practice, then these should also be available when the test is evaluated. However, if the index test is intended to replace other clinical tests, then clinical data should not be available. Thus, before assessing studies for this item it is important to determine what information will be available when test results are interpreted in practice. You should consult the GDG to identify this information.

How to score this item

If clinical data would normally be available when the test results are interpreted in practice and similar data were available when interpreting the index test results in the study, then this item should be scored as 'yes'. Similarly, if clinical data would not be available in practice and these data were not available when the index test results were interpreted, then this item should be scored as 'yes'. If this is not the case, then this item should be scored as 'no'. If this information is not reported, this item should be scored as 'unclear'. If interpretation of the index test is fully automated, this item may not be relevant and can be scored 'N/A'.

Were uninterpretable, indeterminate or intermediate test results reported?

What is meant by this item

A diagnostic test can produce an uninterpretable, indeterminate or intermediate result with varying frequency, depending on the test. These problems are often not reported in studies on diagnostic test accuracy, the uninterpretable results simply being removed from the analysis. This may lead to the biased assessment of the test characteristics. Whether bias will arise depends on the possible correlation between uninterpretable test results and the true disease status. If uninterpretable results occur randomly and are not related to the true disease status of the individual then, in theory, these should not have any effect on test performance. It is important that uninterpretable results are reported so that the impact on test performance can be considered; however, poor quality of reporting means that this is not always the case.

How to score this item

If it is clear that all test results, including uninterpretable, indeterminate or intermediate results, are reported, then this item should be scored as 'yes'. If the authors do not report any uninterpretable, indeterminate or intermediate results, and if the results are reported for all participants who were described as having been entered into the study, then this item should also be scored as 'yes'. If you think that such results occurred but have not been reported, then this item should be scored as 'no'. If it is not clear whether all study results have been reported, then this item should be scored as 'unclear'.

Were withdrawals from the study explained?

What is meant by this item

This occurs when participants withdraw from the study before the results of both the index test and the reference standard are known. If participants lost to follow-up differ systematically from those who remain, for whatever reason, then estimates of test performance may be biased. Poor quality of reporting of withdrawals may make the impact on estimates of test performance difficult to determine.

How to score this item

If it is clear what happened to all participants who entered the study, for example if a flow diagram of study participants is reported, then this item should be scored as 'yes'. If the authors do not report any withdrawals and if results are available for all participants who were reported to have been entered into the study, then this item should also be scored as 'yes'. If it appears that some of the participants who entered the study did not complete the study (that is, did not receive both the index test and the reference standard), and these participants were not accounted for, then this item should be scored as 'no'. If it is not clear whether all participants who entered the study were accounted for, then this item should be scored as 'unclear'.

APPENDIX 12: SEARCH STRATEGIES FOR THE IDENTIFICATION OF HEALTH ECONOMICS EVIDENCE

Search strategies

The search strategies should be referred to in conjunction with information set out in Section 3.6.1. Each search was constructed using the groups of terms as set out in Box 1. The full set of terms for each search in Medline are documented below.

1

Box 1: Summary of systematic search strategies

Chapter: Training				
Review area	**Search type**	**Search construction (applicable to each review area)**	**Study design**	**Databases / date range**
Staff training	New	[(Self-harm terms) AND (Staff training terms) AND (HE/QoL filter)]	Economic evidence (including full and partial economic evaluations) and health technology assessment reports	CINAHL, EMBASE, MEDLINE, PsycINFO, NHS EED, HTA, EconLit [01.01.1995 up to 25 January 2011]
Chapter: Psychosocial assessment				
Review area	**Search type**	**Search construction (applicable to each review area)**	**Study design**	**Databases / date range**
Risk and protective factors	New	[(Self-harm terms) AND (Risk and protective factor terms) AND (HE/QoL filter)]	Economic evidence (including full and partial economic evaluations) and health technology assessment reports	CINAHL, EMBASE, MEDLINE, PsycINFO, NHS EED, HTA, EconLit [01.01.1995 up to 25 January 2011]
Formal risk assessment, needs assessment and psychosocial assessment	New	[(Self-harm terms) AND (Risk assessment, needs assessment, psychosocial assessment terms) AND (HE/QoL filter)]	Economic evidence (including full and partial economic evaluations) and health technology assessment reports	CINAHL, EMBASE, MEDLINE, PsycINFO, NHS EED, HTA, EconLit [01.01.1995 up to 25 January 2011]
Chapter: Psychosocial interventions				

Review area	Search type	Search construction (applicable to each review area)	Study design	Databases / date range
Self management and/or harm reduction strategies	New	[(Self-harm terms) and (Self management and/or harm reduction strategy terms) AND (HE/QoL filter)]	Economic evidence (including full and partial economic evaluations) and health technology assessment reports	CINAHL, EMBASE, MEDLINE, PsycINFO, NHS EED, HTA, EconLit [01.01.1995 up to 25 January 2011]
Psychosocial interventions	New	[(Self-harm terms) and (Psychosocial intervention terms) AND (HE/QoL filter)]	Economic evidence (including full and partial economic evaluations) and health technology assessment reports	CINAHL, EMBASE, MEDLINE, PsycINFO, NHS EED, HTA, EconLit [01.01.1995 up to 25 January 2011]
Chapter: Pharmacological interventions				
Review area	**Search type**	**Search construction (applicable to each review area)**	**Study design**	**Databases / date range**
Pharmacological interventions	New	[(Self harm terms) AND (Pharmacological intervention terms) AND (HE/QoL filter)]	Economic evidence (including full and partial economic evaluations) and health technology assessment reports	CINAHL, EMBASE, MEDLINE, PsycINFO, NHS EED, HTA, EconLit [01.01.1995 up to 25 January 2011]
Safer prescribing	New	[(Self harm terms) AND (Safer prescribing terms) AND (HE/QoL filter)]	Economic evidence (including full and partial economic evaluations) and health technology assessment reports	CINAHL, EMBASE, MEDLINE, PsycINFO, NHS EED, HTA, EconLit [01.01.1995 up to 25 January 2011]

a) Self harm - population search terms

Medline – Ovid SP interface

1. overdose/ or self-injurious behavior/ or self mutilation/ or suicidal ideation/ or suicide/ or suicide, attempted/
2. (autoaggress$ or auto aggress$ or automutilat$ or auto mutilat$ or cutt$ or overdose$ or (self adj2 cut$) or selfdestruct$ or self destruct$ or selfharm$ or self harm$ or selfimmolat$ or self immolat$ or selfinflict$ or self inflict$ or selfinjur$ or self injur$ or selfmutilat$ or self mutilat$ or selfpoison$ or self poison$ or suicid$).ti,ab.
3. or/1-2

<u>Question specific search strategies</u>

a) Staff training

Medline – Ovid SP interface

Does the provision of staff training (knowledge, skills based) improve outcomes?

1. educational, premedical/ or exp education, professional/ or faculty/ or faculty, medical/ or faculty, nursing/ or exp inservice training/ or exp professional competence/ or exp schools, health occupations/
2. accreditation/ or certification/ or competency based education/ or credentialing/ or exp curriculum/ or education/ or knowledge/ or learning/ or mentors/ or teaching/ or ed.fs.
3. (competen$ or course$1 or cpd$1 or curricul$ or educat$ or information or instruct$ or knowledge or learn$ or module$ or posttrain$ or pretrain$ or ((clinical or professional) adj2 (develop$ or improv$ or practice)) or skill$ or teach$ or train$ or workshop$ or work shop$).ti,ab.
4. "attitude of health personnel"/ or exp health personnel/ or exp professional role/ or specialization/ or exp medicine/ or exp nursing/ or exp pharmacy/ or exp psychology/ or exp physicians/ or exp psychiatry/
5. (analyst$ or clinician$ or consultant$1 or counsel?or$ or cpe or doctor$ or employee or gp$1 or health visitor$ or medical expert$ or nurs$ or personnel or pharmacist$ or physician$ or practitioner$ or professional$ or psychiatrist$ or psychoanalyst$ or psychologist$ or psychotherapist$ or specialist$ or staff$ or therapist$ or worker$1).ti,ab.
6. (or/2-3 and or/4-5)
7. exp health personnel/ed
8. or/1,6,7

b) Risk and protective factors

Medline – Ovid SP interface

What are the risk and protective factors (internal and external) amongst people who self harm that predict outcomes?

1. risk factors/
2. (risk$ adj2 relative).ti,ab.
3. ((predict$ or protect$ or risk$) adj2 (associat$ or attribute$ or correlate$ or determinant$ or factor$ or variable$)).ti,ab.
4. or/1-3
5. ((predict$ or risk$) adj2 (ongoing or recur$ or re cur$ or reattempt$ or re attempt$ or recur$ or repeat$ or repetit$)).ti,ab.
6. prospective repetit$.ti,ab.
7. ((associat$ or attribute$ or correlate$ or determinant$ or factor$ or variable$) adj8 (ongoing or recur$ or re cur$ or reattempt$ or re attempt$ or recur$ or repeat$ or repetit$) adj8 (autoaggress$ or aggress$ or automutilat$ or cutt$ or destruct$ or dsh or episode$ or harm$ or immolat$ or inflict$ or injur$ or mutilat$ or overdose$ or (self adj2 cut$) or poison$ or selfdestruct$ or selfharm$ or selfimmolat$ or selfinflict$ or selfinjur$ or selfmutilat$ or selfpoison$ or sh or suicid$)).ti,ab.
8. or/5-7
9. resilience, psychological/
10. (buffer$ or cope$ or recovery or resilien$).ti,ab.
11. or/9-10
12. or/4,8,11

c) Formal risk assessment, needs assessment and psychosocial assessment

Medline – Ovid SP interface

For people who self-harm, does formal risk assessment, needs assessment and psychosocial assessment improve outcomes?

1. (checklist/ or geriatric assessment/ or interview/ or interview, psychological/ or mass screening/ or nursing assessment/ or "outcome and process assessment (health care)"/ or "outcome assessment (health care)"/ or exp personality assessment/ or exp psychiatric status rating scales/ or exp psychological tests/ or questionnaires/)
2. (form$1 or checklist$ or check list$ or index$ or indices or interview$ or instrument$ or inventor$ or item$1 or measure$ or psychometric$ or psycho metric$ or question$ or scale$ or score$ or scoring or self report$ or subscale$ or test$ or tool$).ti,ab.

3. 1 or 2
4. "predictive value of tests"/ or recurrence/ or risk$.hw.
5. (predict$ or ongoing or recur$ or re cur$ or reattempt$ or re attempt$ or recur$ or repeat$ or repetit$ or risk$).ti,ab.
6. 4 or 5
7. area under curve/ or exp sensitivity and specificity/
8. ((area under adj2 curve) or auc or (diagnostic adj2 odds ratio$) or ((false or true) adj negative) or ((false or true) adj positive) or (likelihood adj3 ratio$) or ((pretest or pre test or posttest or post test) adj2 probabilit$) or (predict$ adj3 value$) or receiver operating characteristic or (roc adj2 (analy$ or curv$ or plot$)) or sensititiv$ or specificit$).tw.
9. 7 or 8
10. and/3,6,9
11. needs assessment/ or risk assessment/
12. ((client$ or clinical$ or consumer$ or need$ or patient$ or psychiatric or psychological or psychosocial or psycho social or risk or service user$ or therapeutic) adj2 (assess$ or evaluat$)).ti,ab.
13. (((assess$ or predict$ or risk$) adj2 (form$1 or checklist$ or check list$ or index$ or indices or interview$ or instrument$ or inventor$ or item$1 or measure$ or psychometric$ or question$ or scale$ or score$ or scoring or self report$ or subscale$ or test$ or tool$)) or (comprehensive adj (assessment$ or evaluation$))).ti,ab.
14. (adult suicidal ideation questionnaire or asiq or (beck depression inventory or bdi) or (beck hopelessness scale or bhs) or ((beck scale adj2 suicide ideation) or bsi) or ((brief reasons adj2 living inventory) or brfl) or (brief symptom inventory or bsi) or ((college student reasons adj2 living inventory) or csrli or csr li) or ((edinburgh risk adj2 repetition scale) or errs) or (firestone assessment adj2 self-destructive thoughts) or ((global clinical assessment) or gca) or ((hamilton depression rating scale) or hdrs) or ((hamilton rating scale adj2 depression) or hamd or ham d or hrsd or hrs d) or ((intersept scale adj2 suicidal thinking) or isst) or lethality scale$ or (life satisfaction scale or ls scale) or lifetime parasuicide count or ((linehan reasons adj2 living inventory) or lrfl) or ((manchester self harm rule) or mshr) or ((modified scale adj2 suicide ideation) or mssi) or (parasuicide history interview or phi) or ((quiz adj2 depression adj2 suicide adj2 later life) or qdsll) or (reasons adj2 living inventory) or ((reasons adj2 living scale adj2 older adult questionnaire) or rfloa or rfl oa) or ((reasons adj2 living scale adj2 younger adult questionnaire) or rflya or rfl ya) or risk rescue rating or ((scale adj2 suicide ideation) or ssi) or (self-inflicted injury severity form or siisf or sii sf) or (self-monitoring suicide ideation scale or smsis of sms is) or (suicidal behaviors interview or sbi) or (suicidal ideation questionnaire or siq) or (suicidal ideation screening questionnaire or sisq or sis q) or (suicidal intent scale or sis) or ((suicide assessment scale) or suas) or (suicide behaviors questionnaire or sbq)

or (suicide intervention response inventory or siri) or (suicide opinion questionnaire or soq) or (suicide potential rating scale or suicide lethality scale or spls or spl s) or (suicide probability scale or sps) or (suicide status form or ssf) or ((symptom driven diagnostic system adj2 primary care) or sddspc or sdds pc) or ((positive adj2 negative suicide ideation inventory) or pansi)).ti,ab.

15. or/11-14
16. or/10,15

d) Self management and/or harm minimisation

Medline – Ovid SP interface

For people who self-harm, does the provision of self management and/or harm minimisation strategies, compared with no treatment or treatment as usual, improve outcomes?

1. self care/
2. ((self adj (care or instruct$ or manag$ or monitor$ or regulat$ or reinforc$ or re inforc$)) or selfcare or selfinstruct$ or selfmanag$ or selfmonitor$ or selfregulat$ or (minimal adj (contact or guidance)) or (mutual adj (help or aid or support$))).ti,ab.
3. harm reduction/ or risk management/ or risk reduction behavior/
4. ((autoaggress$ or auto aggress$ or automutilat$ or mutilat$ or cutt$ or overdose$ or (self adj2 cut$) or selfdestruct$ or destruct$ or selfharm$ or harm$ or selfimmolat$ or immolat$ or selfinflict$ or inflict$ or selfinjur$ or injur$ or selfmutilat$ or mutilat$ or selfpoison$ or poison$ or suicid$) adj2 (minimi$ or reduc$)).ti,ab.
5. ((autoaggress$ or auto aggress$ or automutilat$ or mutilat$ or cutt$ or overdose$ or (self adj2 cut$) or selfdestruct$ or destruct$ or selfharm$ or harm$ or selfimmolat$ or immolat$ or selfinflict$ or inflict$ or selfinjur$ or injur$ or selfmutilat$ or mutilat$ or selfpoison$ or poison$ or suicid$) adj4 (((decreas$ or diminish$ or fall$ or fell or less$ or limit$ or low or lower$) adj2 risk$) or minimi$ or reduc$) adj8 (approach$ or communicat$ or counsel$ or educat$ or instruct$ or interven$ or learn$ or manag$ or module$ or network$ or program$ or psychoanaly$ or psychotherap$ or rehab$ or skill$ or strateg$ or support$ or taught or teach$ or technique$ or therap$ or train$ or treat$ or workshop$ or work shop$)).ti,ab.
6. ((advice$ or advis$ or deal$ or instruct$ or educat$ or learn$ or taught or teach$) adj8 (injur$ or scar$ or wound$)).ti,ab.
7. (((advice$ or instruct$ or educat$ or learn$ or taught$ or teach$) adj3 risk$)) or ((advice$ or advis$ or discuss$ or educat$ or learn$ or taught$ or teach$) adj8 risk$ adj8 (autoaggress$ or auto aggress$ or automutilat$ or mutilat$ or cutt$ or overdose$ or (self adj2 cut$) or selfdestruct$ or destruct$ or selfharm$ or harm$ or selfimmolat$ or

immolat$ or selfinflict$ or inflict$ or selfinjur$ or injur$ or selfmutilat$ or mutilat$ or selfpoison$ or poison$ or suicid$))).ti,ab.

