9. APPENDICES

APPENDIX 1: SCOPE FOR THE DEVELOPMENT OF THE CLINICAL GUIDELINE

Final version

28 September 2005

GUIDELINE TITLE

Drug misuse: opiate detoxification of drug misusers in the community, hospital and prison.[12]

Short title

Drug misuse – detoxification.

BACKGROUND

The National Institute for Health and Clinical Excellence ('NICE' or 'the Institute') has commissioned the National Collaborating Centre for Mental Health to develop a clinical guideline on opiate[13] detoxification of drug misusers[14] in the community, hospital and prison settings for use in the NHS in England and Wales. This follows referral of the topic by the Department of Health and Welsh Assembly Government (see Appendix [to the scope] below). The guideline will provide recommendations for good practice that are based on the best available evidence of clinical and cost effectiveness.

The Institute has simultaneously commissioned the National Collaborating Centre for Mental Health to develop a clinical guideline on psychosocial interventions for people who misuse drugs in the community and in prison settings for use in the NHS in England and Wales.

The Institute's clinical guidelines will support the implementation of National Service Frameworks (NSFs) in those aspects of care where a Framework has been published.

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[12]The guideline title changed during the development process to *Drug Misuse: Opioid Detoxification.*

[13]The term *opiates* has been replaced with the generic term *opioids* throughout the guideline, with the exception of the scope (where it originally appeared) and where the term relates specifically to the subset of opioids that are naturally occurring or semi-synthetic derivatives of the opium poppy, including heroin.

[14]The term *drug misusers* has been replaced with *people who misuse drugs* throughout the guideline, with the exception of the scope, where it originally appeared.

The statements in each NSF reflect the evidence that was used at the time the Framework was prepared. The clinical guidelines and technology appraisals published by the Institute after an NSF has been issued will have the effect of updating the Framework.

NICE clinical guidelines support the role of healthcare professionals in providing care in partnership with patients, taking account of their individual needs and preferences, and ensuring that patients (and their carers and families, where appropriate) can make informed decisions about their care and treatment.

CLINICAL NEED FOR THE GUIDELINE

The term opiate is used throughout this scope. Although this term normally implies substances containing natural opium, in this scope the term is used more broadly to include opioids (synthetic substances with similar properties).

It is estimated that there are between 250,000 and 500,000 problem drug users in the United Kingdom, of whom about 125,500 are in treatment in any year. There is a government target of ensuring 200,000 are in effective treatment in 2008. The majority of those requiring treatment are opiate dependent (and currently or previously using illicit heroin), although the use of other drugs such as stimulants (for example, cocaine) is known to be increasing.

Severe opiate dependence is a disorder of multi-factorial aetiology, with multiple and varied perpetuating factors. It has a central feature of psychological reinforcement of repeated drug-taking behaviour and it also has a marked withdrawal syndrome. Disturbances of the brain reward pathways may be important underlying pathological mechanisms. For this reason, it is usually considered that a range of interventions may be required in addition to pharmacological treatments.

There may be associated problems of family, social, criminal justice difficulties, health problems including blood borne viruses and other drug and alcohol problems. Families themselves may be affected by the drug misuse and are often a major resource in resolving problems and supporting the family member through treatment.

For people with severe drug dependency and others with long-standing dependency, the disorder has characteristics as a long-term chronic relapsing disorder with periods of remission and relapse, so while abstinence may be one of a range of long-term goals of treatment this is not always achieved. Even when abstinence is achieved, the benefits are not always maintained, and periods of relapse may still occur.

The evidence for detoxification programmes including the use of a range of pharmacological treatments (including methadone, buprenorphine and lofexidine) and the appropriate settings in which to best provide these interventions is not as strong as the evidence for maintenance and harm-reduction programmes.

The societal costs of drug misuse have been estimated at many billions of pounds, with opiate dependence and use of Class A drugs constituting the main cause of these costs.

Opiate substitution therapies (methadone and buprenorphine are most commonly used) allow the patient to replace street heroin with a longer-acting, less euphoriant

and safer drug while avoiding the withdrawal syndrome. Once stabilised, many patients remain on maintenance treatment, which brings improvements in illicit drug use, physical health, well-being, social stabilisation and reduced criminality and costs to society.

People who misuse drugs in prison sometimes receive assistance with withdrawal symptoms and some receive a treatment programme in prison. Access to regular high levels of illicit drugs in prisons is limited, so most people with drug dependency lose tolerance and are at risk of overdose if – as commonly happens – they begin using again on release.

Determining when to offer detoxification and where to provide it is often a difficult clinical decision. Clarity about the purpose of any treatment strategy is crucial because confusion between detoxification and maintenance programmes can lead to a lack of clear treatment aims and a poorer quality of care.

THE GUIDELINE

The guideline development process is described in detail in two publications which are available from the NICE website (see 'Further information'). *The Guideline Development Process – An Overview for Stakeholders, the Public and the NHS (Second Edition)* (NICE, 2006b) describes how organisations can become involved in the development of a guideline. *The Guidelines Manual* (NICE, 2006a) provides advice on the technical aspects of guideline development.

This document is the scope. It defines exactly what this 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 (see Appendix [to the scope] below). The areas that will be addressed by the guideline are described in the following sections.

POPULATION

Groups that will be covered

- adults and young people who are dependent on opiates and have been identified as suitable for a detoxification programme.