8. hotlines.sh.
9. (call in or callline$ or call line$ or help line$ or helpline$ or hotline$ or hot line$ or phone in or phonein or (caller$1 adj3 (interven$ or program$ or therap$ or treat$)) or (talk$ adj2 friend$) or ((phone$ or telephone$) adj2 support$)).ti,ab.
10. relaxation/ or relaxation therapy/
11. (relaxation or ((autogen$ or relax$) adj5 (apply or applied or approach$ or assist$ or coach$ or educat$ or help$ or imagery or instruct$ or interven$ or learn$ or manag$ or modif$ or program$ or seminar$ or strateg$ or support$ or teach$ or technique$ or therap$ or train$ or treat$ or workshop$ or work shop$)) or relaxed state or ((breath$ or movement or respirat$ or relax$) adj2 (exercis$ or interven$ or physiotherap$ or technique$ or therap$ or train$)) or ((control?ed or deep) adj breathing)).ti,ab.
12. ((replacement$ or substitut$) adj3 (approach$ or educat$ or instruct$ or interven$ or learn$ or manag$ or network$ or program$ or promot$ or rehab$ or strateg$ or taught or teach$ or technique$ or therap$ or train$ or treat$ or workshop$ or work shop$)).ti,ab.
13. (giggl$ or humo?r or laugh or laughter).ti,ab.
14. ((positive$ adj2 (emotion$ or therap$ or think$ or psycho$)) or (emotion$ adj2 (cope or coping or psychotherap$ or therap$))).ti,ab.
15. (damag$ adj2 limit$).ti,ab.
16. (manag$ risk$ or (positive$ adj2 risk$ adj2 tak$) or (relation$ adj2 secur$)).ti,ab.
17. (comforts or distractions or (((divert adj2 attention) or distract$) adj5 (automutilat$ or mutilat$ or cutt$ or overdose$ or (self adj2 cut$) or selfdestruct$ or destruct$ or selfharm$ or harm$ or selfimmolat$ or immolat$ or selfinflict$ or inflict$ or selfinjur$ or injur$ or selfmutilat$ or mutilat$ or selfpoison$ or poison$ or suicid$))).ti,ab.
18. (ice or icecube$ or marker pen$ or pillow$1 or pinch or pinching or ((elastic or rubber) adj band$) or toothbrush$ or tooth brush$ or (tak$ adj2 (bath$ or shower$)) or ((clean or sterile) adj2 (cutt$ or instrument))).ti,ab.
19. (goal$ adj2 set$).ti,ab.
20. (diary or diaries).ti,ab.
21. therapeutic contract.ti,ab.
22. ((cope$ or coping) adj3 (approach$ or assist$ or coach$ or educat$ or help$ or imagery or instruct$ or interven$ or learn$ or manag$ or modif$ or program$ or seminar$ or strateg$ or support$ or teach$ or technique$ or therap$ or train$ or treat$ or workshop$ or work shop$)).ti,ab.
23. (risk$ adj2 (minimi$ or reduc$)).ti,ab.
24. creativeness/ or exercise/ or exp recreation/

25. (active living or bicycling or (cycling not rapid cycling) or gardening or ((a?robic$ or physical$) adj (activit$ or agil$ or educat$ or fitness$)) or hobby or hobbies or kinesiotherap$ or kinesitherap$ or recreation$ or running or sport$ or swimming or tidying or walking or yoga).ti,ab.
26. community networks/ or friends/ or group processes/ or peer group/ or self help groups/
27. ((support$ adj (based or cent$ or focus?ed)) or (support$ adj2 (approach$ or educat$ or friend$ or family or instruct$ or interven$ or learn$ or module$ or network$ or peer$1 or program$ or strateg$ or technique$ or therap$ or train$ or treat$ or workshop$ or work shop$)) or ((community or emotion$ or network$ or organi?ation$ or peer$) adj2 support$) or (network$ adj2 (discuss$ or exchang$ or interact$ or meeting$))).ti,ab.
28. exp consumer health information/ or "patient education as topic"/
29. ((health adj2 (educat$ or informat$ or promot$)) or ((adult$ or client$ or consumer$ or inpatient$ or outpatient$ or participant$ or patient$ or people or user$) adj4 (educat$ or knowledge or information$ or promot$))).ti,ab.
30. or/1-29

e) Psychosocial interventions

For people who self-harm, do psychosocial interventions (compared with no treatment or other interventions) improve outcomes? What are the associated adverse effects?

<u>General psychotherapy terms</u>

1. psychotherapy/ or adaption, psychological/ or psychotherapy, brief/
2. (psychotherap$ or psycho therap$ or psychotherapeutic or ((humanistic or opportunistic or psychologic$) adj3 (approach$ or assist$ or coach$ or educat$ or instruct$ or interven$ or manag$ or module$ or program$ or rehab$ or strateg$ or support$ or technique$ or therap$ or train$ or treat$ or workshop$ or work shop$)) or ((integrated or multimodal or multi modal) adj2 therap$) or ((brief or short term or shortterm or timelimited or time limited) adj2 (intervention$ or program$ or solution$ or therap$ or treat$))).tw.

<u>Interpersonal therapy</u>

3. interpersonal relations/ and (th.fs. or (psychotherap$ or therap$ or treatment).hw.)
4. (((interpersonal$ or inter personal$ or interrelation$ or inter relation$) adj5 (analy$ or approach$ or assist$ or coach$ or communicat$ or counsel$ or educat$ or help$ or instruct$ or interven$ or learn$ or manag$ or module$ or network$ or program$ or psychoanaly$ or psychotherap$ or rehab$ or skill$ or strateg$ or support$ or teach$ or

technique$ or therap$ or train$ or treat$ or workshop$ or work shop$)) or ((interpersonal$ or inter personal$ or interrelation$ or inter relation$) adj5 (deficit$ or difficult$ or instab$ or issue$ or problem$ or unstab$) adj5 (analy$ or approach$ or assist$ or coach$ or communicat$ or counsel$ or educat$ or help$ or instruct$ or interven$ or learn$ or manag$ or module$ or network$ or program$ or psychoanaly$ or psychotherap$ or rehab$ or skill$ or strateg$ or support$ or teach$ or technique$ or therap$ or train$ or treat$ or workshop$ or work shop$)) or ipsst or ipsrt or (ipt not ipth) or (intermittent preventive adj (therap$ or treatment$)) or ((interpersonal$ or inter personal$) adj2 social rhythm$)).ti,ab.

Problem solving

5. problem solving/
6. (problem$ adj3 (collaborat$ or cope or coping or counsel$ or help$ or manag$ or program$ or re mediat$ or remediat$ or resolution$ or resolv$ or skill$ or solv$ or solution$ or support$ or technique$ or therap$ or treat$)).ti,ab.

Behaviour therapy/CBT

7. behavior therapy/ or psychotherapy, rational emotive/ or (self care/ and (cognit$ or behavio?r$ or metacognit$ or recover$).tw,hw.)
8. (((cognit$ or behavio?r$ or metacognit$) adj3 (analy$ or interven$ or modif$ or program$ or psychotherap$ or restructur$ or retrain$ or technique$ or therap$ or train$ or treat$)) or behavio?r$ activat$ or cbt or selfinstruct$ or selfmanag$ or selfattribut$ or (self$ adj (instruct$ or manag$ or attribution$)) or (rational$ adj3 emotiv$) or (rational adj (living or psychotherap$ or therap$)) or (ret adj (psychotherap$ or therap$)) or rebt or (active directive adj (psychotherap$ or therap$))).tw.

Psychodynamic interventions

9. exp psychoanalytic therapy/ or psychoanalysis/
10. (free association or psychoanal$ or psycho anal$ or psychodynamic$ or psycho dynamic$ or transference or ((analytic or dynamic$) adj3 (approach$ or assist$ or coach$ or communicat$ or counsel$ or educat$ or instruct$ or interven$ or learn$ or manag$ or modif$ or module$ or network$ or program$ or psychotherap$ or rehab$ or short term or skill$ or strateg$ or support$ or teach$ or technique$ or therap$ or time limited or train$ or treat$ or workshop$ or work shop$)) or ((dream or psychologic or self transactional) adj anal$) or b app$1).tw.

Multi-systematic therapy

11. ((multisystemic or systemic) adj2 (interven$ or therap$ or treat$)).ti,ab.

Crisis management

12. community health nursing/ or community health services/ or community mental health services/ or community-institutional relations/ or exp community psychiatry/ or crisis intervention/ or emergency medical services/ or emergency services, psychiatric/ or exp emergency service, hospital/ or mobile health units/ or exp preventive health service/
13. ((time adj5 limit$) or (hospital$ adj5 (diversion or alternative$)) or ((acute or cris$ or emergenc$ or intensive$ or mobile) adj5 (care$ or manag$ or interven$ or treat$ or therap$ or management$ or model$ or program$ or team$ or service$ or base$1))).tw.

Counselling

14. exp counseling/
15. (counsel$ or ((((client$ or person) adj2 (centred or centered or focus?ed)) or non directive$ or nondirective$ or rogerian) adj5 (approach$ or assist$ or coach$ or communicat$ or counsel$ or educat$ or help$ or instruct$ or interven$ or learn$ or manag$ or module$ or network$ or program$ or psychotherap$ or rehab$ or skill$ or strateg$ or support$ or teach$ or technique$ or therap$ or train$ or treat$ or workshop$ or work shop$)) or pastoral care or ((individual or personal or talk$) adj (psycho$ or therap$))).ti,ab.

Dialectic

16. dialectic$.ti,ab.

Postcards

17. postal service/
18. (postcard$ or post card$ or (contact$ adj3 post$)).ti,ab.

Emergency cards

19. (emergenc$ adj2 card$).ti,ab.

Group therapy/peer support groups

20. community networks/ or friends/ or group processes/ or peer group/ or exp psychotherapy, group/ or social support/

21. (((group$1 or support$) adj (based or cent$ or focus?ed)) or (group$1 adj3 (advocacy or approach$ or coach$ or educat$ or instruct$ or learn$ or module$ or network$ or participat$ or program$ or psychoanaly$ or psychotherap$ or skill$ or strateg$ or support$ or teach$ or train$ or workshop$ or work shop$)) or (support$ adj3 (approach$ or educat$ or instruct$ or interven$ or learn$ or module$ or network$ or program$ or psychoanaly$ or psychotherap$ or strateg$ or technique$ or therap$ or train$ or treat$ or workshop$ or work shop$)) or (groupwork or (group adj2 work)) or ((emotion$ or network$ or organi?ation$ or peer$) adj2 support$) or ((group$ or network$ or peer$1) adj2 (discuss$ or exchang$ or interact$ or meeting$))).ti,ab.

Family interventions

22. couples therapy/ or family therapy/ or marital therapy/
23. (conjoint therap$ or family responsive or family relation$ or ((couples or family or guardian$ or marital or marriage$ or mother$ or father$ or parent$) adj (based or cent$ or focus?ed or intervention$ or therap$ or treatment$)) or ((couples or family or guardian$ or marital or marriage$ or mother$ or father$ or parent$) adj3 (advocacy or approach$ or assist$ or coach$ or communicat$ or counsel$ or educat$ or help$ or instruct$ or learn$ or module$ or network$ or participat$ or program$ or psychotherap$ or rehab$ or skill$ or strateg$ or support$ or teach$ or train$ or workshop$ or work shop$)) or ((couples or family or guardian$ or marital or marriage$ or mother$ or father$ or parent$) adj (discuss$ or exchang$ or interact$ or meeting$))).tw.

Self help

24. self administration/ or self care/ or self help/ or self help groups/
25. ((self adj (administer$ or care or change or directed or help$ or instruct$ or manag$ or monitor$ or regulat$ or reinforc$ or re inforc$)) or selfhelp$ or smart recover$ or (minimal adj (contact or guidance)) or helpseek$ or (help$ adj2 seek$) or (mutual adj (help or aid or support$))).ti,ab.

Computer based interventions

26. telemedicine/ or therapy, computer assisted/
27. attitude to computers/ or audiovisual aids/ or computer literacy/ or computer user training/ or computer-assisted instruction/ or computing methodologies/ or decision support systems, clinical/ or hotlines/ or information systems/ or medical informatics computing/ or medical informatics/ or multimedia/ or telemedicine/ or exp audiovisual aids/ or exp computer systems/ or exp decision making,

computer assisted/ or exp optical storage devices/ or exp software/ or exp telecommunications/ or comput$.hw.
28. (etherap$ or e therap$ or telehealth or tele health).ti,ab.
29. ((selfharm or self harm) adj3 (package$ or program$)).ti,ab.
30. (e communication$ or ecommunication$ or e consult$ or econsult$ or e visit$ or evisit$ or e therap$ or etherap$ or telehealth or tele health).ti,ab.
31. ((audio$ or cd$1 or cd rom or cdrom or computer$ or cyber$ or digital assistant$ or dvd or electronic$ or floppy or handheld or hand held or information or interactiv$ or internet or mobile or multimedia or multi media or online or palmtop or palm top or pc$1 or pda or pdas or personal digital or phone$ or sms$1 or telephone$ or text or texts or texting or video$ or virtual or web$ or www) adj5 (advocacy or approach$ or coach$ or discussion or educat$ or exchang$ or guide$1 or help$ or instruct$ or interact$ or interven$ or learn$ or manag$ or meeting$ or module$ or network$ or online or participat$ or program$
32. or psychoanaly$ or psychotherap$ or rehab$ or retrain$ or re train$ or self guide$ or self help or selfguide$ or selfhelp or skill$ or strateg$ or support$ or teach$ or technique$ or telephone$ or therap$ or train$ or treat$ or work shop$ or workshop$)).ti,ab.
33. ((audio$ or cd$1 or cd rom or cdrom or computer$ or cyber$ or digital assistant$ or dvd or electronic$ or floppy or handheld or hand held or information or interactiv$ or internet or mobile or multimedia or multi media or online or palmtop or palm top or pc$1 or pda or pdas or personal digital or phone$ or sms$1 or telephone$ or text or texts or texting or video$ or virtual or web$ or www) adj2 (assist$ or based)).ti,ab.
34. ((audio$ or cd$1 or cd rom or cdrom or computer$ or cyber$ or digital assistant$ or dvd or electronic$ or floppy or handheld or hand held or interactiv$ or internet or mobile or multimedia or multi media or online or palmtop or palm top or pc$1 or pda or pdas or personal digital or phone$ or sms$1 or telephone$ or text or texts or texting or video$ or virtual or web$ or www) adj5 (aid or aided or appointment$ or booking$ or communicat$ or consult$ or deliver$ or feedback or forum or guided or input$ or interactiv$ or letter$ or messag$ or referral$ or remind$ or send$ or transfer$ or transmi$ or visit$)).ti,ab.
35. ((audio$ or cd$1 or cd rom or cdrom or computer$ or cyber$ or digital assistant$ or dvd or electronic$ or floppy or handheld or hand held or information or interactiv$ or internet or mobile or multimedia or multi media or online or palmtop or palm top or pc$1 or pda or pdas or personal digital or phone$ or sms$1 or telephone$ or text or texts or
36. texting or video$ or virtual or web$ or www) adj5 group$).ti,ab.
37. ((client$ or consumer$ or inpatient$ or outpatient$ or patient$) adj5 (audio$ or cd$1 or cd rom or cdrom or computer$ or cyber$ or digital assistant$ or dvd or electronic$ or floppy or handheld or hand held or interactiv$ or internet or mobile or multimedia or multi media or

online or palmtop or palm top or pc$1 or pda or pdas or personal digital or phone$ or sms$1 or telephone$ or text or texts or texting or video$ or virtual or web$ or www)).ti,ab.