Groups that will not be covered

- adults and young people whose primary drug of misuse is a non-opiate
- adults and young people who misuse alcohol, where the primary diagnosis and focus of intervention is alcohol misuse
- adults and young people who misuse other prescription drugs – for example, benzodiazepines
- adults and young people who misuse solvents (for example, aerosols and glue) or other street drugs (for example, LSD [lysergic acid diethylamide])
- adults and young people prescribed opiates and related drugs for therapeutic purposes unrelated to substance misuse.

HEALTHCARE SETTING

The guideline will be of relevance to the NHS and related organisations, including:

- prison services
- inpatient and specialist residential and community-based treatment settings.

This is an NHS guideline. Although it will comment on the interface with other services such as those provided by social services, educational services and the voluntary sector, it will not provide specific recommendations directed solely to non-NHS services, except insofar as they are provided under contract to the NHS.

CLINICAL MANAGEMENT – AREAS THAT WILL BE COVERED

The guideline will cover the following areas of clinical practice and will do so in a way that is sensitive to the cultural, ethnic and religious backgrounds of people who misuse drugs/are drug dependent and their families and carers.

- The guideline will cover detoxification programmes for people who misuse opiates in community, residential, prison and inpatient settings including the type and duration of the programme.
- The guideline will identify the most appropriate programmes for specific populations of people who misuse opiates.
- The guideline will make recommendations on the use of methadone, buprenorphine, lofexidine and other related products in opiate detoxification programmes, and the dose and duration of use.
- The guideline will include the treatment and management of non-opiate drug and alcohol misuse in the context of an opiate detoxification programme.
- When referring to pharmacological treatments, the guideline will, wherever possible, recommend use within their licensed indications. However, where the evidence clearly supports it, recommendations for use outside the licensed indications may be made in exceptional circumstances.
- The guideline will include the appropriate use of psychosocial interventions to support detoxification programmes.
- The safety, side effects and other disbenefits of the interventions reviewed will be considered.
- The guideline will address the integration of the interventions reviewed with a broad approach to the care and treatment of people who misuse drugs/are drug dependent and their families and carers.
- The guideline will consider the separate needs of families and carers as well as addressing the potential positive contribution of family and carers in the treatment and support of people who misuse drugs/are drug dependent.
- The guideline will address the various needs for information of patients, families and carers, at different stages of their treatment and in different settings, including the role of self-help interventions and of support and self-help groups, and the importance of agreeing objectives with patients before they agree to treatment.

Appendix 1

CLINICAL MANAGEMENT – AREAS THAT WILL NOT BE COVERED

- The guideline will not consider diagnosis or primary prevention.
- The guideline will not consider pharmacological maintenance programmes.

STATUS

Scope

This is the final draft of the scope following consultation, which will be reviewed by the Guidelines Review Panel and the Institute's Guidance Executive.

The guideline will incorporate the following NICE guidance, which is published or in development:

Methadone and Buprenorphine for the Treatment of Opiate Drug Misuse. NICE Technology Appraisal. (Publication expected March 2007.)[15]

Naltrexone to Prevent Relapse in Drug Misuse. NICE Technology Appraisal. (Publication expected March 2007.)[16]

Drug Misuse: Psychosocial Management of Drug Misuse. NICE Clinical Guideline. (Publication expected July 2007.)[17]

Schizophrenia: Core Interventions in the Treatment and Management of Schizophrenia in Primary and Secondary Care. NICE Clinical Guideline No. 1. (2002).

Anxiety: Management of Anxiety (Panic Disorder, with or without Agoraphobia, and Generalised Anxiety Disorder) in Adults in Primary, Secondary and Community Care. NICE Clinical Guideline No. 22. (2004).

Depression: Management of Depression in Primary and Secondary Care. NICE Clinical Guideline No. 23. (2004).

Self-Harm: the Short-Term Physical and Psychological Management and Secondary Prevention of Self-Harm in Primary and Secondary Care. NICE Clinical Guideline No. 16. (2004).

GUIDELINE

The development of the guideline recommendations will begin in October 2005.

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[15]This technology appraisal has now been published with a different title: NICE (2006c) *Methadone and Buprenorphine for the Management of Opioid Dependence. Evaluation Report.* London: NICE.

[16]This technology appraisal has now been published with a different title: NICE (2006a) *Naltrexone for the Management of Opioid Dependence. Evaluation Report.* London: NICE.

[17]This guideline has now been published with a different title: NICE (2007) *Drug Misuse: Psychosocial Interventions. NICE Clinical Guideline no. 51.* London: NICE.

FURTHER INFORMATION

Information on the guideline development process is provided in:

- *The Guideline Development Process – An Overview for Stakeholders, the Public and the NHS (Second Edition)*
- *The Guidelines Manual.*

These booklets are available as PDF files from the NICE website (www.nice.org.uk). Information on the progress of the guideline will also be available from the website.

Appendix – Referral from the Department of Health and Welsh Assembly Government

The Department of Health and Welsh Assembly Government asked the Institute to prepare a guideline for the NHS in England and Wales on opiate detoxification of drug misusers in the community, hospital and prison settings.

The guidance will:

- by using the evidence base examine the effectiveness and cost effectiveness of detoxification regimes for the management of opiate misusers
- identify those groups of drug misusers who are most likely to benefit from detoxification regimes, and
- identify the key components of the effectiveness of detoxification within a wider package of pharmacological interventions, and the overall care provided for the drug misuser.

APPENDIX 2: DECLARATIONS OF INTEREST BY GUIDELINE DEVELOPMENT GROUP MEMBERS

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

To minimise and manage any potential conflicts of interest, and to avoid any public concern that commercial or other financial interests have affected the work of the GDG and influenced guidance, members of the GDG must declare as a matter of public record any interests held by themselves or their families that fall under specified categories (see below). These categories include any relationships they have with the healthcare industries, professional organisations and organisations for people who misuse drugs and their families and 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 interests related to drug misuse**: payment in cash or kind and/or funding from the drug misuse-related healthcare industry, including consultancies, grants, fee-paid work and shareholdings or other beneficial interests.
- **Personal interests not specifically related to drug misuse:** any other payment and/or funding from the healthcare industry, including consultancies, grants and shareholdings or other beneficial interests.
- **Non-personal interests**: funding from the healthcare industry 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.
- **Personal non-monetary interests:** these include, but are not limited to, clear opinions or public statements you have made about drug misuse, holding office in a professional organisation or advocacy group with a direct interest in drug misuse, other reputational risks relevant to drug misuse.

- **Personal family interests:** payments in cash or kind that were received by a member of your family.
- **Other interests relating to drug misuse:** funding from governmental or non-governmental organisations, charities, and so on, and/or ownership in a company that provides therapy or treatments likely to be covered in the guideline.

Declarations of interest	
Dr Clare Gerada – Chair, Guideline Development Group	
Employment	General Practitioner, Lambeth Primary Care, Trust, London Practice; Primary Care Lead for Drug Misuse and Chair at the Royal College of General Practitioners
Personal interests related to drug misuse	Member of Suboxone Expert Group at Schering-Plough (attended two meetings, received payment of £1000); member of Specialist Opioid Advisory Group at Napp Pharmaceuticals (reimbursed expenses for attending only)
Personal interests not specifically related to drug misuse	Member of Hepatitis C Expert Group at Roche (attended two meetings, received payment of £800)
Non-personal interests	Royal College of General Practitioners received funding from Schering-Plough for educational material
Personal non-monetary interests	Spoken publicly about heroin treatment: against heroin treatment until methadone treatment is adequately resourced
Personal family interests	None
Other interests related to drug misuse	Consultancy fees from Royal College of General Practitioners for training GPs in substance misuse; Advisor to Royal College of General Practitioners on all matters relating to substance misuse; Given evidence to General Medical Council on GPs' level of performance. Attended number of meetings run by Schering-Plough looking at feasibility of Suboxone as a treatment in the UK Attended Roche-funded hepatitis C meeting

Continued

Appendix 2

Declarations of interest (*Continued*)	
Mrs Pauline Bissett	
Employment	Retired (previously Chief Executive, Broadway Lodge until December 2006)
Personal interests related to drug misuse	None
Personal interests not specifically related to drug misuse	None
Non-personal interests	None
Personal non-monetary interests	None
Personal family interests	None
Other interests related to drug misuse	None
Mr Neil Connelly	
Employment	Voluntary Support Worker, Littledale Hall Therapeutic Community, Lancaster
Personal interests related to drug misuse	None
Personal interests not specifically related to drug misuse	None
Non-personal interests	None
Personal non-monetary interests	None
Personal family interests	None
Other interests related to drug misuse	None
Dr Paul Davis	
Employment	Consultant Lead Clinical Psychologist and Head of Psychology for Substance Misuse Services, Camden and Islington Mental Health and Social Care Trust
Personal interests related to drug misuse	None

Declarations of interest (*Continued*)	
Personal interests not specifically related to drug misuse	None
Non-personal interests	None
Personal non-monetary interests	Employed 1 day per week by National Treatment Agency for Substance Misuse as Clinical Psychology Advisor (September 2006–2008)
Personal family interests	None
Other interests related to drug misuse	Current grant funded projects: A study of the feasibility of routine screening and 'Stepped Care' psychological interventions with hazardous and problem drinkers in three inner London General Hospitals (London Health Action Zone 2003–2005, £47,000)
Ms Vivienne Evans	
Employment	Chief Executive, Adfam; Non-executive director of Charnwood and North West Leicestershire Primary Care Trust
Personal interests related to drug misuse	None
Personal interests not specifically related to drug misuse	None
Non-personal interests	£6000 sponsorship from Schering-Plough to cover expenses of hosting Adfam's 21st birthday celebration, October 2005
Personal non-monetary interests	None
Personal family interests	None
Other interests related to drug misuse	None
Dr Emily Finch	
Employment	Addiction Psychiatrist, South London and Maudsley NHS Foundation Trust; Clinical Team Lead, National Treatment Agency for Substance Misuse

Continued

Declarations of interest (*Continued*)	
Personal interests related to drug misuse	None
Personal interests not specifically related to drug misuse	None
Non-personal interests	None
Personal non-monetary interests	Trustee of Phoenix House
Personal family interests	None
Other interests related to drug misuse	Trustee of Phoenix House; Seconded two days per week to the NTA (October 2004 – January 2007)
Professor Robert Forrest	
Employment	Consultant in Clinical Chemistry and Toxicology, Sheffield Teaching Hospitals NHS Foundation Trust
Personal interests related to drug misuse	None
Personal interests not specifically related to drug misuse	None
Non-personal interests	None
Personal non-monetary interests	President of Forensic Science Society; Assistant Deputy Coroner, South Yorkshire (West); Programme Chair, Jurisprudence Section, American Academy of Forensic Sciences; expert witness in many cases where the issues are relevant to drug misuse; member of the editorial board for Science and Justice; member of Secretary of State's Medical Advisory Committee on Alcohol, Driving and Drugs
Personal family interests	None
Other interests related to drug misuse	Consultancy work (remitted to employer) for Forensic Alliance Ltd, now part of the Laboratory of the Government Chemist (LGC)