38. ((client$ or consumer$ or inpatient$ or outpatient$ or patient$ or health or information or web or internet) adj3 portal$).ti,ab.

Case management/Assertive outreach

39. (((case or care) adj5 management) or (care adj5 program$ adj5 approach$) or (assertive adj5 community adj5 treatment) or (training adj5 community adj5 living) or (madison adj5 model$)).ti,ab,hw. or (cpa or pact or tcl).tw.

Respite care

40. respite care/
41. (daycare or day care or respite$ or ((alleviat$ or decreas$ or less$ or limit$ or lower$ or prevent$ or reduce$ or relief or relieve) adj5 burden$ adj5 (carer$1 or caregiver$ or care giv$ or custodian$ or guardian$ or father$ or mother$ or parent$ or stepparent$)) or ((carer$ or care giver$ or care giv$) adj2 (assist$ or help$ or intervention$ or network$ or program$ or rehab$ or support$ or therap$))).ti,ab.

42. or/1-41

f) Pharmacological interventions

For people who self-harm, do drug treatments improve outcomes? What are the associated adverse effects?

Analgesics

1. exp analgesics/or exp salicylic acids/ or (ana?lges$ or salicyl$).ti,ab.
2. (acetylsalicylic acid or 2 acetoxybenzoate or acenterine or acesal or acetan or acetard or aceticyl or acetilum or acetonyl or acetophen or acetosal or acetosalicylic acid or acetosalin or acetosalum or acetyl salicylate or acetyl salicylic acid or acetylic salicylic acid or acetylin or acetylo or acetylon or acetylosalicylic acid or acetylsal or acetylsalicyclic acid or acetylsalicyl or acetylsalicylate or acetylsalicylate strontium or acetylsalicylic acid or acetylsalycic acid or acetylsalycylic acid or acetysal or acidulatum or acidum acetyl salicylicum or acidum acetylosalicylicum or acidum acetylsalicylicum or acylpyrin or acylpyrine or acytosal or adiro or alabukun or alasil or alka seltzer or alkaspirin or aloxiprimum or anopyrin or arthralgyl or asaflow or asaphen or aspergum or aspirgran or aspirin or aspirina or

aspirine or aspirinine or aspisol or aspro or asrivo or asteric or astrix or bebesan or biprin or boxazin or breoprin or bufferin or cafenol or catalgine or catalgix or cemerit or cemirit or claradin or claragine or colfarit or colfarit or contrheuma or contrheuma retard or daga or darosal or depot aspirin or dispirin or dispril or dolean or easprin or ecotrin or egalgic or emocin or empirin or encaprin or endosprin or endosprin or entericin or enterosarine or enterospirine or entrophen or euthermine or extren or genasprin or godamed or gotosan or helicon or infatabs a or istopirin or istopyrine or ivepirine or juvepirine or kilios or kinderaspirin or magnecyl or measurin or mejoral or micristin or micristin or micropyrin or mikristin or miniasal or mycristin or nu seal or nuseals or ortho acetoxybenzoate or ortho acetoxybenzoic acid or ortho acetyloxybenzoate or ortho acetyloxybenzoic acid or ostoprin or pancemol or para acetylsalicylic acid or paracin or paynocil or pengo or polopirin or polopiryna or polopiryna or premaspin or primaspan or pyronoval or reumyl or rhodine or rhonal or salacetin or salacetogen or saletin or sargepirine or slow release aspirin or sodium acetylsalicylate or sodium bicarbonate acetyl salicylate or sodium bicarbonate acetylsalicylate or soldral or solprin or solpyron or solucetyl or solupsa or solupsan or super tru or tapal or temagin or treupahlin or treuphalin or turivital or verin or vitalink or xaxa or zorprin).ti,ab.

3. alfentanil/or (alfentanil or alfenta or alfentanil or alfentanil hydrochloride or alfentanyl or alfentanyl or fanaxal or limifen or rapifen).ti,ab.
4. (almotriptan or almogran or almotriptan malate or axert).ti,ab.
5. (buprenorphin$ or buprenex or buprex or finibron or lepetan or prefin or suboxone or subutex or temgesic or transtec).ti,ab.
6. caffeine/or caffeine$.ti,ab.
7. cannabis/or (cannabis or cannabi or cannabis or ganja or ganjas or hemp or hemps or marihuana or marihuanas or marijuana or marijuanas or opiate).ti,ab.
8. (cocodamol or acetaminophen plus codeine phosphate or empracet or hypertussin or lindilane or nedolon or panadeine or paracodal or percogesic with codeine or talvosilen or treuphadol plus).ti,ab.
9. (codeine phosphate or ardinex or codein phosphate or codeine or codeine phosphate or codicompren retard or colrex compound or galcodine or isocodeine or kodein or n methylmorphine or tricodein or tussipect).ti,ab.
10. (codydramol or codidramol).ti,ab.
11. cyclizine/or (cyclizine or collox or cyclizine or marazine or marezine or marzine or neo devomit or valoid).ti,ab.
12. dextromoramide/or (dextromoramide or d moramide or dextro moramide or dextromoramide or dextromoramine or dimorlin or d-moramide or jetrium or moramide or palfium or palfium or palphium or pyrrolamidol or pyrrolamidole or pyrroloamidol).ti,ab.

13. dextropropoxyphene/or (co proxamol or coproxamol or cosalgesic or d propoxyphene or darvon or dextropropoxyphene or diantalvic or distalgesic or d-propoxyphene or dystalgesic or paradex or propoxyphene).ti,ab.
14. (dihydrocodeine or cis dihydrocodeine or codhydrin or codhydrine or codicontin or cohydrin or dehacodin or dh codeine or didrate or dihydrin or dihydroneopine or drocode or hydrocodeine or hydrocodin or nadein or nadeine or napacodin or novicodin or paracodein or paracodin or paramol or parzone or rapacodin or remedacen or tiamon mono or trans dihydrocodeine).ti,ab.
15. (dipipanone or pipadone or piperidyl amidone).ti,ab.
16. eletriptan.ti,ab.
17. ergotamine/ or (ergate or ergomar or ergostat or ergotamine tartrate or ergotaminetartras or exmigra or femergin or gynergen or lingraine or medihaler ergotamine or relpax or virdex or wigrettes).ti,ab.
18. fentanyl/or (fentanyl$ or duragesic or duragesic or durogesic or fentamyl or fentanest or fentanil or fentora or fetnanyl or ionsys or leptanal or phentanyl or sublimaze or transfenta).ti,ab.
19. (frovatriptan allegro or frova or migard or miguard).ti,ab.
20. (heroin$1 or acetomorphine or diacephine or diacetyl morphine or diacetylmorphine or diagesil or diamorf or diamorphine or diaphorin or morphacetin).ti,ab.
21. (hydromorphone or biomorphyl or cofalaudid or dihydromorphinone or dihydromorphone or dilaudid or dimorphone or hydromorphinone hydrochloride hydromorphon or hydromorphone or hymorphan or laudacon or laudaconum or novolaudon or palladon or palladone or palladone or semcox or sophidone).ti,ab.
22. isometheptene mucate.ti,ab.
23. ketorolac$.sh. or (droal or isometheptenemucate or isometheptine mucate or ketocol or ketorolac or midrin or taradyl or toradol or toratex).ti,ab.
24. meptazinol/ or (meptazinol or meptazinol or meptid).ti,ab.
25. exp methadone/ or (methadone$ or adanon or adanon hydrochloride or algidon or algolysin or algoxale or althose or amidon or amidone or amidosan or anadon or biodone or butalgin or deamin or depridol or diaminon or dianone or dolafin or dolamid or dolesone or dolophine or dolophine hydrochloride or dorex or dorexol or fenadon or heptadon or heptanon or ketalgin or mecodin or mepecton or mephenon or metadol or metasedin or methaddict or methadose or methex or miadone or moheptan or phenadon$1 or phymet or physepton or physeptone or pinadone or polamidon or polamivet or polamivit or sinalgin or symoron).ti,ab.
26. methysergide/or (methysergide$ or deseril or desernil sandoz or desril or dimethylergometrin or dimethylergometrine or dimethylergonovine or methisergid or methisergide or methyl sergide or

methylmethylergonovine or methylsergide or methysergid or methysergide or sansert).ti,ab.
27. exp morphine/ or morphinans/or (morphine or astramorph or avinza or depodur or depomorphine or dolcontin or duramorph or duramorple or kadian or kapanol or moraxen or morphia or morphinesulfate or moscontin or ms contin or mst continus or mst mundipharma or noceptin or oblioser or oramorph or roxanol or sevredol or skenan lp).ti,ab.
28. exp naloxone/or (naloxone or maloxone or nalaxone or nalone or nalonee or narcan or narcanti or narcon or narvcam).ti,ab.
29. (naratriptan or amerge or naramig).ti,ab.
30. nefopam/ or (nefopam or acupan or ajan or fenazoxine or lenipan or nocipan).ti,ab.
31. opiate alkaloids/or opium/ or (opiate$ or opioid$ or opium).ti,ab.
32. (oxycodone or bionine or bionone or bolodorm or broncodal or bucodal or cafacodal or cardanon or codenon or dihydrohydroxydodeinone or dihydrone or dinarkon or endone or eubine or eucodal or eucodale or eudin or eukdin or eukodal or eumorphal or eurodamine or eutagen or hydrocodal or hydroxycodeinoma or hydroxycodeinon or ludonal or medicodal or narcobasina or narcobasine or narcosin or nargenol or narodal or nucodan or opton or ossicodone or oxanest or oxicone or oxiconum or oxikon or oxycodeinon or oxycodeinonhydrochloride or oxycodone or oxycodonhydrochlorid or oxycodyl or oxycone or oxycontin or oxygesic or oxykon or oxynorm or pancodine or pavinal or pronarcin or remoxy or roxicodone or roxycodone or sinthiodal or stupenal or tebodal or tekodin or thecodin or theocodin).ti,ab.
33. acetaminophen/or (paracetamol or acetaminophen or acamol or acephen or acetaco or acetamidophenol or acetominophen or algotropyl or anacin 3 or anacin3 or apap or datril or hydroxyacetanilide or p-acetamidophenol or panadol or tylenol).ti,ab.
34. pentazocine/or (pentazocine or dolapent or fortal or fortalgesic or fortral or fortraline or fortwin or lexir or liticon or peltazon or pentacozine or pentafen or pentagin or pentalgina or pentazocin or pentozocine or perutagin or sosegon or sosigon or talioin or talwin).ti,ab.
35. exp meperidine/ or (pethidine or algil or alodan or centralgin or centralgine or demerol or dispadol or dolanquifa or dolantal or dolantin or dolantine or dolargan or dolcontral or dolenal or dolestin or dolin or dolocontral or doloneurin or doloneurotrat or dolor or dolosa or dolosal or dolosan or dolsin or dolvanol or endolate or isonipecain or isonipecaine or l pethidine or lidol or lydol or mefedina or mepadin or meperiden or meperidin or meperidine or mephedine or mepiridine or mialgin or pantalgin or petadin or petantin or petantina or pethanol or pethedine or pethidin or pethidine or petidin or

phetidine or piridosal or sauteralgyl or simesalgina or supplosal or synlaudine).ti,ab.
36. (pizotifen or mosegor or sanmigran or sanomigran).ti,ab.
37. (rizatriptan or maxalt).ti,ab.
38. sumatriptan/ or (sumatriptan succinate or imigran or imiject or imitrex or sumadol or sumigrene).ti,ab.
39. (tolfenamic acid or clotam or clotan or rociclyne or tolfedine or tolfenamate).ti,ab.
40. tramadol/or (tramadol or adolonta or amadol or biodalgic or biokanol or contramal or dolzam or jutadol or kontram xl or melanate or mtwtramadol or nobligan or prontofort or ranitidin 1a pharma or takadol or theradol or tiral or topalgic or tradol or tradolpuren or tradonal or tralgiol or trama abz or trama dorsch or trama kd or tramabeta or tramadin or tramadoc or tramadoldolgit or tramadolhameln or tramadolium chloride or tramadolor or tramadolratiopharm or tramadorsch or tramadura or tramagetic or tramagit or tramake or tramal or tramex or tramundin or trasedal or trodon or trondon or ultram or xymel 50 or zamudol or zumalgic or zydol or zytram).ti,ab.
41. (zolmitriptan or ascotop or zomig or zomigon).ti,ab.
42. (zopiclone or amoban or imovance or imovane or ximovan or zimovane or zoplicon).ti,ab.

Antidepressants

43. exp antidepressive agents, tricyclic/
44. (tricyclic$ or tca$1).ti,ab.
45. amitriptyline.sh. or (amitriptyl$1 or amitryptil$1 or amitryptin$1 or amitryptylin$1 or amytriptil$1 or amytriptyl$1 or amytryptil$1 or adepress or adepril$1 or ambivalon$1 or amineurin$1 or amitid$1 or amitril$1 or amitrip or amitrol$1 or anapsique or antitriptylin$1 or apoamitriptylin$1 or damilen$1 or damylen$1 or domical$1 or elatrol$1 or elavil$1 or endep or enovil$1 or etafon$1 or etafron$1 or euplit$1 or lantron$1 or laroxal$1 or laroxyl$1 or lentizol$1 or novoprotect or proheptadien$1 or redomex or sarboten retard or saroten$1 or sarotex or stelminal$1 or sylvemid$1 or syneudon$1 or teperin$1 or terepin$1 or triptafen$1 or triptanol$1 or triptizol$1 or triptyl or triptylin$1 or tryptanol$1 or tryptin$1 or tryptizol$1).ti,ab.
46. chlomipramine.sh. or (chlomipramin$1 or chlorimipramin$1 or chloroimipramin$1 or clomipramin$1 or anafranil$1 or anafranilin$1 or anafranyl or domipramin$1 or hydiphen$1 or monochlor imipramin$1 or monochlorimipramin$1 or monochloroimipramin$1).ti,ab.
47. dothiepin.sh. or (dothiepin$1 or dosulepin$1 or altapin$1 or depresym$1 or dopress or dothep or idom or prothiaden$1 or prothiadien$1 or prothiadin$1 or protiaden$1 or thaden).ti,ab.

48. doxepin.sh. or (doxepin$1 or adapin$1 or apodoxepin$1 or aponal$1 or co dox or curatin$1 or deptran$1 or desidox or doneurin$1 or doxepia or espadox or mareen or prudoxin$1 or quitaxon$1 or silenor or sinepin or sinequan$1 or sinquan$1 or xepin$1 or zonalon$1).ti,ab.
49. imipramine.sh. or (imipramin$1 or antideprin$1 or berkomin$1 or chrytemin$1 or deprimin or deprinol$1 or depsonil or dynaprin or eupramin or ia pram or imavate or imidobenzyl$1 or imidol$1 or imipramid$1 or imipramil or imiprex or imiprin$1 or imizin$1 or irmin or janimin$1 or melipramin$1 or norchlorimipramin$1 or norpramin$1 or novopramin$1 or presamin$1 or pryleugan$1 or psychoforin$1 or psychoforin$1 or servipramin$1 or sk pramin$1 or surplix or tofranil$1 or trofanil$1).ti,ab.
50. lofepramine.sh. or (lofepramin$1 or lopramin$1 or amplit$1 or deftan$1 or feprapax or gamanil$1 or gamonil$1 or lomont or lopramin$1 or tymelyt).ti,ab.
51. mianserin.sh. or (mianserin$1 or athymil$1 or bolvidon$1 or investig or lantanon$1 or lanthanon$1 or lerivon$1 or miaxan$1 or norval or serelan$1 or tetramid$1 or tolvin$1 or tolvon$1).ti,ab.
52. nortriptyline.sh. or (nortriptylin$1 or acetexa or allegron$1 or altilev or atilev or avantyl or aventyl or desitriptylin$1 or desmethylamitriptylin$1 or martimil$1 or noramitriptylin$1 or norfenazin$1 or noritren$1 or norpress or nortrilen$1 or nortryptilin$1 or nortryptylin$1 or pamelor or paxtibi or propylamin$1 or psychostyl or sens?val).ti,ab.
53. opipramol.sh. or (opipramol$1 or dinsidon$1 or ensidon$1 or eusidon$1 or insidon$1 or nisidan$1 or oprimol or pramolan$1).ti,ab.
54. trazodone.sh. or (trazodon$1 or beneficat or deprax or desirel or desyrel$1 or molipaxin$1 or pesyrel$1 or rpragazon$1 or pragmarel$1 or pragmazon$1 or thombran$1 or thrombin$1 or thrombran$1 or tombran$1 or trasodon$1 or trazolan$1 or trazorel or trazon$1 or trialodine or trittico).ti,ab.
55. trimepramine.sh. or (trimepramin$1 or trimeprimin$1 or trimepropimin$1 or trimidura or trimineurin$1 maleate or trimipramin$1 or trimoprimin$1 or eldoral$1 or herphonal$1 or trimineurin$1 or novo tripramin$1 or novotripramin$1 or nutrimipramin$1 or rhotrimin$1 or stangyl or surmontil$1 or apo trimip or apotrimip or herphonal$1 or stangyl or surmontil$1).ti,ab.
56. exp serotonin uptake inhibitors/
57. (ssri$ or ((serotonin or 5 ht or 5 hydroxytryptamine) adj (uptake or reuptake or re uptake) adj inhibit$)).ti,ab.
58. citalopram.sh. or (citalopram or celexa or cipramil$1 or cytalopram or elopram or escitalopram or lexapro or nitalapram or sepram or seropram).ti,ab.
59. (escitalopram or cipralex or lexapro or seroplex).ti,ab.
60. fluoxetine.sh. or (fluoxetin$1 or fluctin$1 or flunirin$1 or fluoxifar or prosac or prozac or prozamin or sarafem or symbyax).ti,ab.