Declarations of interest (*Continued*)	
Dr Eilish Gilvarry	
Employment	Clinical Director, Newcastle Drug and Alcohol Unit, Newcastle upon Tyne
Personal interests related to drug misuse	None
Personal interests not specifically related to drug misuse	None
Non-personal interests	None
Personal non-monetary interests	None
Personal family interests	None
Other interests related to drug misuse	None
Mr David Harding-Price	
Employment	Team Coordinator, Community Mental Health Team, Skegness, Lincolnshire
Personal interests related to drug misuse	None
Personal interests not specifically related to drug misuse	None
Non-personal interests	Eli Lilly 2005 funded mental health educational event at RCN congress; Janssen-Cilag 2005 sponsored European mental health educational conference
Personal non-monetary interests	None
Personal family interests	None
Other interests related to drug misuse	None
Mr Paul Hawkins	
Employment	None
Personal interests related to drug misuse	None

Continued

Declarations of interest (*Continued*)	
Personal interests not specifically related to drug misuse	None
Non-personal interests	Member of executive board for Cumbria Alcohol and Drugs Advisory Service
Personal non-monetary interests	None
Personal family interests	None
Other interests related to drug misuse	None
Dr Anne Lingford-Hughes	
Employment	Reader in Biological Psychiatry and Addiction, Academic Unit of Psychiatry, University of Bristol; Addiction Psychiatrist, Avon and Wiltshire Mental Health Trust
Personal interests related to drug misuse	None
Personal interests not specifically related to drug misuse	Member of core faculty and steering group for Bristol-Myers Squibb, 2004, £2000; Honorarium from Janssen-Cilag for presentation, 2005; Honorarium from Bristol-Myers Squibb for plenary lecture, £499.23, 2007; Consultancy fee from Sanofi-Aventis, £1000, 2006; Health hearing systems for Johnson and Johnson Pharmaceutical services, 2003, £1451.72; Unrestricted grants for research; Merck, £50,000, 2004; Wyeth, £70,000, 2000
Non-personal interests	Psychopharmacology Unit, University of Bristol: Fellowship – Lundbeck; Within last 5 years department received various unrestricted grants from GSK, Astra-Zeneca, MSD, Wyeth, Novartis, Bristol-Myers Squibb
Personal non-monetary interests	Hon General Secretary of British Association for Psychopharmacology (BAP) – responsible for educational activities including opioid detoxification and coordinated BAP Consensus Guidelines, 2004, covering management of opioid detoxification.

Declarations of interest (*Continued*)	
Personal family interests	None
Other interests related to drug misuse	None
Ms Jan Palmer	
Employment	Nurse Consultant, Clinical Substance Misuse Lead, Offender Health
Personal interests related to drug misuse	None
Personal interests not specifically related to drug misuse	None
Non-personal interests	None
Personal non-monetary interests	None
Personal family interests	None
Other interests related to drug misuse	None
Mrs Kay Roberts	
Employment	Pharmacist; Chairman, PharMAG
Personal interests related to drug misuse	Wells Healthcare (for Schering-Plough) consultancy fees for training events; advisory board for Scotland: Suboxone, £800 in 2002, £360 in 2003; member of advisory board for Frontier Medical
Personal interests not specifically related to drug misuse	None
Non-personal interests	PharMAG receives in sponsorship and printing costs: Britannia Pharmaceuticals £250 per annum Reckitt Benckiser Ltd £1500, 2006; Rosemont Pharmaceuticals Ltd £1350, 2003–2005 Frontier Medical Ltd £250 per annum Cardinal Healthcare (Martindale Pharmaceuticals) £2000, 2006

Continued

Declarations of interest (*Continued*)	
Personal non-monetary interests	Royal College of General Practitioners, Lead Pharmacist (England) on Management of Substance Misuse in Primary Care; Royal College of General Practitioners (Scotland) tutor for Certificate in Management of Substance Misuse in Primary Care; Advisor to the Royal Pharmaceuticals Society of Great Britain on substance misuse; consultancy work for National Treatment Agency for Substance Misuse; member of the advisory council on misuse of drugs; member of UK Harm Reduction Alliance; member of Glasgow Children's Hearings Panel; member of International Harm Reduction Association; member of Scottish Medico-legal Society
Personal family interests	None
Other interests related to drug misuse	None

NCCMH STAFF

Mr Stephen Pilling – Facilitator, Guideline Development Group	
Employment	Joint Director, NCCMH; Director, Centre for Outcomes Research and Effectiveness, University College London; Consultant Clinical Psychologist and Deputy Head of Psychology Services, Camden and Islington Mental Health and Social Care Trust
Personal interests related to drug misuse	None
Personal interests not specifically related to drug misuse	Lecture for UK Psychiatric Pharmacy Group, October 2006, £300 including expenses; Lecture at Andrew Simms Centre, Leeds, December 2006, £300 including expenses
Non-personal interests	Grants for production of clinical guidelines and evidence-related practice: British Psychological Society Clinical Effectiveness Programme with Professor P. Fonagy and

	Professor S. Michie supporting production of NICE guidelines and related policy implementation work (£5.4 million, 2001–2010) Health service research grants: NHS Service Development and Organisation Research and Development Programme developing evidence-based and acceptable stepped-care systems in mental healthcare, an operational research project with Professor D. Richards, Professor S. Gallivan, Dr S. Gilbody, Professor K. Lovell, Dr J. Cape, Dr P. Bower and Ms J. Leibowitz (£299,642, 2006–2009); NHS Service Development and Organisation Research and Development Programme – The 100 Ward Study: a National Survey of Psychiatric Inpatient Unit Morale with Dr S. Johnson, Professor P. Bebbington, Professor M. King, Professor S. Woods, Professor N. Wellman, Dr D. Osborn and Dr R. Arraya (£296,999, 2006–2009)
Personal non-monetary interests	None
Personal family interests	None
Other interests related to drug misuse	None
Ms Sarah Hopkins	
Employment	Project Manager, NCCMH
Personal interests related to drug misuse	None
Personal interests not specifically related to drug misuse	None
Non-personal interests	None
Personal non-monetary interests	None
Personal family interests	None
Other interests related to drug misuse	None
Ms Rebecca King	
Employment	Project Manager, NCCMH (2005–2006)

Personal interests related to drug misuse	None
Personal interests not specifically related to drug misuse	None
Non-personal interests	None
Personal non-monetary interests	None
Personal family interests	None
Other interests related to drug misuse	None
Mr Ryan Li	
Employment	Research Assistant, NCCMH
Personal interests related to drug misuse	None
Personal interests not specifically related to drug misuse	None
Non-personal interests	None
Personal non-monetary interests	None
Personal family interests	None
Other interests related to drug misuse	None
Dr Nicholas Meader	
Employment	Systematic Reviewer, NCCMH
Personal interests related to drug misuse	None
Personal interests not specifically related to drug misuse	None
Non-personal interests	None
Personal non-monetary interests	None
Personal family interests	None
Other interests related to drug misuse	None

Ms Poonam Sood	
Employment	Research Assistant, NCCMH
Personal interests related to drug misuse	None
Personal interests not specifically related to drug misuse	None
Non-personal interests	None
Personal non-monetary interests	None
Personal family interests	None
Other interests related to drug misuse	None
Ms Sarah Stockton	
Employment	Information Scientist, NCCMH
Personal interests related to drug misuse	None
Personal interests not specifically related to drug misuse	None
Non-personal interests	None
Personal non-monetary interests	None
Personal family interests	None
Other interests related to drug misuse	None
Dr Clare Taylor	
Employment	Editor, NCCMH
Personal interests related to drug misuse	None
Personal interests not specifically related to drug misuse	None
Non-personal interests	None
Personal non-monetary interests	None

Personal family interests	None
Other interests related to drug misuse	None
Mr Loukas Xaplanteris	
Employment	Health Economist, NCCMH
Personal interests related to drug misuse	None
Personal interests not specifically related to drug misuse	None
Non-personal interests	None
Personal non-monetary interests	None
Personal family interests	None
Other interests related to drug misuse	None

APPENDIX 3: SPECIAL ADVISORS TO THE GUIDELINE DEVELOPMENT GROUP

The Guideline Development Group and the National Collaborating Centre for Mental Health review team would like to thank the following people who acted as advisors on specialist topics:

Ed Day	University of Birmingham
Michael Gossop	Institute of Psychiatry
Kim Wolff	Institute of Psychiatry

APPENDIX 4: STAKEHOLDERS WHO RESPONDED TO EARLY REQUESTS FOR EVIDENCE

Britannia Pharmaceuticals
Derbyshire Mental Health Services NHS Trust
Oxford and Buckinghamshire Mental Health Partnership NHS Trust
Pfizer
Rethink
Rosemont Pharmaceuticals
Royal College of Nursing
Royal College of Psychiatrists
Sheffield Teaching Hospitals NHS Foundation Trust

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

Stakeholders
Altrix Healthcare plc
Birmingham Drug Action Team
Bolton Salford & Trafford Mental Health
British Association for Counselling and Psychotherapy (BACP)
British Psychological Society, The
CASPE Research
Department of Health
DrugScope
National Treatment Agency for Substance Misuse
North Staffordshire Combined Healthcare NHS Trust
Nottinghamshire Acute Trust
PharMAG
Release
Royal College of Midwives
Royal College of Nursing
Royal College of Paediatrics and Child Health
Royal College of Pathologists
Schering-Plough Ltd
Specialist Clinical Addiction Network
Substance Misuse Management in General Practice
Western Counselling

Experts
None

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

Robert Ali
Seyed Assadi
Jenny Bearn
James Bell
David Best
Eric Collins
Jon Currie
Shane Darke
Cor De Jong
Detox 5
Michael Farrell
Bernard Favrat
Gilberto Gerra
Mark Gold
Michael Gossop
Paul Griffiths
Nick Heather
Paul Krabbe
Fergus Law
Walter Ling
Nicholas Lintzeris
Catherine McGregor
Lisa Marsch
John Marsden
Kenzie Preston
Duncan Raistrick
Alison Ritter
Roy Robertson
John Saunders
Udo Schneider
Juergen Seifert
Dwayne Simpson
Nora Volkow
Jason White

APPENDIX 7:
CLINICAL QUESTIONS

TOPIC GROUP 1: PHARMACOLOGICAL AND PHYSICAL INTERVENTIONS

1) For people who are opioid dependent, what detoxification treatments are associated with abstinence, completion of treatment and improvements on secondary outcomes (entry rate for naltrexone maintenance, use of other drugs, severity of withdrawal)?
   - 1.1) For people who are opioid dependent, what durations of detoxification treatment are associated with abstinence, completion of treatment and improvements on secondary outcomes (same as above)?