61. fluvoxamine.sh. or (fluvoxamin$1 or depromel$1 or desiflu or dumirox or faverin$1 or fevarin$1 or floxyfral$1 or fluoxamin$1 or fluroxamin$1 or fluvoxadura or luvox).ti,ab.
62. (nefazadon$1 or dutonin or nefadar or reseril$1 or serzon$1).ti,ab.
63. paroxetine.sh. or (paroxetin$1 or aropax or deroxat or motivan$1 or paxil or pexeva or seroxat or tagonis).ti,ab.
64. sertraline.sh. or (sertralin$1 or altrulin$1 or aremis or besitran$1 or gladem or lustral$1 or naphthylamin$1 or sealdin$1 or serad or serlain$1 or tresleen or zoloft).ti,ab.
65. exp antidepressive agents/ or exp monoamine oxidase inhibitors/
66. (antidepress$ or anti depress$ or maoi$1 or ((adrenaline or amine or mao or mono amin$ or monoamin$ or tyramin$) adj2 inhibit$)).ti,ab.
67. (agomelatin$1 or melitor or thymanax or valdoxan$1).ti,ab.
68. chlorprothixene.sh. or (chlorprothixen$1 or aminasin$1 or aminasin$1 or aminazin$1 or aminazin$1 or ampliactil$1 or amplictil$1 or ancholactil$1 or chlopromazin$1 or chlor pz or chlorbromasin$1 or chlordelazin$1 or chlorderazin$1 or chloropromazin$1 or chlorpromanyl or chlorpromazin$1 or chlorprotixen$1 or clordelazin$1 or clorpromazin$1 or cloxan or contomin$1 or elmarin$1 or fenactil$1 or hibanil$1 or hibernal$1 or hibernol$1 or klorpromex or largactil$1 or largactyl or megaphen$1 or neurazin$1 or novomazin$1 or phenathyl$1 or plegomazin$1 or plegomazin$1 or proma or promacid$1 or promactil$1 or promapar or promazil$1 or propaphen$1 or propaphenin$1 or prozil$1 or psychozin$1 or sanopron$1 or solidon$1 or sonazin$1 or taractan$1 or taroctil$1 or thor prom or thorazen$1 or thorazin$1 or torazina or truxal or vegetamin a or vegetamin b or wintamin$1 or wintermin$1 or zuledin$1).ti,ab.
69. desvenlafaxine.sh. or (desvenlafaxin$1 or o desmethylvenlafaxin$1 or o norvenlafaxin$1 or pristiq).ti,ab.
70. (duloxetin$1 or ariclaim or cymbalta or xeristar or yentreve).ti,ab.
71. fezolamin$1.ti,ab.
72. (isocarboxacid$1 or bmih or enerzer or isocarboazid$1 or isocarboxazid$1 or marplan$1 or marplon).ti,ab.
73. (mirtazapin$1 or avanza or 6 azamianserin$1 or lerivon$1 or remergil$1 or remergon$1 or remeron$1 or tolvon$1 or zispin).ti,ab.
74. moclobemide.sh. or (moclobemid$1 or arima or aurorex or aurorix or deprenorm or feraken$1 or manerix or moclamin$1 or moclix or moclobamid$1 or moclobeta or moclodura or moclonorm or novomoclobemid$1 or numoclobemid$1 or rimoc).ti,ab.
75. phenelzine.sh. or (phenelzin$1 or 2 phenethylhydrazin$1 or 2 phenylethylhydrazin$1 or benzylmethylhydrazin$1 or beta phenethylhydrazin$1 or beta phenylethylhydrazine or fenelzin or fenizin$1 or mao rem or nardelzin$1 or nardil$1 or phenalzin$1 or phenethylhydrazin$1 or phenylethylhydrazin$1 or stinerval$1).ti,ab.
76. (reboxetin$1 or davedax or edronax or norebox or prolift or solvex or vestra).ti,ab.

77. tranylcypromine.sh. or (tranylcypromin$1 or phenylcyclopropylamin$1 or dl trans 2 phenylcyclopropylamin$1 or jatrosom$1 or parmodalin$1 or parnate or parniten$1 or parnitin$1 or trancilpromin$1 or trancylpromin$1 or trancylprominesulfate or tranilacipromin$1 or trans 2 phenylcyclopropylamin$1 or transamin$1 or tylciprin$1).ti,ab.
78. (venlafaxin$1 or efexor or effexor or foraven or tifaxin or trevilor or venaxx or venlalic or winfex).sh,tw.
79. exp serotonin uptake inhibitors/
80. (snri$ or ssnri$ or ((noradrenalin or norepinephrine) adj serotonin adj (uptake or reuptake or re uptake) adj inhibitor$) or (serotonin adj (noradrenalin or norepinephrine) adj (uptake or reuptake or re uptake) adj inhibitor$)).ti,ab.
81. tetracyclic$.ti,ab.

Antipsychotics

82. exp antipsychotic agents/
83. (antipsychotic$ or anti psychotic$ or (major adj2 (butyrophenon$ or phenothiazin$ or tranquil$)) or neuroleptic$).ti,ab.
84. (amisulprid$1 or aminosultoprid$1 or amisulpirid$1 or sertol$1 or socian or solian).ti,ab.
85. (aripiprazol$1 or abilify or abilitat).ti,ab.
86. (benperidol$1 or anquil or benperidon$1 or benzoperidol$1 or benzperidol$1 or frenactil$1 or frenactyl or glianimon$1 or phenactil$1).ti,ab.
87. chlorpromazine.sh. or (chlorpromazin$1 or aminazin$1 or chlorazin$1 or chlordelazin$1 or contomin$1 or fenactil$1 or largactil$1 or propaphenin$1 or thorazin$1).ti,ab.
88. chlorprothixene.sh. or (chlorprothixen$1 or aminasin$1 or aminasin$1 or aminazin$1 or aminazin$1 or ampliactil$1 or amplictil$1 or ancholactil$1 or chlopromazin$1 or chlor pz or chlorbromasin$1 or chlordelazin$1 or chlorderazin$1 or chloropromazin$1 or chlorpromanyl or chlorpromazin$1 or chlorprotixen$1 or clordelazin$1 or clorpromazin$1 or cloxan or contomin$1 or elmarin$1 or fenactil$1 or hibanil$1 or hibernal$1 or hibernol$1 or klorpromex or largactil$1 or largactyl or megaphen$1 or neurazin$1 or novomazin$1 or phenathyl or plegomazin$1 or plegomazin$1 or proma or promacid$1 or promactil$1 or promapar or promazil$1 or propaphen$1 or propaphenin$1 or prozil or psychozin$1 or sanopron$1 or solidon$1 or sonazin$1 or taractan$1 or taroctil$1 or thor prom or thorazen$1 or thorazin$1 or torazin$1 or truxal or vegetamin a or vegetamin b or wintamin$1 or wintermin$1 or zuledin$1).ti,ab.
89. clozapine.sh. or (clozapin$1 or alemoxan$1 or azaleptin$1 or clopine or clozaril$1 or denzapin$1 or dorval or dozapin$1 or fazaclo or froidir or klozapol or lapenax or leponex or wander compound or zaponex).ti,ab.

90. flupenthixol.sh. or (flupentixol$1 or flupenthixol$1 or depixol$1 or emergil$1 or fluanxol$1 or flupentixol$1 or emergil$1 or fluanxol$1 or piperazineethanol$1 or viscoleo).ti,ab.
91. fluspirilene.sh. or (fluspirilen$1 or fluspi or imap or kivat or redeptin$1 or spirodiflamin$1).ti,ab.
92. haloperidol.sh. or (haloperidol$1 or aloperidin$1 or bioperidolo or brotopon or celenase or cerenace or dozic or duraperidol or einalon s or eukystol or fortunan$1 or haldol or halidol or haloneural$1 or haloperitol$1 or halosten or keselan or linton or peluces or serenace or serenase or siegoperidol$1 or sigaperidol$1).ti,ab.
93. methotrimeprazine.sh. or (levomepromazin$1 or 2 methoxytrimeprazin$1 or hirnamin$1 or levo promazin$1 or levomeprazin$1 or levopromazin$1 or levoprom$1 or mepromazin$1 or methotrimeprazin$1 or methotrimperazin$1 or milezin$1 or minozinan$1 or neozin$1 or neuractil$1 or neurocil$1 or nirvan or nosinan$1 or nozinan$1 or sinogan or tisercin$1 or tizercin$1 or tizertsin$1 or veractil$1).ti,ab.
94. (olanzapin$1 or lanzac or midax or olansek or olzapin or rexapin or zalasta or zolafren or zydis or zypadhera or zyprex$1).ti,ab.
95. (paliperidon$1 or 9 hydroxyrisperidon$1 or invega).ti,ab.
96. paroxetine.sh. or (paroxetin$1 or aropax or deroxat or motivan or paxil$1 or pexeva or seroxat or tagonis).ti,ab.
97. (pericyazin$1 or aolept or neulactil$1 or neuleptil$1 or periciazin$1 or properciazin$1 or propericiazin$1).ti,ab.
98. perphenazine.sh. or (perphenazin$1 or chlorperphenazin$1 or chlorpiprazin$1 or chlorpiprozin$1 or decentan$1 or etaperazin$1 or ethaperazin$1 or etrafon or fentazin$1 or perfenazin$1 or perfenazin$1 or perferazin$1 or perphenan$1 or perphenezin$1 or thilatazin$1 or tranquisan$1 or triavail or trifalon$1 or trilafan$1 or trilafon$1 or trilifan$1 or triliphan$1).ti,ab.
99. pimozide.sh. or (pimozid$1 or antalon$1 or opiran$1 or orap or pimocid$1 or pimorid$1 or pinozid$1).ti,ab.
100. prochlorperazine.sh. or (prochlorperazin$1 or buccastem or capazin$1 or chlormeprazin$1 or chlorpeazin$1 or chlorperazin$1 or compazin$1 or dicopal$1 or emelent or kronocin$1 or meterazin$1 or metherazin$1 or nipodal$1 or phenotil or prochlor perazin$1 or prochlorpemazin$1 or prochlorperacin$1 or prochlorperzin$1 or prochlorpromazin$1 or proclorperazin$1 or stemetil or stemzine or tementil$1 or temetil$1).ti,ab.
101. promazine.sh. or (promazin$1 or alofen$1 or alophen$1 or ampazin$1 or amprazim$1 or centractyl or delazin$1 or esparin$1 or lete or liranol$1 or neo hibernex or neuroplegil$1 or piarin$1 or prazin$1 or pro tan or promantin$1 or promanyl$1 or promilen$1 or promwill or protactil$1 or protactyl$1 or romthiazin$1 or romtiazin$1 or sediston$1 or sinophenin$1 or sparin$1 or tomil or varophen$1 or verophen$1).ti,ab.

102. (quetiapin$1 or ketipinor or quepin or seroquel or tienapin$1).ti,ab.
103. risperidone.sh. or (risperidon$1 or belivon$1 or ridal or riscalin or risolept or rispen or risperdal$1 or sizodon).ti,ab.
104. (sertindol$1 or indole or serdolect or serlect).ti,ab.
105. sulpiride.sh. or (sulpirid$1 or abilit or aiglonyl$1 or arminol$1 or bosnyl or deponerton$1 or desisulpid$1 or digton or dobren or dogmatil$1 or dogmatyl or dolmatil$1 or eglonyl or ekilid or equilid or guastil$1 or isnamid$1 or leboprid$1 or levopraid or levosulpirid$1 or meresa or miradol$1 or modal or neogama or pontirid$1 or psicocen$1 or sulfirid$1 or sulp$1 or sulperid$1 or sulpitil$1 or sulpivert or sulpor or sulpyride or synedil$1 or tepavil$1 or vertigo meresa or vertigo neogama or vipral).sh,tw.
106. trifluoperazine.sh. or (trifluoperazin$1 or apotrifluoperazine$1 or calmazin$1 or dihydrochlorid$1 or eskazin$1 or eskazin$1 or eskazinyl or fluoperazin$1 or flupazin$1 or jatroneural$1 or modalina or stelazin$1 or terfluzin$1 or terfluzin$1 or trifluoperazid$1 or trifluoperazin$1 or trifluoperzin$1 or trifluoroperazin$1 or trifluorperacin$1 or trifluperazin$1 or triflurin$1 or triftazin$1 or triftazinum or triphtazin$1 or triphthasin$1 or triphthazin$1).ti,ab.
107. (zotepin$1 or lodopin$1 or losizopilon or nipolept or setous or zoleptil).ti,ab.
108. clopenthixol.sh. or (zuclopenthixol$1 or acuphase or clopenthixol$1 or clopixol or cisordinol$1 or sedanxol$1).ti,ab.

Lithium

109. lithium$.sh. or (lithium$1 or camcolit or candamid$1 or carbolith or carbolitium or cibalith s or contemnol$1 or dilithium or eskalith or hypnorex or li salt or limas or linthane or liskonium or liskonum or litarex or lithane or lithiofor or lithionit or lithiophor or lithobid or lithocarb or lithonate or lithotabs or maniprex or mesin or micalith or neurolepsin or neurolithium or plenur or priadel or quilinormretard or quilonorm or quilonum or teralithe or theralite or theralithe).ti,ab.

Benzodiazepines

110. exp benzodiazepines/
111. (benzo$1 or benzodiazepin$).ti,ab.
112. alprazolam.sh. or (alprazolam or alprox or apo alpraz or apoalpraz or aprazolam$1 or cassadan$1 or esparon$1 or helex or kalma or novo alprazol$1 or novoalprazol$1 or nu alpraz or nualpraz or ralozam or solanax or tafil$1 or trankimazin$1 or valeans or xanax or xanor).ti,ab.
113. bromazepam.sh. or (bromazepam or anxyrex or bartul or bromalich or bromaz 1a pharma or bromazanil$1 or bromazep von ct or durazanil$1 or lectopam$1 or lexamil$1 or lexatin$1 or lexaurin$1 or lexilium or

lexomil$1 or lexotan$1 or lexotanil$1 or lexotanil$1 or normoc or sintrogel$1).ti,ab.