TOPIC GROUP 2: PSYCHOSOCIAL ADJUNCTS/PREDICTORS OF BENEFIT

2) For people who are opioid dependent, are there particular groups that are more likely to benefit from detoxification?
3) For people who are opioid dependent, are psychosocial interventions in combination with detoxification compared with detoxification with standard care associated with increased levels of abstinence, completion of treatment and improvements on secondary outcomes?

TOPIC GROUP 3: TREATMENT SETTING

4) For people who are opioid dependent, is inpatient detoxification in comparison with community-based detoxification associated with increased levels of abstinence, completion of treatment and improvements of secondary outcomes?
   - 4.1) For people who are opioid dependent, are there particular groups that respond better/worse to particular treatment settings?
5) For people who are opioid dependent and who are in prison, what detoxification treatment settings are associated with safety, abstinence, completion of treatment and improvements on secondary outcomes?
   - 5.1) For people who are opioid dependent and who are in contact with the community criminal justice system, what detoxification treatment settings are associated with abstinence, completion of treatment and improvements on secondary outcomes?

TOPIC GROUP 4: TESTING

6) For people in whom opioid dependence is suspected, are oral fluid and urine testing reliable methods, for example in terms of sensitivity and specificity, for identifying, confirming, quantifying and monitoring drug use?

7) In the context of opioid detoxification, what is good clinical practice in the assessment of dependence and monitoring of withdrawal?

   7.1) In the context of opioid detoxification, are there reliable and valid rating scales for the assessment of dependence and monitoring of withdrawal?

APPENDIX 8: SEARCH STRATEGIES FOR THE IDENTIFICATION OF CLINICAL STUDIES

1. GENERAL SEARCH FILTERS

Drug misuse

a. CINAHL, HMIC, EMBASE, MEDLINE, PsycINFO – OVID interface

1 exp narcotic dependence/ or exp opioid-related disorders/
2 (addiction or analgesic agent abuse or drug abuse or drug abuse pattern or drug dependenc$ or drug misuse or intravenous drug abuse or psychoses, substance-induced or substance abuse, intravenous or substance abuse, perinatal or substance abuse or substance dependence or substance withdrawal syndrome or substance-related disorders).sh.
3 "substance use disorders"/
4 ((drug$1 or substance$) adj3 (abstain$ or abstinen$ or abus$ or addict$ or dependen$ or disorder$ or intoxicat$ or misus$ or over dos$ or overdos$ or use$2 or using or withdraw$)).tw.
5 or/1-4
6 diamorphine/ or exp heroin/ or morphine/
7 exp narcotic agent/ or exp narcotics/ or exp narcotic drugs/
8 (acetomorphine or diacephine or diacetylmorphine or diamorphine or diaphorin or heroin$ or morphacetin or morphine).mp. or 1502-95-0, 561-27-3.rn.
9 (anpec or duromorph or epimorph or morfin$ or morphia or morphin$ or morphinium or morphium or opso$1 or skenan).mp. or 57-27-2.rn.
10 opiate$.mp. or 8008-60-4.rn.
11 (opioid$ or opium or narcotic$).tw.
12 (abstain$ or abstinen$ or abus$ or addict$ or (excessive adj use$) or dependen$ or (inject$ adj2 drug$) or intoxicat$ or misus$ or over dos$ or overdos$ or (use$ adj (disorder$ or illicit)) or withdraw$).mp.
13 (or/6-11) and 12
14 or/5,13

b. Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Cochrane Central Register of Controlled Trials (CENTRAL) – Wiley Interscience interface

#1	MeSH descriptor Opioid-Related Disorders explode all trees
#2	MeSH descriptor Substance-Related Disorders, this term only
#3	MeSH descriptor Substance Abuse, Intravenous, this term only
#4	MeSH descriptor Substance Withdrawal Syndrome, this term only
#5	MeSH descriptor Psychoses, Substance-Induced, this term only
#6	(drug* or substance*) near (abstain* or abstinen* or abus* or addict* or dependen* or disorder* or intoxicat* or misuse* or over dos* or overdos* or use or user* or using or withdraw*): ti or (drug* or substance*) near (abstain* or abstinen* or abus* or addict* or dependen* or disorder* or intoxicat* or misuse* or over dos* or overdos* or use or user* or using or withdraw*): ab or (drug* or substance*) near (abstain* or abstinen* or abus* or addict* or dependen* or disorder* or intoxicat* or misuse* or over dos* or overdos* or use or user* or using or withdraw*): kw
#7	(#1 OR #2 OR #3 OR #4 OR #5 OR #6)
#8	MeSH descriptor Heroin, this term only
#9	MeSH descriptor Morphine explode all trees
#10	MeSH descriptor Narcotics explode all trees
#11	(acetomorphine or diacephine or diacetylmorphine or diamorphine or diaphorin or heroin* or morphacetin or morphin*):ti or (acetomorphine or diacephine or diacetylmorphine or diamorphine or diaphorin or heroin* or morphacetin or morphin*):ab or (acetomorphine or diacephine or diacetylmorphine or diamorphine or diaphorin or heroin* or morphacetin or morphin*):kw
#12	(anpec or duromorph or epimorph or morfin* or morphia or morphin* or morphinium or morphium or opso* or skenan):ti or (anpec or duromorph or epimorph or morfin* or morphia or morphin* or morphinium or morphium or opso* or skenan):ab or (anpec or duromorph or epimorph or morfin* or morphia or morphin* or morphinium or morphium or opso* or skenan):kw
#13	(opiate*):ti or (opiate*):ab or (opiate*):kw
#14	(opioid* or opium or narcotic*):ti or (opioid* or opium or narcotic*):ab or (opioid* or opium or narcotic*):kw
#15	(abstain* or abstinen* or abus* or addict* or (drug near use*) or (excessive* near use*) or dependen* or (inject* near drug*) or intoxicat* or misus* or over dos* or overdos* or (use* near (disorder* or illicit)) or withdraw*):ti or (abstain* or abstinen* or abus* or addict* or (drug near use*) or (excessive* near use*) or dependen* or (inject* near drug*) or intoxicat* or misus* or over dos* or overdos* or (use* near (disorder* or illicit)) or withdraw*):ab or (abstain* or abstinen* or abus* or addict* or (drug near use*) or (excessive* near use*) or dependen* or (inject* near drug*) or intoxicat* or misus* or over dos* or overdos* or (use* near (disorder* or illicit)) or withdraw*):kw
#16	((#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14) AND #15)
#17	(#7 OR #16)

2. SYSTEMATIC REVIEW SEARCH FILTERS

a. MEDLINE, EMBASE, PsycINFO, CINAHL – OVID interface

1 exp meta analysis/ or exp systematic review/ or exp literature review/ or exp literature searching/ or exp cochrane library/ or exp review literature/
2 ((systematic or quantitative or methodologic$) adj5 (overview$ or review$)).mp.
3 (metaanaly$ or meta analy$).mp.
4 (research adj (review$ or integration)).mp.
5 reference list$.ab.
6 bibliograph$.ab.
7 published studies.ab.
8 relevant journals.ab.
9 selection criteria.ab.
10 (data adj (extraction or synthesis)).ab.
11 ((handsearch$3 or (hand or manual)) adj search$).tw.
12 ((mantel adj haenszel) or peto or dersimonian or der simonian).tw.
13 (fixed effect$ or random effect$).tw.
14 review$.pt,mp. and (bids or cochrane or index medicus or isi citation or medlars or psyclit or psychlit or scisearch or science citation or web adj1 science).mp.
15 (systematic$ or meta$).pt.
16 or/1-15

3. RCT SEARCH FILTERS

a. MEDLINE, EMBASE, PsycINFO, CINAHL – OVID interface

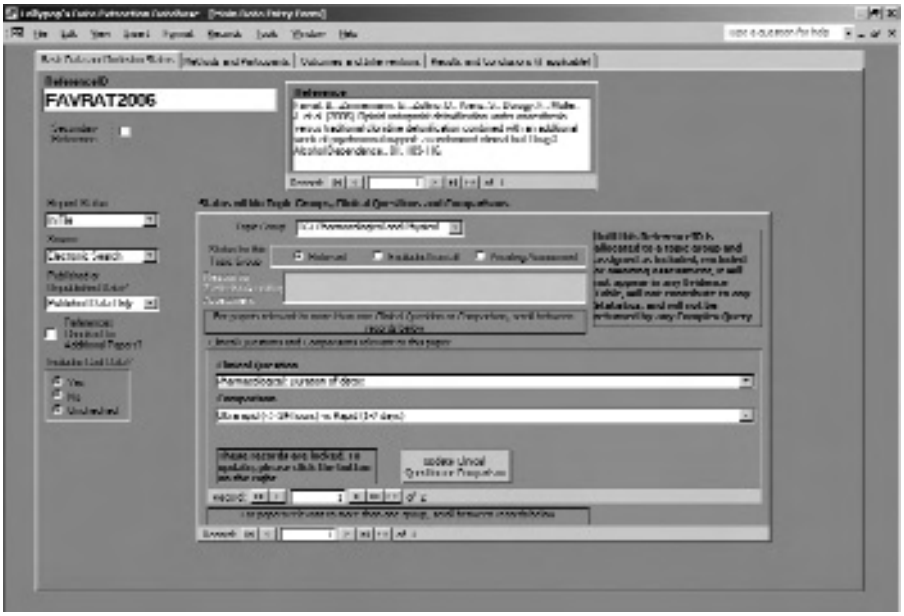
1 exp clinical trials/ or exp clinical trial/ or exp controlled clinical trials/
2 exp crossover procedure/ or exp cross over studies/ or exp crossover design/
3 exp double blind procedure/ or exp double blind method/ or exp double blind studies/ or exp single blind procedure/ or exp single blind method/ or exp single blind studies/
4 exp random allocation/ or exp randomization/ or exp random assignment/ or exp random sample/ or exp random sampling/
5 exp randomized controlled trials/ or exp randomized controlled trial/
6 (clinical adj2 trial$).tw.
7 (crossover or cross over).tw.
8 (((single$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$ or dummy)) or (singleblind$ or doubleblind$ or trebleblind$)).tw.
9 (placebo$ or random$).mp.
10 (clinical trial$ or clinical control trial or random$).pt.
11 animals/ not (animals/ and human$.mp.)