114. chlordiazepoxide.sh. or (chlordiazepoxid$1 or methaminodiazepoxid$1 or elenium$1 or librium$1 or chlozepid$1 or ansiacal$1 or benzodiapin$1 or cebrum$1 or chlordiazepoxyd$1 or chlorodiazepoxid$1 or clopoxid$1 or contol$1 or decacil$1 or defobin$1 or disarim$1 or dizepin$1 or dopoxid$1 or droxol$1 or eden psich or elenium$1 or elenum$1 or equibral$1 or kalmocaps or labican$1 or librelease or libritabs or librium or lipoxide or mesural$1 or metaminodiazepoxid$1 or methaminodiazepoxid$1 or mildmen$1 or mitran$1 or multum$1 or murcil$1 or napoton$1 or napoton$1 or novosed$1 or psichial$1 or psicosan$1 or psicoterin$1 or radepur or reliberan$1 or reposans 10 or risolid or seren vita or servium or silibrin$1 or sk lygen or sonimen$1 or timosin$1 or viansin$1 or viopsicol$1).ti,ab.
115. (clobazam or chlorepin$1 or clobazepam or clorepin$1 or frisium or noiafren$1 or urbadan$1 or urbanil$1 or urbanyl).ti,ab.
116. clonazepam.sh. or (clonazepam or antelepsin$1 or clonopin$1 or iktorivil$1 or klonazepam or klonopin$1 or landsen$1 or rivotril$1).ti,ab.
117. clorazepate dipotassium.sh. or (clorazepat$1 or carboxylic acid or chlorazepat$1 or chloroazepat$1 or clorazepic acid or tranxen$1 or tranxilium).ti,ab.
118. (delorazepam or briantum$1 or chlordemethyldiazepam or chlordesmethyldiazepam or chloro n demethyldiazepam or chlorodemethyldiazepam or chlorodesmethyldiazepam or chloronordiazepam).ti,ab.
119. diazepam.sh. or (diazepam or alupram or ansiolin$1 or antenex or apaurin$1 or apaurin$1 or apozepam or assival$1 or audium$1 or bialzepam or bialzepan$1 or calmpos$1 or cercin$1 or cersin$1 or chlordiazepam or dialar or diastat or diazelium or diazemuls or diazidem or ducen$1 or duxen$1 or eridan or eurosan$1 or evacalm$1 or fanstan$1 or faustan$1 or gewacalm$1 or lamra or lembrol$1 or lipodiazepam or lorinon$1 or methyldiazepinon$1 or methyldiazepinon$1 or morosan$1 or neocalm$1 or neurolytril$1 or noan or novazam or paceum or plidan or psychopax or relanium or rimapam or sedapam or seduxen$1 or serendin$1 or setonil$1 or sibazon$1 or sonacon$1 or stesolid$1 or stesolin$1 or tanquo tablinen$1 or tensium or tranimul$1 or tranquo puren or umbrium$1 or valaxon$1 or valclair or valiquid$1 or valium or valpam or valreleas$1 or vatran$1 or vival$1 or vivol4 or zetran$1).ti,ab.
120. flunitrazepam.sh. or (flunitrazepam or flurazepam or fluridrazepam or darken$1 or fluni 1a pharma or flunibeta or flunimerck or fluninoc or flunipam or flunita or flunitrax or flunizep von ct or hypnodorm$1 or hypnosedon$1 or inervon$1 or narcozep or parnox or rohipnol$1 or rohypnol$1 or roipnol$1 or silece or valsera).ti,ab.

121. flurazepam.sh. or (flurazepam or benozil$1 or dalmadorm$1 or dalman$1 or dalmate or dormodor$1 or lunipax or staurodorm$1 or dalman$1 or dormodor$1 or dalmadorm$1).ti,ab.
122. (flutoprazepam or restas).ti,ab.
123. loprazolam .ti,ab.
124. lorazepam.sh. or (lorazepam or almazin$1 or alzapam or apolorazepam or ativan or bonatranquan$1 or donix or duralozam or durazolam or idalprem or kendol$1 or laubeel or lorabenz or loranas$1 or loranaz$1 or lorans or lorax or lorazep von ct or loridem$1 or lorivan$1 or mesmerin$1 or novo lorazem$1 or novolorazem$1 or novo lorazem$1 or nu loraz or nuloraz or orfidal or orifadal$1 or pro dorm or quait or securit or sedicepan$1 or sinestron$1 or somagerol$1 or tavor or temesta or tolid or wypax).ti,ab.
125. (lormetazepam or loramet or (lorazepam adj2 methyl) or methyllorazepam or minians or minias or noctamid$1 or pronoctan$1).ti,ab.
126. (mexazolam or melex or sedoxil$1).ti,ab.
127. midazolam.sh. or (midazolam or dormicum or dormonid$1 or hypnoval$1 or hypnovel$1 or hypnoyvel$1 or versed).ti,ab.
128. nitrazepam.sh. or (nitrazepam or alodorm or atempol$1 or benzalin$1 or dormalon$1 or dormo puren or dumolid or eatan or eunoctin$1 or hypnotex or imadorm or imeson$1 or insomin$1 or mogadan$1 or mogadon$1 or nelbon$1 or nirven$1 or nitra zepam or nitrados or nitravet or nitrazadon$1 or nitrazep or nitrodiazepam or novanox or pacisyn or radedorm$1 or remnos or restorem$1 or sedamon$1 or serenade or somnased$1 or somnibel$1 n or somnit$1).ti,ab.
129. oxazepam.sh. or (oxazepam or abboxapam or adumbran$1 or alopam or anxiolit$1 or azutranquil$1 or durazepam or expidet$1 or hilong or isodin$1 or linbial$1 or noctazepam or oxapuren$1 or oxepam or praxiten$1 or serax or serenid$1 or serepax or seresta or serpax or sigacalm$1 or sobril$1 or tazepam$1 or uskan).ti,ab.
130. prazepam.sh. or (prazepam or centrax or demetrin$1 or lysanxia or mono demetrin$1 or monodemetrin$1 or reapam or sedapran$1 or verstran).ti,ab.
131. temazepam.sh. or (temazepam or apo temazepam or dasuen or euhypnos or hydroxydiazepam or levanxol$1 or methyloxazepam or nocturne$1 or norkotral tema or normison$1 or normitab or nortem or oxydiazepam or planum or pronervon t or remestan$1 or restoril$1 or signopam or temaz$1 or temazep von ct or temazepax or temtabs or tenox or texapam).ti,ab.

132. or/1-131

g) Safer prescribing

Medline – Ovid SP interface

For people who self-harm, what are the key principles underlying safer prescribing?

1. exp analgesics/or exp salicylic acids/ or (ana?lges$ or salicyl$).ti,ab.
2. (acetylsalicylic acid or 2 acetoxybenzoate or acenterine or acesal or acetan or acetard or aceticyl or acetilum or acetonyl or acetophen or acetosal or acetosalicylic acid or acetosalin or acetosalum or acetyl salicylate or acetyl salicylic acid or acetylic salicylic acid or acetylin or acetylo or acetylon or acetylosalicylic acid or acetylsal or acetylsalicyclic acid or acetylsalicyl or acetylsalicylate or acetylsalicylate strontium or acetylsalicylic acid or acetylsalycic acid or acetylsalycylic acid or acetysal or acidulatum or acidum acetyl salicylicum or acidum acetylosalicylicum or acidum acetylsalicylicum or acylpyrin or acylpyrine or acytosal or adiro or alabukun or alasil or alka seltzer or alkaspirin or aloxiprimum or anopyrin or arthralgyl or asaflow or asaphen or aspergum or aspirgran or aspirin or aspirina or aspirine or aspirinine or aspisol or aspro or asrivo or asteric or astrix or bebesan or biprin or boxazin or breoprin or bufferin or cafenol or catalgine or catalgix or cemerit or cemirit or claradin or claragine or colfarit or colfarit or contrheuma or contrheuma retard or daga or darosal or depot aspirin or dispirin or dispril or dolean or easprin or ecotrin or egalgic or emocin or empirin or encaprin or endosprin or endosprin or entericin or enterosarine or enterospirine or entrophen or euthermine or extren or genasprin or godamed or gotosan or helicon or infatabs a or istopirin or istopyrine or ivepirine or juvepirine or kilios or kinderaspirin or magnecyl or measurin or mejoral or micristin or micristin or micropyrin or mikristin or miniasal or mycristin or nu seal or nuseals or ortho acetoxybenzoate or ortho acetoxybenzoic acid or ortho acetyloxybenzoate or ortho acetyloxybenzoic acid or ostoprin or pancemol or para acetylsalicylic acid or paracin or paynocil or pengo or polopirin or polopiryna or polopiryna or premaspin or primaspan or pyronoval or reumyl or rhodine or rhonal or salacetin or salacetogen or saletin or sargepirine or slow release aspirin or sodium acetylsalicylate or sodium bicarbonate acetyl salicylate or sodium bicarbonate acetylsalicylate or soldral or solprin or solpyron or solucetyl or solupsa or solupsan or super tru or tapal or temagin or treupahlin or treuphalin or turivital or verin or vitalink or xaxa or zorprin).ti,ab.
3. alfentanil/or (alfentanil or alfenta or alfentanil or alfentanil hydrochloride or alfentanyl or alfentanyl or fanaxal or limifen or rapifen).ti,ab.
4. (almotriptan or almogran or almotriptan malate or axert).ti,ab.
5. (buprenorphin$ or buprenex or buprex or finibron or lepetan or prefin or suboxone or subutex or temgesic or transtec).ti,ab.
6. caffeine/or caffeine$.ti,ab.

7. cannabis/or (cannabis or cannabi or cannabis or ganja or ganjas or hemp or hemps or marihuana or marihuanas or marijuana or marijuanas or opiate).ti,ab.
8. (cocodamol or acetaminophen plus codeine phosphate or empracet or hypertussin or lindilane or nedolon or panadeine or paracodal or percogesic with codeine or talvosilen or treuphadol plus).ti,ab.
9. (codeine phosphate or ardinex or codein phosphate or codeine or codeine phosphate or codicompren retard or colrex compound or galcodine or isocodeine or kodein or n methylmorphine or tricodein or tussipect).ti,ab.
10. (codydramol or codidramol).ti,ab.
11. cyclizine/or (cyclizine or collox or cyclizine or marazine or marezine or marzine or neo devomit or valoid).ti,ab.
12. dextromoramide/or (dextromoramide or d moramide or dextro moramide or dextromoramide or dextromoramine or dimorlin or d-moramide or jetrium or moramide or palfium or palfium or palphium or pyrrolamidol or pyrrolamidole or pyrroloamidol).ti,ab.
13. dextropropoxyphene/or (co proxamol or coproxamol or cosalgesic or d propoxyphene or darvon or dextropropoxyphene or diantalvic or distalgesic or d-propoxyphene or dystalgesic or paradex or propoxyphene).ti,ab.
14. (dihydrocodeine or cis dihydrocodeine or codhydrin or codhydrine or codicontin or cohydrin or dehacodin or dh codeine or didrate or dihydrin or dihydroneopine or drocode or hydrocodeine or hydrocodin or nadein or nadeine or napacodin or novicodin or paracodein or paracodin or paramol or parzone or rapacodin or remedacen or tiamon mono or trans dihydrocodeine).ti,ab.
15. (dipipanone or pipadone or piperidyl amidone).ti,ab.
16. eletriptan.ti,ab.
17. ergotamine/ or (ergate or ergomar or ergostat or ergotamine tartrate or ergotaminetartras or exmigra or femergin or gynergen or lingraine or medihaler ergotamine or relpax or virdex or wigrettes).ti,ab.
18. fentanyl/or (fentanyl$ or duragesic or duragesic or durogesic or fentamyl or fentanest or fentanil or fentora or fetnanyl or ionsys or leptanal or phentanyl or sublimaze or transfenta).ti,ab.
19. (frovatriptan allegro or frova or migard or miguard).ti,ab.
20. (heroin$1 or acetomorphine or diacephine or diacetyl morphine or diacetylmorphine or diagesil or diamorf or diamorphine or diaphorin or morphacetin).ti,ab.
21. (hydromorphone or biomorphyl or cofalaudid or dihydromorphinone or dihydromorphone or dilaudid or dimorphone or hydromorphinone hydrochloride hydromorphon or hydromorphone or hymorphan or laudacon or laudaconum or novolaudon or palladon or palladone or palladone or semcox or sophidone).ti,ab.
22. isometheptene mucate.ti,ab.

23. ketorolac$.sh. or (droal or isometheptenemucate or isometheptine mucate or ketocol or ketorolac or midrin or taradyl or toradol or toratex).ti,ab.
24. meptazinol/ or (meptazinol or meptazinol or meptid).ti,ab.
25. exp methadone/ or (methadone$ or adanon or adanon hydrochloride or algidon or algolysin or algoxale or althose or amidon or amidone or amidosan or anadon or biodone or butalgin or deamin or depridol or diaminon or dianone or dolafin or dolamid or dolesone or dolophine or dolophine hydrochloride or dorex or dorexol or fenadon or heptadon or heptanon or ketalgin or mecodin or mepecton or mephenon or metadol or metasedin or methaddict or methadose or methex or miadone or moheptan or phenadon$1 or phymet or physepton or physeptone or pinadone or polamidon or polamivet or polamivit or sinalgin or symoron).ti,ab.
26. methysergide/or (methysergide$ or deseril or desernil sandoz or desril or dimethylergometrin or dimethylergometrine or dimethylergonovine or methisergid or methisergide or methyl sergide or methylmethylergonovine or methylsergide or methysergid or methysergide or sansert).ti,ab.
27. exp morphine/ or morphinans/or (morphine or astramorph or avinza or depodur or depomorphine or dolcontin or duramorph or duramorple or kadian or kapanol or moraxen or morphia or morphinesulfate or moscontin or ms contin or mst continus or mst mundipharma or noceptin or oblioser or oramorph or roxanol or sevredol or skenan lp).ti,ab.
28. exp naloxone/or (naloxone or maloxone or nalaxone or nalone or nalonee or narcan or narcanti or narcon or narvcam).ti,ab.
29. (naratriptan or amerge or naramig).ti,ab.
30. nefopam/ or (nefopam or acupan or ajan or fenazoxine or lenipan or nocipan).ti,ab.
31. opiate alkaloids/or opium/ or (opiate$ or opioid$ or opium).ti,ab.
32. (oxycodone or bionine or bionone or bolodorm or broncodal or bucodal or cafacodal or cardanon or codenon or dihydrohydroxydodeinone or dihydrone or dinarkon or endone or eubine or eucodal or eucodale or eudin or eukdin or eukodal or eumorphal or eurodamine or eutagen or hydrocodal or hydroxycodeinoma or hydroxycodeinon or ludonal or medicodal or narcobasina or narcobasine or narcosin or nargenol or narodal or nucodan or opton or ossicodone or oxanest or oxicone or oxiconum or oxikon or oxycodeinon or oxycodeinonhydrochloride or oxycodone or oxycodonhydrochlorid or oxycodyl or oxycone or oxycontin or oxygesic or oxykon or oxynorm or pancodine or pavinal or pronarcin or remoxy or roxicodone or roxycodone or sinthiodal or stupenal or tebodal or tekodin or thecodin or theocodin).ti,ab.
33. acetaminophen/or (paracetamol or acetaminophen or acamol or acephen or acetaco or acetamidophenol or acetominophen or

algotropyl or anacin 3 or anacin3 or apap or datril or hydroxyacetanilide or p-acetamidophenol or panadol or tylenol).ti,ab.
34. pentazocine/or (pentazocine or dolapent or fortal or fortalgesic or fortral or fortraline or fortwin or lexir or liticon or peltazon or pentacozine or pentafen or pentagin or pentalgina or pentazocin or pentozocine or perutagin or sosegon or sosigon or talioin or talwin).ti,ab.
35. exp meperidine/ or (pethidine or algil or alodan or centralgin or centralgine or demerol or dispadol or dolanquifa or dolantal or dolantin or dolantine or dolargan or dolcontral or dolenal or dolestin or dolin or dolocontral or doloneurin or doloneurotrat or dolor or dolosa or dolosal or dolosan or dolsin or dolvanol or endolate or isonipecain or isonipecaine or l pethidine or lidol or lydol or mefedina or mepadin or meperiden or meperidin or meperidine or mephedine or mepiridine or mialgin or pantalgin or petadin or petantin or petantina or pethanol or pethedine or pethidin or pethidine or petidin or phetidine or piridosal or sauteralgyl or simesalgina or supplosal or synlaudine).ti,ab.
36. (pizotifen or mosegor or sanmigran or sanomigran).ti,ab.
37. (rizatriptan or maxalt).ti,ab.
38. sumatriptan/ or (sumatriptan succinate or imigran or imiject or imitrex or sumadol or sumigrene).ti,ab.
39. (tolfenamic acid or clotam or clotan or rociclyne or tolfedine or tolfenamate).ti,ab.
40. tramadol/or (tramadol or adolonta or amadol or biodalgic or biokanol or contramal or dolzam or jutadol or kontram xl or melanate or mtwtramadol or nobligan or prontofort or ranitidin 1a pharma or takadol or theradol or tiral or topalgic or tradol or tradolpuren or tradonal or tralgiol or trama abz or trama dorsch or trama kd or tramabeta or tramadin or tramadoc or tramadoldolgit or tramadolhameln or tramadolium chloride or tramadolor or tramadolratiopharm or tramadorsch or tramadura or tramagetic or tramagit or tramake or tramal or tramex or tramundin or trasedal or trodon or trondon or ultram or xymel 50 or zamudol or zumalgic or zydol or zytram).ti,ab.
41. (zolmitriptan or ascotop or zomig or zomigon).ti,ab.
42. (zopiclone or amoban or imovance or imovane or ximovan or zimovane or zoplicon).ti,ab.
43. or/1-42
44. exp benzodiazepines/ or (benzo$1 or benzodiazepin$).ti,ab.
45. (alprazolam or alprox or apo alpraz or apoalpraz or aprazolam$1 or cassadan$1 or esparon$1 or helex or kalma or novo alprazol$1 or novoalprazol$1 or nu alpraz or nualpraz or ralozam or solanax or tafil$1 or trankimazin$1 or valeans or xanax or xanor).ti,ab.
46. (bromazepam or anxyrex or bartul or bromalich or bromaz pharma or bromazanil$1 or bromazep von ct or durazanil$ or lectopam$1 or

lexamil$1 or lexatin$1 or lexaurin$1 or lexilium or lexomil$1 or lexotan$1 or lexotanil$1 or lexotanil$1 or normoc or sintrogel$1).ti,ab.

47. (chlordiazepoxid$1 or methaminodiazepoxid$1 or elenium$1 or librium$1 or chlozepid$1 or ansiacal$1 or benzodiapin$1 or cebrum$1 or chlordiazepoxyd$1 or chlorodiazepoxid$1 or clopoxid$1 or contol$1 or decacil$1 or defobin$1 or disarim$1 or dizepin$1 or dopoxid$1 or droxol$1 or eden psich or elenium$1 or elenum$1 or equibral$1 or kalmocaps or labican$1 or librelease or libritabs or librium or lipoxide or mesural$1 or metaminodiazepoxid$1 or methaminodiazepoxid$1 or mildmen$1 or mitran$1 or multum$1 or murcil$1 or napoton$1 or napoton$1 or novosed$1 or psichial$1 or psicosan$1 or psicoterin$1 or radepur or reliberan$1 or reposans or risolid or seren vita or servium or silibrin$1 or sk lygen or sonimen$1 or timosin$1 or viansin$1 or viopsicol$1).ti,ab.
48. (clobazam or chlorepin$1 or clobazepam or clorepin$1 or frisium or noiafren$1 or urbadan$1 or urbanil$1 or urbanyl).ti,ab.
49. (clonazepam or antelepsin$1 or clonopin$1 or iktorivil$1 or klonazepam or klonopin$1 or landsen$1 or rivotril$1).ti,ab.
50. (clorazepat$1 or carboxylic acid or chlorazepat$1 or chloroazepat$1 or clorazepic acid or tranxen$1 or tranxilium).ti,ab.
51. (delorazepam or briantum$1 or chlordemethyldiazepam or chlordesmethyldiazepam or chloro n demethyldiazepam or chlorodemethyldiazepam or chlorodesmethyldiazepam or chloronordiazepam).ti,ab.
52. (diazepam or alupram or ansiolin$1 or antenex or apaurin$1 or apaurin$1 or apozepam or assival$1 or audium$1 or bialzepam or bialzepan$1 or calmpos$1 or cercin$1 or cersin$1 or chlordiazepam or dialar or diastat or diazelium or diazemuls or diazidem or ducen$1 or duxen$1 or eridan or eurosan$1 or evacalm$1 or fanstan$1 or faustan$1 or gewacalm$1 or lamra or lembrol$1 or lipodiazepam or lorinon$1 or methyldiazepinon$1 or methyldiazepinon$1 or morosan$1 or neocalm$1 or neurolytril$1 or noan or novazam or paceum or plidan or psychopax or relanium or 1 rimapam or sedapam or seduxen$1 or serendin$1 or setonil$1 or sibazon$1 or sonacon$1 or stesolid$1 or stesolin$1 or tanquo tablinen$ or tensium or tranimul$1 or tranquo puren or umbrium$1 or valaxon$1 or valclair or valiquid$1 or valium or valpam or valreleas$ or vatran$1 or vival$1 or vivol or zetran$1).ti,ab.
53. (flunitrazepam or flurazepam or fluridrazepam or darken$1 or fluni 1a pharma or flunibeta or flunimerck or fluninoc or flunipam or flunita or flunitrax or flunizep von ct or hypnodorm$1 or hypnosedon$1 or inervon$1 or narcozep or parnox or rohipnol$1 or rohypnol$1 or roipnol$1 or silece or valsera).ti,ab.
54. (flurazepam or benozil$1 or dalmadorm$1 or dalman$1 or dalmate or dormodor$1 or lunipax or staurodorm$1 or dalman$1 or dormodor$1 or dalmadorm$1).ti,ab.

55. (flutoprazepam or restas).ti,ab.
56. loprazolam.ti,ab.
57. (lorazepam or almazin$1 or alzapam or apolorazepam or ativan or bonatranquan$1 or donix or duralozam or durazolam or idalprem or kendol$1 or laubeel or lorabenz or loranas$1 or loranaz$1 or lorans or lorax or lorazep von ct or loridem$1 or lorivan$1 or mesmerin$1 or novo lorazem$1 or novolorazem$1 or novo lorazem$1 or nu loraz or nuloraz or orfidal or orifadal$1 or pro dorm or quait or securit or sedicepan$1 or sinestron$1 or somagerol$1 or tavor or temesta or tolid or wypax).ti,ab.
58. (lormetazepam or loramet or (lorazepam adj2 methyl) or methyllorazepam or minians or minias or noctamid$1 or pronoctan$1).ti,ab.
59. (mexazolam or melex or sedoxil$1).ti,ab.
60. (midazolam or dormicum or dormonid$1 or hypnoval$1 or hypnovel$1 or hypnoyvel$1 or versed).ti,ab.
61. (nitrazepam or alodorm or atempol$1 or benzalin$1 or dormalon$1 or dormo puren or dumolid or eatan or eunoctin$1 or hypnotex or imadorm or imeson$1 or insomin$1 or mogadan$1 or mogadon$1 or nelbon$1 or nirven$1 or nitra zepam or nitrados or nitravet or nitrazadon$1 or nitrazep or nitrodiazepam or novanox or pacisyn or radedorm$1 or remnos or restorem$1 or sedamon$1 or serenade or somnased$1 or somnibel$1 n or somnit$1).ti,ab.
62. (oxazepam or abboxapam or adumbran$1 or alopam or anxiolit$1 or azutranquil$1 or durazepam or expidet$1 or hilong or isodin$1 or linbial$1 or noctazepam or oxapuren$1 or oxepam or praxiten$1 or serax or serenid$1 or serepax or seresta or serpax or sigacalm$1 or sobril$1 or tazepam$1 or uskan).ti,ab.
63. (prazepam or centrax or demetrin$1 or lysanxia or mono demetrin$1 or monodemetrin$1 or reapam or sedapran$1 or verstran).ti,ab.
64. (temazepam or apo temazepam or dasuen or euhypnos or hydroxydiazepam or levanxol$1 or methyloxazepam or nocturne$1 or norkotral tema or normison$1 or normitab or nortem or oxydiazepam or planum or pronervon t or remestan$1 or restoril$1 or signopam or temaz$1 or temazep von ct or temazepax or temtabs or tenox or texapam).ti,ab.
65. or/44-64
66. exp antidepressive agents, tricyclic/ or (tca$1 or tricyclic$).ti,ab.
67. (amitriptyl$1 or amitryptil$1 or amitryptin$1 or amitryptylin$1 or amytriptil$1 or amytriptyl$1 or amytryptil$1 or adepress or adepril$1 or ambivalon$1 or amineurin$1 or amitid$1 or amitril$1 or amitrip or amitrol$1 or anapsique or antitriptylin$1 or apoamitriptylin$1 or damilen$1 or damylen$1 or domical$1 or elatrol$1 or elavil$1 or endep or enovil$1 or etafon$1 or etafron$1 or euplit$1 or lantron$1 or laroxal$1 or laroxyl$1 or lentizol$1 or novoprotect or proheptadien$1 or redomex or sarboten retard 75 or saroten$1 or sarotex or stelminal$1

or sylvemid$1 or syneudon$1 or teperin$1 or terepin$1 or triptafen$1 or triptanol$1 or triptizol$1 or triptyl or triptylin$1 or tryptanol$1 or tryptin$1 or tryptizol$1).ti,ab.

68. (chlomipramin$1 or chlorimipramin$1 or chloroimipramin$1 or clomipramin$1 or anafranil$1 or anafranilin$1 or anafranyl or domipramin$1 or hydiphen$1 or monochlor imipramin$1 or monochlorimipramin$1 or monochloroimipramin$1).ti,ab.
69. (dothiepin$1 or dosulepin$1 or altapin$1 or depresym$1 or dopress or dothep or idom or prothiaden$1 or prothiadien$1 or prothiadin$1 or protiaden$1 or thaden).ti,ab.
70. (doxepin$1 or adapin$1 or apodoxepin$1 or aponal$1 or co dox or curatin$1 or deptran$1 or desidox or doneurin$1 or doxepia or espadox or mareen or prudoxin$1 or quitaxon$1 or silenor or sinepin or sinequan$1 or sinquan$1 or xepin$1 or zonalon$1).ti,ab.
71. (imipramin$1 or antideprin$1 or berkomin$1 or chrytemin$1 or deprimin or deprinol$1 or depsonil or dynaprin or eupramin or ia pram or imavate or imidobenzyl$1 or imidol$1 or imipramid$1 or imipramil or imiprex or imiprin$1 or imizin$1 or irmin or janimin$1 or melipramin$1 or norchlorimipramin$1 or norpramin$1 or novopramin$1 or presamin$1 or pryleugan$1 or psychoforin$1 or psychoforin$1 or servipramin$1 or sk pramin$1 or surplix or tofranil$1 or trofanil$1).ti,ab.
72. (lofepramin$1 or lopramin$1 or amplit$1 or deftan$1 or feprapax or gamanil$1 or gamonil$1 or lomont or lopramin$1 or tymelyt).ti,ab.
73. (mianserin$1 or athymil$1 or bolvidon$1 or investig or lantanon$1 or lanthanon$1 or lerivon$1 or miaxan$1 or norval or serelan$1 or tetramid$1 or tolvin$1 or tolvon$1).ti,ab.
74. (nortriptylin$1 or acetexa or allegron$1 or altilev or atilev or avantyl or aventyl or desitriptylin$1 or desmethylamitriptylin$1 or martimil$1 or noramitriptylin$1 or norfenazin$1 or noritren$1 or norpress or nortrilen$1 or nortryptilin$1 or nortryptylin$1 or pamelor or paxtibi or propylamin$1 or psychostyl or sens?val).ti,ab.
75. opipramol/or (opipramol$1 or dinsidon$1 or ensidon$1 or eusidon$1 or insidon$1 or nisidan$1 or oprimol or pramolan$1).ti,ab.
76. (trazodon$1 or beneficat or deprax or desirel or desyrel$1 or molipaxin$1 or pesyrel$1 or rpragazon$1 or pragmarel$1 or pragmazon$1 or thombran$1 or thrombin$1 or thrombran$1 or tombran$1 or trasodon$1 or trazolan$1 or trazorel or trazon$1 or trialodine or trittico).ti,ab.
77. (trimepramin$1 or trimeprimin$1 or trimepropimin$1 or trimidura or trimineurin$1 maleate or trimipramin$1 or trimoprimin$1 or eldoral$1 or herphonal$1 or trimineurin$1 or novo tripramin$1 or novotripramin$1 or nutrimipramin$1 or rhotrimin$1 or stangyl or surmontil$1 or apo trimip or apotrimip or herphonal$1 or stangyl or surmontil$1).ti,ab.

78. exp serotonin uptake inhibitors/ or (((serotonin or 5 ht or 5 hydroxytryptamine) adj (uptake or reuptake or re uptake) adj inhibit$) or ssri$).ti,ab.
79. (citalopram or celexa or cipramil$1 or cytalopram or elopram or escitalopram or lexapro or nitalapram or sepram or seropram).ti,ab.
80. (escitalopram or cipralex or lexapro or seroplex).ti,ab.
81. (fluoxetin$1 or fluctin$1 or flunirin$1 or fluoxifar or prosac or prozac or prozamin or sarafem or symbyax).ti,ab.
82. (fluvoxamin$1 or depromel$1 or desiflu or dumirox or faverin$1 or fevarin$1 or floxyfral$1 or fluoxamin$1 or fluroxamin$1 or fluvoxadura or luvox).ti,ab.
83. (nefazadon$1 or dutonin or nefadar or reseril$1 or serzon$1).ti,ab.
84. (paroxetin$1 or aropax or deroxat or motivan$1 or paxil or pexeva or seroxat or tagonis).ti,ab.
85. (sertralin$1 or altrulin$1 or aremis or besitran$1 or gladem or lustral$1 or naphthylamin$1 or sealdin$1 or serad or serlain$1 or tresleen or zoloft).ti,ab.
86. or/66-85
87. or/1-86
88. (ae or ct or po or to).fs.
89. exp abnormalities, drug induced/ or exp adverse drug reaction reporting systems/ or exp death/ or exp drug hypersensitivity/ or exp drug-induced liver injury / or drug interactions/ or exp intraoperative complications/ or drug monitoring/ or exp drug tolerance/ or overdose/ or exp poisoning/ or exp postoperative complications/ or exp product surveillance, postmarketing/ or respiration depression/ or risk/ or risk assessment/ or risk factors/ or exp toxemia/
90. (causa$ or ((adverse or negativ$ or side or undesir$ or unwanted) adj2 (effect$ or event$ or outcome$ or reaction$)) or death$ or discontinuation effect$ or (caution$ or complication$ or contraindicat$ or contra indicat$ or harm$ or hazard$ or interaction$1 or intolerab$ or lethal$ or noxious$ or overdos$ or safety or safe or tolerab$ or toxic$ or warning$) or (treatment emergent or adrs)).ti,ab.
91. or/88-90
92. 87 and 91

Search filters

a) Health economics and quality of life search filter – an adaptation of a filter designed by the Centre for Reviews and Dissemination (CRD) (2007).

Medline – Ovid SP interface

1. budgets/ or capital expenditures/ or cost allocation/ or cost benefit analysis/ or cost control/ or "cost of illness"/or cost savings/ or cost sharing/ or cost-benefit analysis/ or "costs and cost analysis"/ or

"deductibles and coinsurance"/ or direct service costs/ or drug costs/ or economics/ or economics, hospital/ or economics, medical/ or economics, nursing/ or economics, pharmaceutical/ or employer health costs/ or "fees and charges"/ or financial management/ or financial management, hospital/ or health care costs/ or health care rationing/ or health expenditures/ or health priorities/ or health resources/ or "health services needs and demand"/ or hospital costs/ or medical savings accounts/ or models, econometric/or models, economic/ or quality-adjusted life years/ or "quality of life"/ or resource allocation/ or "value of life"/

2. (budget$ or cost$ or econom$ or expenditure$ or financ$ or fiscal or funding or pharmacoeconomic$ or socioeconomic$ or price or prices or pricing or (value adj3 money) or (burden adj3 (disease$ or illness$))).ti,ab.
3. (daly or qol or hql or hqol or hrqol or hr ql or hrql or (quality adj2 life) or (adjusted adj2 life) or qaly$ or (health adj2 stat$) or well being or wellbeing or qald$ or qale$ or qtime$ or eq5d or eq 5d or qwb or ((quality or value$) adj3 (life or survival or well$)) or hui$1 or (utilit$ adj1 (health or score$ or weigh$)) or (life adj2 year$) or health year equivalent$ or ((disability or quality) adj adjusted) or utility value$ or (weight$ adj3 preference$) or euroqol or euro qol or visual analog$ or standard gamble or time trade or qtwist or q twist or (valu$ adj2 quality)).tw.
4. decision trees/
5. (decision analy$ or monte carlo or markov or simulation model$ or rosser or disutili$ or willingness to pay or tto or hye or hyes or (resource adj (allocat$ or use$ or utilit$))).tw.
6. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
7. (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
8. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
9. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
10. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
11. ec.fs. *[ANDed with subject heading searches for the main population/topic]*
12. or/1-11

APPENDIX 13: METHODOLOGY CHECKLIST FOR ECONOMIC STUDIES

This checklist is designed to determine whether an economic evaluation provides evidence that is useful to inform the decision-making of the guideline development group (GDG) (see chapter 7). It is not intended to judge the quality of the study per se or the quality of reporting.

Byford, S., Knapp, M., Greenshields, J., *et al.* (2003) Cost-effectiveness of brief cognitive behaviour therapy versus treatment as usual in recurrent deliberate self-harm: a decision-making approach. *Psychological Medicine, 33,* 977-986.		
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/ Partially/ No /Unclear /NA**	**Comments**
Is the patient population appropriate for the guideline?	Yes	
Are the interventions appropriate for the guideline?	Yes	
Is the healthcare system in which the study was conducted sufficiently similar to the current UK NHS context?	Yes	
Are costs measured from the NHS and PSS perspective?	Partially	Voluntary sector, community accommodation, criminal justice system and productivity costs included
Are all health effects on individuals included?	Yes	
Are both costs and health effects discounted at an annual rate of 3.5%?	NA	
Is the value of health effects expressed in terms of QALYs?	Yes	
Are changes in health related quality of life (HRQL) reported directly from patients and/or carers?	Yes	
Is the value of changes in HRQL (that is utilities) obtained from a representative sample of the public?	Unclear	Not specified in article
Overall judgement: Directly 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/ Partially /No/ Unclear/NA**	**Comments**
Does the model structure adequately reflect the nature of the health condition under evaluation?	NA	
Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Partially	12-month study
Are all important and relevant health outcomes included?	Partially	Unclear whether QALY estimates included suicides
Are the estimates of baseline health outcomes from the best available source?	Yes	
Are the estimates of relative treatment effects from the best available source?	Yes	
Are all important and relevant costs included?	Partially	No costs to patients' family/carers included (within societal perspective)
Are the estimates of resource use from the best available source?	Yes	
Are the unit costs of resources from the best available source?	Yes	
Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
Are all important parameters, whose values are uncertain, subjected to appropriate sensitivity analysis?	Yes	
Is there no potential conflict of interest?	No	
Overall assessment: Minor limitations		
Other comments:		

1
2

1

Byford, S., Harrington, R., Torgerson, D., et al. (1999) Cost-effectiveness analysis of a home-based social work intervention for children and adolescents who have deliberately poisoned themselves: results of a randomised controlled trial. *British Journal of Psychiatry, 174,* 56-62.		
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/ Partially/ No /Unclear /NA**	**Comments**
Is the patient population appropriate for the guideline?	Yes	
Are the interventions appropriate for the guideline?	Yes	
Is the healthcare system in which the study was conducted sufficiently similar to the current UK NHS context?	Yes	
Are costs measured from the NHS and PSS perspective?	Partially	Educational sector costs included
Are all health effects on individuals included?	Partially	Suicidal ideation; hopelessness scale; family assessment device
Are both costs and health effects discounted at an annual rate of 3.5%?	NA	
Is the value of health effects expressed in terms of QALYs?	No	
Are changes in health related quality of life (HRQL) reported directly from patients and/or carers?	NA	
Is the value of changes in HRQL (that is utilities) obtained from a representative sample of the public?	NA	
Overall judgement: Partially applicable		
Other comments:		

2
3

1

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/ Partially /No/ Unclear/NA**	**Comments**
Does the model structure adequately reflect the nature of the health condition under evaluation?	NA	
Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Partially	6-month study
Are all important and relevant health outcomes included?	Partially	
Are the estimates of baseline health outcomes from the best available source?	Yes	
Are the estimates of relative treatment effects from the best available source?	Yes	
Are all important and relevant costs included?	Partially	Educational sector costs included
Are the estimates of resource use from the best available source?	Yes	
Are the unit costs of resources from the best available source?	Yes	
Is an appropriate incremental analysis presented or can it be calculated from the data?	No	No significant differences detected in primary outcomes
Are all important parameters, whose values are uncertain, subjected to appropriate sensitivity analysis?	Partially	One way sensitivity analyses on cost estimates
Is there no potential conflict of interest?	No	
Overall assessment: Minor limitations		
Other comments:		

2
3

Notes on use of Methodology checklist: economic evaluations

For all questions:

- answer 'yes' if the study fully meets the criterion
- answer 'partly' if the study largely meets the criterion but differs in some
- important respect
- answer 'no' if the study deviates substantively from the criterion
- answer 'unclear' if the report provides insufficient information to judge
- whether the study complies with the criterion
- answer 'NA (not applicable)' if the criterion is not relevant in a particular instance.

For 'partly' or 'no' responses, use the comments column to explain how the study deviates from the criterion.

Section 1: applicability

1.1 Is the study population appropriate for the guideline?

The study population should be defined as precisely as possible and should be in line with that specified in the guideline scope and any related review protocols.
This includes consideration of appropriate subgroups that require special attention. For many interventions, the capacity to benefit will differ for participants with differing characteristics. This should be explored separately for each relevant subgroup as part of the base-case analysis by the provision of estimates of clinical and cost effectiveness. The characteristics of participants in each subgroup should be clearly defined and, ideally, should be identified on the basis of an a priori expectation of differential clinical or cost effectiveness as a result of biologically plausible known mechanisms, social characteristics or other clearly justified factors.

Answer 'yes' if the study population is fully in line with that in the guideline question(s) and if the study differentiates appropriately between important subgroups. Answer 'partly' if the study population is similar to that in the guideline question(s) but: (i) it differs in some important respects; or (ii) the study fails to differentiate between important subgroups. Answer 'no' if the study population is substantively different from that in the guideline question(s).

1.2 Are the interventions appropriate for the guideline?

All relevant alternatives should be included, as specified in the guideline scope and any related review protocols. These should include routine and

best practice in the NHS, existing NICE guidance and other feasible options. Answer 'yes' if the analysis includes all options considered relevant for the guideline, even if it also includes other options that are not relevant. Answer 'partly' if the analysis omits one or more relevant options but still contains comparisons likely to be useful for the guideline. Answer 'no' if the analysis does not contain any relevant comparisons.

1.3 Is the healthcare system in which the study was conducted sufficiently similar to the current UK NHS context?

This relates to the overall structure of the healthcare system within which the interventions were delivered. For example, an intervention might be delivered on an inpatient basis in one country whereas in the UK it would be provided in the community. This might significantly influence the use of healthcare resources and costs, thus limiting the applicability of the results to a UK setting. In addition, old UK studies may be severely limited in terms of their relevance to current NHS practice.

Answer 'yes' if the study was conducted within the UK and is sufficiently recent to reflect current NHS practice. For non-UK or older UK studies, a answer 'partly' if differences in the healthcare setting are unlikely to substantively change the cost-effectiveness estimates. Answer 'no' if the healthcare setting is so different that the results are unlikely to be applicable in the current NHS.

1.4 Are costs measured from the NHS and personal social services (PSS) perspective?

The decision-making perspective of an economic evaluation determines the range of costs that should be included in the analysis. NICE works in a specific context; in particular, it does not set the budget for the NHS. The objective of NICE is to offer guidance that represents an efficient use of available NHS and PSS resources. For these reasons, the perspective on costs used in the NICE reference case is that of the NHS and PSS. Productivity costs and costs borne by patients and carers that are not reimbursed by the NHS or PSS are not included in the reference case. The reference case also excludes costs to other government bodies, although these may sometimes be presented in additional analyses alongside the reference case.

Answer 'yes' if the study only includes costs for resource items that would be paid for by the NHS and PSS. Also answer 'yes' if other costs have been included in the study, but the results are presented in such a way that the cost effectiveness can be calculated from an NHS and PSS perspective. Answer 'partly' if the study has taken a wider perspective but the other non-NHS/PSS costs are small in relation to the total expected costs and are unlikely to change the cost-effectiveness results. Answer 'no' if non-NHS/PSS costs are significant and are likely to change the cost-effectiveness results. Some interventions may have a substantial impact on non-health outcomes or costs

to other government bodies (for example, treatments to reduce illicit drug misuse may have the effect of reducing drug-related crime). In such situations, if the economic study includes non-health costs in such a way that they cannot be separated out from NHS/PSS costs, answer 'no' but consider retaining the study for critical appraisal. If studies containing non-reference-case costs are retained, use the comments column to note why.

1.5 Are all direct health effects on individuals included?

In the NICE reference case, the perspective on outcomes should be all direct health effects, whether for patients or, when relevant, other people principally carers). This is consistent with an objective of maximising health gain from available healthcare resources. Some features of healthcare delivery that are often referred to as 'process characteristics' may ultimately have health consequences; for example, the mode of treatment delivery may have health consequences through its impact on concordance with treatment. Any significant characteristics of healthcare technologies that have a value to people that is independent of any direct effect on health should be noted. These characteristics include the convenience with which healthcare is provided and the level of information available for patients.

This question should be viewed in terms of what is **excluded** in relation to the NICE reference case; that is, non-health effects.

Answer 'yes' if the measure of health outcome used in the analysis excludes non-health effects (or if such effects can be excluded from the results). Answer 'partly' if the analysis includes some non-health effects but these are small and unlikely to change the cost-effectiveness results. Answer 'no' if the analysis includes significant non-health effects that are likely to change the cost-effectiveness results.

1.6 Are both costs and health effects discounted at an annual rate of 3.5%?

The need to discount to a present value is widely accepted in economic evaluation, although the specific rate varies across jurisdictions and over time. NICE considers it appropriate to discount costs and health effects at the same rate. The annual rate of 3.5%, based on the recommendations of the UK Treasury for the discounting of costs, applies to both costs and health effects.

Answer 'yes' if both costs and health effects (for example, quality-adjusted life years [QALYs]) are discounted at 3.5% per year. Answer 'partly' if costs and effects are discounted at a rate similar to 3.5% (for example, costs and effects are both discounted at 3% per year). Answer 'no' if costs and/or health effects are not discounted, or if they are discounted at a rate (or rates) different from 3.5% (for example, 5% for both costs and effects, or 6% for costs and 1.5% for effects). Note in the comments column what discount rates have been used. If

all costs and health effects accrue within a short time (roughly a year), answer 'NA'.

1.7 Is the value of health effects expressed in terms of qualityadjusted life years (QALYs)?

The QALY is a measure of a person's length of life weighted by a valuation of their health-related quality of life (HRQoL) over that period.

Given its widespread use, the QALY is considered by NICE to be the most appropriate generic measure of health benefit that reflects both mortality and effects on HRQoL. It is recognised that alternative measures exist (such as the healthy-year equivalent), but few economic evaluations have used these methods and their strengths and weaknesses are not fully established.

NICE's position is that an additional QALY should be given the same weight regardless of the other characteristics of the patients receiving the health benefit.

Answer 'yes' if the effectiveness of the intervention is measured using QALYs; answer 'no' if not. There may be circumstances when a QALY cannot be obtained or where the assumptions underlying QALYs are considered inappropriate. In such situations answer 'no', but consider retaining the study for appraisal. Similarly, answer 'no' but retain the study for appraisal if it does not include QALYs but it is still thought to be useful for GDG decision-making: for example, if the clinical evidence indicates that an intervention might be dominant, and estimates of the relative costs of the interventions from a costminimisation study are likely to be useful. When economic evaluations not using QALYs are retained for full critical appraisal, use the comments column to note why.

1.8 Are changes in health-related quality of life (HRQoL) reported directly from patients and/or carers?

In the NICE reference case, information on changes in HRQoL as a result of treatment should be reported directly by patients (and directly by carers when the impact of treatment on the carer's health is also important). When it is not possible to obtain information on changes in patients' HRQoL directly from them, data should be obtained from carers (not from healthcare professionals).

For consistency, the EQ-5D is NICE's preferred measure of HRQoL in adults. However, when EQ-5D data are not available or are inappropriate for the condition or the effects of treatment, other multi-attribute utility questionnaires (for example, SF6D, QWB or HUI) or mapping methods from disease-specific questionnaires may be used to estimate QALYs. For studies not reporting QALYs, a variety of generic or disease-specific methods may be used to measure HRQoL.

Answer 'yes' if changes in patients' HRQoL are estimated by the patients themselves. Answer 'partly' if estimates of patients' HRQoL are provided by carers. Answer 'no' if estimates come from healthcare professionals or researchers. Note in the comments column how HRQoL was measured (EQ-5D, QWB, HUI and so on). Answer 'NA' if the cost-effectiveness study does not include estimates of HRQoL (for example, studies reporting 'cost per life year gained' or cost-minimisation studies).

1.9 Is the valuation of changes in HRQoL (utilities) obtained from a representative sample of the general public?

The NICE reference case specifies that the valuation of changes in HRQoL (utilities) reported by patients should be based on public preferences elicited using a choice-based method (such as the time trade-off or standard gamble) in a representative sample of the UK population.

Answer 'yes' if HRQoL valuations were obtained using the EQ-5D UK tariff. Answer 'partly' if the valuation methods were comparable to those used for the EQ-5D. Answer 'no' if other valuation methods were used. Answer 'NA' if the study does not apply valuations to HRQoL (for studies not reporting QALYs). In the comments column note the valuation method used (such as time trade-off or standard gamble) and the source of the preferences (such as patients or healthcare professionals).

1.10 Overall judgement

Classify the applicability of the economic evaluation to the clinical guideline, the current NHS situation and the context for NICE guidance as one of the following:

- **Directly applicable** – the study meets all applicability criteria, or fails to meet one or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness.
- **Partially applicable** – the study fails to meet one or more applicability criteria, and this could change the conclusions about cost effectiveness.
- **Not applicable** – the study fails to meet one or more applicability criteria, and this is likely to change the conclusions about cost effectiveness. Such studies would be excluded from further consideration and there is no need to continue with the rest of the checklist.

Section 2: study limitations

2.1 Does the model structure adequately reflect the nature of the health condition under evaluation?

This relates to the choice of model and its structural elements (including cycle length in discrete time models, if appropriate). Model type and its structural aspects should be consistent with a coherent theory of the health condition under evaluation. The selection of treatment pathways, whether health states or branches in a decision tree, should be based on the underlying biological processes of the health issue under study and the potential impact (benefits and adverse consequences) of the intervention(s) of interest.

Answer 'yes' if the model design and assumptions appropriately reflect the health condition and intervention(s) of interest. Answer 'partly' if there are aspects of the model design or assumptions that do not fully reflect the health condition or intervention(s) but that are unlikely to change the costeffectiveness results. Answer 'no' if the model omits some important aspect of the health condition or intervention(s) and this is likely to change the costeffectiveness results. Answer 'NA' for economic evaluations based on data from a clinical study which do not extrapolate treatment outcomes or costs beyond the study context or follow-up period.

2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?

The time horizon is the period of analysis of the study: the length of follow-up for participants in a trial-based evaluation, or the period of time over which the costs and outcomes for a cohort are tracked in a modelling study. This time horizon should always be the same for costs and outcomes, and should be long enough to include all relevant costs and outcomes relating to the intervention. A time horizon shorter than lifetime could be justified if there is no differential mortality effect between options, and the differences in costs and HRQoL relate to a relatively short period (for example, in the case of an acute infection).

Answer 'yes' if the time horizon is sufficient to include all relevant costs and outcomes. Answer 'partly' if the time horizon may omit some relevant costs and outcomes but these are unlikely to change the cost-effectiveness results. Answer 'no' if the time horizon omits important costs and outcomes and this is likely to change the cost-effectiveness results.

2.3 Are all important and relevant health outcomes included?

All relevant health outcomes should include direct health effects relating to harms from the intervention (adverse effects) as well as any potential benefits.

Answer 'yes' if the analysis includes all relevant and important harms and benefits. Answer 'partly' if the analysis omits some harms or benefits but these would be unlikely to change the cost-effectiveness results. Answer 'no' if the analysis omits important harms and/or benefits that would be likely to change the cost-effectiveness results.

2.4 Are the estimates of baseline health outcomes from the best available source?

The estimate of the overall net treatment effect of an intervention is determined by the baseline risk of a particular condition or event and/or the relative effects of the intervention compared with the relevant comparator treatment. The overall net treatment effect may also be determined by other features of the people comprising the population of interest.

The process of assembling evidence for economic evaluations should be systematic – evidence must be identified, quality assessed and, when appropriate, pooled, using explicit criteria and justifiable and reproducible methods. These principles apply to all categories of evidence that are used to estimate clinical and cost effectiveness, evidence for which will typically be drawn from a number of different sources.

The sources and methods for eliciting baseline probabilities should be described clearly. These data can be based on 'natural history' (patient outcomes in the absence of treatment or with routine care), sourced from cohort studies. Baseline probabilities may also be derived from the control arms of experimental studies. Sometimes it may be necessary to rely on expert opinion for particular parameters.

Answer 'yes' if the estimates of baseline health outcomes reflect the best available evidence as identified from a recent well-conducted systematic review of the literature. Answer 'partly' if the estimates are not derived from a systematic review but are likely to reflect outcomes for the relevant group of patients in routine NHS practice (for example, if they are derived from a large UK-relevant cohort study). Answer 'no' if the estimates are unlikely to reflect outcomes for the relevant group in routine NHS practice.

2.5 Are the estimates of relative treatment effects from the best available source?

The objective of the analysis of clinical effectiveness is to produce an unbiased estimate of the mean clinical effectiveness of the interventions being compared.

The NICE reference case indicates that evidence on outcomes should be obtained from a systematic review, defined as the systematic location, inclusion, appraisal and synthesis of evidence to obtain a reliable and valid overview of the data relating to a clearly formulated question.

Synthesis of outcome data through meta-analysis is appropriate provided that there are sufficient relevant and valid data obtained using comparable measures of outcome.

Head-to-head randomised controlled trials (RCTs) provide the most valid evidence of relative treatment effect. However, such evidence may not always be available. Therefore, data from non-randomised studies may be required to supplement RCT data. Any potential bias arising from the design of the studies used in the assessment should be explored and documented.

Data from head-to-head RCTs should be presented in the base-case analysis, if available. When head-to-head RCTs exist, evidence from indirect or mixed treatment comparison analyses may be presented if it is considered to add information that is not available from the head-to-head comparison. This indirect or mixed treatment comparison must be fully described and presented as additional to the base-case analysis. (A 'mixed treatment comparison' estimates effect sizes using both head-to-head and indirect comparisons.)

If data from head-to-head RCTs are not available, indirect treatment comparison methods should be used. (An 'indirect comparison' is a synthesis of data from a network of trials that compare the interventions of interest with other comparators.)

When multiple interventions are being assessed that have not been compared within a single RCT, data from a series of pairwise head-to-head RCTs should be presented. Consideration should also be given to presenting a combined analysis using a mixed treatment comparison framework if it is considered to add information that is not available from the head-to-head comparison.

Only indirect or mixed treatment comparison methods that preserve randomisation should be used. The principles of good practice for standard meta-analyses should also be followed in mixed and indirect treatment comparisons.

The methods and assumptions that are used to extrapolate short-term results to final outcomes should be clearly presented and there should be documentation of the reasoning underpinning the choice of survival function.

Evidence for the evaluation of diagnostic technologies should normally incorporate evidence on diagnostic accuracy. It is also important to incorporate the predicted changes in health outcomes and costs resulting from treatment decisions based on the test result. The general principles guiding the assessment of the clinical and cost effectiveness of diagnostic interventions should be the same as for other technologies. However, particular consideration of the methods of analysis may be required, particularly in relation to evidence synthesis. Evidence for the effectiveness of diagnostic technologies should include the costs and outcomes for people whose test results lead to an incorrect diagnosis, as well as for those who are diagnosed correctly.

As for other technologies, RCTs have the potential to capture the pathway of care involving diagnostic technologies, but their feasibility and availability may be limited. Other study designs should be assessed on the basis of their fitness for purpose, taking into consideration the aim of the study (for example, to evaluate outcomes, or to evaluate sensitivity and specificity) and the purpose of the diagnostic technology.

Answer 'yes' if the estimates of treatment effect appropriately reflect all relevant studies of the best available quality, as identified through a recent well-conducted systematic review of the literature. Answer 'partly' if the estimates of treatment effect are not derived from a systematic review but are similar in magnitude to the best available estimates (for example, if the economic evaluation is based on a single large study with treatment effects similar to pooled estimates from all relevant studies). Answer 'no' if the estimates of treatment effect are likely to differ substantively from the best available estimates.

2.6 Are all important and relevant costs included?

Costs related to the condition of interest and incurred in additional years of life gained as a result of treatment should be included in the base-case analysis. This should include the costs of handling non-adherence to treatment and treating side effects. Costs that are considered to be unrelated to the condition or intervention of interest should be excluded. If introduction of the intervention requires additional infrastructure to be put in place, consideration should be given to including such costs in the analysis.

Answer 'yes' if all important and relevant resource use and costs are included given the perspective and the research question under consideration. Answer 'partly' if some relevant resource items are omitted but these are unlikely to affect the cost-effectiveness results. Answer 'no' if important resource items are omitted and these are likely to affect the cost-effectiveness results.

2.7 Are the estimates of resource use from the best available source?

It is important to quantify the effect of the interventions on resource use in terms of physical units (for example, days in hospital or visits to a GP) and valuing those effects in monetary terms using appropriate prices and unit costs. Evidence on resource use should be identified systematically. When expert opinion is used as a source of information, any formal methods used to elicit these data should be clearly reported.

Answer 'yes' if the estimates of resource use appropriately reflect all relevant evidence sources of the best available quality, as identified through a recent well-conducted systematic review of the literature. Answer 'partly' if the estimates of resource use are not derived from a systematic review but are similar in magnitude to the best available estimates. Answer 'no' if the

estimates of resource use are likely to differ substantively from the best available estimates.

2.8 Are the unit costs of resources from the best available source?

Resources should be valued using the prices relevant to the NHS and PSS. Given the perspective of the NICE reference case, it is appropriate for the financial costs relevant to the NHS/PSS to be used as the basis of costing, although these may not always reflect the full social opportunity cost of a given resource. A first point of reference in identifying costs and prices should be any current official listing published by the Department of Health and/or the Welsh Assembly Government.

When the acquisition price paid for a resource differs from the public list price (for example, pharmaceuticals and medical devices sold at reduced prices to NHS institutions), the public list price should be used in the base-case analysis. Sensitivity analysis should assess the implications of variations from this price. Analyses based on price reductions for the NHS will only be considered when the reduced prices are transparent and can be consistently available across the NHS, and if the period for which the specified price is available is guaranteed.

National data based on healthcare resource groups (HRGs) such as the Payment by Results tariff can be used when they are appropriate and available. However, data based on HRGs may not be appropriate in all circumstances (for example, when the definition of the HRG is broad, or the mean cost probably does not reflect resource use in relation to the intervention(s) under consideration). In such cases, other sources of evidence, such as micro-costing studies, may be more appropriate. When cost data are taken from the literature, the methods used to identify the sources should be defined. When several alternative sources are available, a justification for the costs chosen should be provided and discrepancies between the sources explained. When appropriate, sensitivity analysis should have been undertaken to assess the implications for results of using alternative data sources.

Answer 'yes' if resources are valued using up-to-date prices relevant to the NHS and PSS. Answer 'partly' if the valuations of some resource items differ from current NHS/PSS unit costs but this is unlikely to change the cost effectiveness results. Answer 'no' if the valuations of some resource items differ substantively from current NHS/PSS unit costs and this is likely to change the cost-effectiveness results.

2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?

An appropriate incremental analysis is one that compares the expected costs and health outcomes of one intervention with the expected costs and health outcomes of the next-best non-dominated alternative.

Standard decision rules should be followed when combining costs and effects, and should reflect any situation where there is dominance or extended dominance. When there is a trade-off between costs and effects, the results should be presented as an incremental cost-effectiveness ratio (ICER): the ratio of the difference in mean costs to the difference in mean outcomes of a technology compared with the next best alternative. In addition to ICERs, expected net monetary or health benefits can be presented using values placed on a QALY gained of £20,000 and £30,000.

For cost-consequence analyses, appropriate incremental analysis can only be done by selecting one of the consequences as the primary measure of effectiveness.

Answer 'yes' if appropriate incremental results are presented, or if data are presented that allow the reader to calculate the incremental results. Answer 'no' if: (i) simple ratios of costs to effects are presented for each alternative compared with a standard intervention; or (ii) if options subject to simple or extended dominance are not excluded from the incremental analyses.

2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?

There are a number of potential selection biases and uncertainties in any evaluation (trial- or model-based) and these should be identified and quantified where possible. There are three types of bias or uncertainty to consider:

- Structural uncertainty – for example in relation to the categorisation of different states of health and the representation of different pathways of care. These structural assumptions should be clearly documented and the evidence and rationale to support them provided. The impact of structural uncertainty on estimates of cost effectiveness should be explored by separate analyses of a representative range of plausible scenarios.
- Source of values to inform parameter estimates – the implications of different estimates of key parameters (such as estimates of relative effectiveness) must be reflected in sensitivity analyses (for example, through the inclusion of alternative scenarios). Inputs must be fully justified, and uncertainty explored by sensitivity analysis using alternative input values.
- Parameter precision – uncertainty around the mean health and cost inputs in the model. Distributions should be assigned to characterise

the uncertainty associated with the (precision of) mean parameter values. Probabilistic sensitivity analysis is preferred, as this enables the uncertainty associated with parameters to be simultaneously reflected in the results of the model. In non-linear decision models – when there is not a straight-line relationship between inputs and outputs of a model (such as Markov models) – probabilistic methods provide the best estimates of mean costs and outcomes. Simple decision trees are usually linear.

The mean value, distribution around the mean, and the source and rationale for the supporting evidence should be clearly described for each parameter included in the model.

Evidence about the extent of correlation between individual parameters should be considered carefully and reflected in the probabilistic analysis. Assumptions made about the correlations should be clearly presented.

Answer 'yes' if an extensive sensitivity analysis was undertaken that explored all key uncertainties in the economic evaluation. Answer 'partly' if the sensitivity analysis failed to explore some important uncertainties in the economic evaluation. Answer 'no' if the sensitivity analysis was very limited and omitted consideration of a number of important uncertainties, or if the range of values or distributions around parameters considered in the sensitivity analysis were not reported.

2.11 Is there no potential conflict of interest?

The BMJ defines competing interests for its authors as follows: "A competing interest exists when professional judgment concerning a primary interest (such as patients' welfare or the validity of research) may be influenced by a secondary interest (such as financial gain or personal rivalry). It may arise for the authors of a BMJ article when they have a financial interest that may influence, probably without their knowing, their interpretation of their results or those of others."

Whenever a potential financial conflict of interest is possible, this should be declared.

Answer 'yes' if the authors declare that they have no financial conflicts of interest. Answer 'no' if clear financial conflicts of interest are declared or apparent (for example, from the stated affiliation of the authors). Answer 'unclear' if the article does not indicate whether or not there are financial conflicts of interest.

2.12 Overall assessment

The overall methodological study quality of the economic evaluation should be classified as one of the following:

- **Minor limitations** – the study meets all quality criteria, or the study fails to meet one or more quality criteria but this is unlikely to change the conclusions about cost effectiveness.
- **Potentially serious limitations** – the study fails to meet one or more quality criteria and this could change the conclusions about cost effectiveness.
- **Very serious limitations** – the study fails to meet one or more quality criteria and this is highly likely to change the conclusions about cost effectiveness. Such studies should usually be excluded from further consideration.

1 APPENDIX 14: EVIDENCE TABLES FOR ECONOMIC STUDIES

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Study ID **Country** **Study type**	**Intervention details**	**Study population** **Study design** **Data sources**	**Costs: description and values** **Outcomes: description and values**	**Results: Cost-effectiveness**	**Comments**
BYFORD2003 UK CEA/CUA	Manual-assisted cognitive behaviour therapy (MACT) – patients are given a manual and offered up to 7 treatment sessions of CBT with a trained therapist over 3 months versus Treatment as usual (TAU)	Population: Patients with history of recurrent deliberate self-harm and no requirement for inpatient psychiatric treatment. Multi-centre RCT: MACT (n=197) TAU (n=200) Source of clinical effectiveness data: Single RCT (Tyrer et al. 2003) Source of resource use: RCT – CSRI and patient questionnaire Source of unit costs: UK national sources	**Costs:** Hospital services, community health services, social services, voluntary sector services, community accommodation, criminal justice system, productivity losses, patient living expenses Results: Total Costs per patient MACT: £13,454 (SD £5,313) TAU: £14,288 (SD £7,669) **Outcomes:** Primary outcome was proportion of patients who experienced an episode of self-harm during 12-month follow-up. QALYs were also estimated from EQ-5D utility scores. Results: % of patients with a self-harm episode was 7% lower in the MACT group QALYs were 0.0118 lower in the MACT group	Cost of a 1% reduction in the % of patients with a repeat self-harm episode was -£120 using MACT. Thus, MACT was dominant strategy. Incremental cost per QALY gained was £66,000 using TAU. CEACs showed >90% probability that MACT was more cost-effective than TAU (using % self-harming). Using cost per QALY threshold < £66,000, MACT had higher probability of being cost-effective	Perspective: Societal Currency: UK£ Cost Year: 1999/2000 Time horizon: 12 months Discounting: Not applicable Funded by: UK MRC

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Study ID **Country** **Study type**	**Intervention details**	**Study population** **Study design** **Data sources**	**Costs: description and values** **Outcomes: description and values**	**Results: Cost-effectiveness**	**Comments**
BYFORD1999 UK CEA	Home-based social work intervention (in addition to routine care) – four intensive, family-centred home-based intervention sessions. Versus Routine care (routine clinical assessment and psychiatric care – out-patient clinic visits)	Self-poisoned young people (age 10-16) who have been referred to mental health care teams with diagnosis of self-poisoning Study design: RCT Home-based social work (n=85) Routine care (n=77) Data sources: Single study based on community sample in Manchester Source of unit costs: UK national sources	**Costs:** NHS (assessments, intervention sessions, outpatient, inpatient, intensive care, staff – GP, CPN, psychiatrist); education (welfare officers, educational psychologists); social services (social worker, residential care) **Outcomes:** Suicidal ideation questionnaire and hopelessness scale; family assessment device - all completed at baseline, two and six months)	Total Mean Costs: Intervention: £1,177 (excluding cost of intervention) Intervention: £1,455 (including cost of intervention) Control: £1,751 No statistically significant differences detected between intervention and control in primary outcome measures No synthesis of costs and outcomes performed by authors.	Perspective: Societal Currency: UK £ Cost Year: 1997/98 Time horizon: 6 months Discounting: NA Funded by: Dept of Health, UK

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