12	animal$/ not (animal$/ and human$/)
13	(animal not (animal and human)).po.
14	(or/1-10) not (or/11-13)

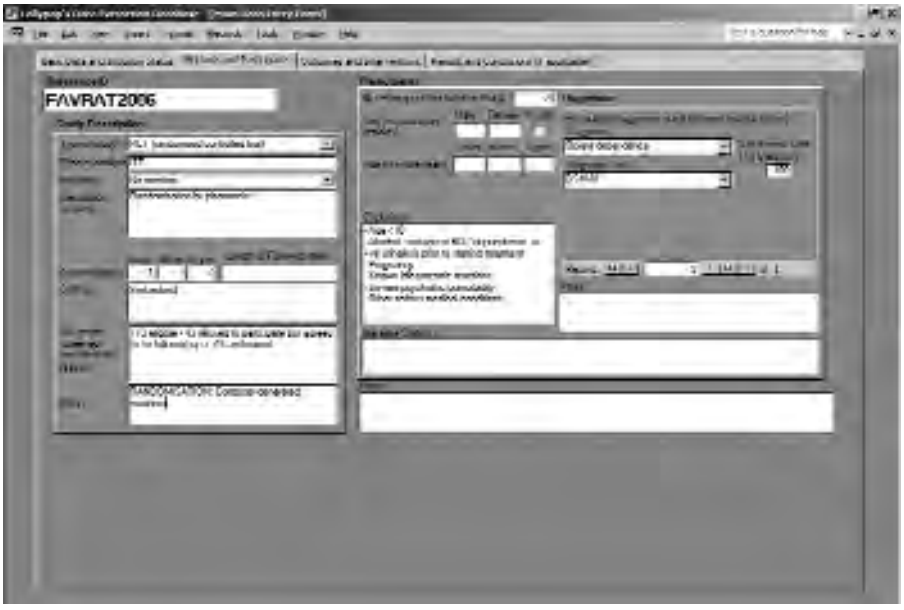
Details of additional searches undertaken to support the development of this guideline are available on request.

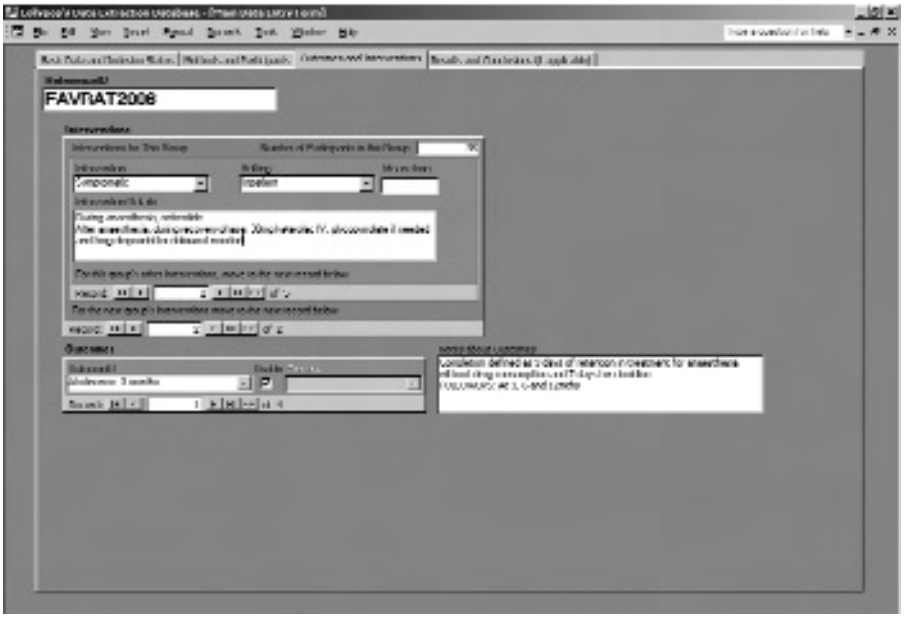
APPENDIX 9:
CLINICAL STUDY DATA EXTRACTION FORM

Information about each study was entered into an Access database using specially designed forms (see below for an example).



Appendix 9





APPENDIX 10:
QUALITY CHECKLISTS FOR CLINICAL STUDIES AND REVIEWS

The methodological quality of each study was evaluated using dimensions adapted from SIGN (SIGN, 2002). SIGN originally adapted its quality criteria from checklists developed in Australia (Liddel *et al.*, 1996). Both groups reportedly undertook extensive development and validation procedures when creating their quality criteria.

Quality Checklist for a Systematic Review or Meta-Analysis			
Study ID:			
Guideline topic:		Key question no:	
Checklist completed by:			
SECTION 1: INTERNAL VALIDITY			
In a well-conducted systematic review:		In this study this criterion is: *(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
1.2	A description of the methodology used is included.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.3	The literature search is sufficiently rigorous to identify all the relevant studies.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.4	Study quality is assessed and taken into account.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.5	There are enough similarities between the studies selected to make combining them reasonable.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
SECTION 2: OVERALL ASSESSMENT OF THE STUDY			
2.1	How well was the study done to minimise bias? *Code ++, + or –*		

NOTES ON THE USE OF THE METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS AND META-ANALYSES

Section 1 identifies the study and asks a series of questions aimed at establishing the internal validity of the study under review – that is, making sure that it has been

carried out carefully and that the outcomes are likely to be attributable to the intervention being investigated. Each question covers an aspect of methodology that research has shown makes a significant difference to the conclusions of a study.

For each question in this section, one of the following should be used to indicate how well it has been addressed in the review:

- well covered
- adequately addressed
- poorly addressed
- not addressed (that is, not mentioned or indicates that this aspect of study design was ignored)
- not reported (that is, mentioned but 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 in the report of the review, it will be difficult to assess how well it has met its objectives or how relevant it is to the question to be answered on the basis of the conclusions.

1.2 A DESCRIPTION OF THE METHODOLOGY USED IS INCLUDED

One of the key distinctions between a systematic review and a general review is the systematic methodology used. A systematic review should include a detailed description of the methods used to identify and evaluate individual studies. If this description is not present, it is not possible to make a thorough evaluation of the quality of the review, and it should be rejected as a source of level-1 evidence (though it may be useable as level-4 evidence, if no better evidence can be found).

1.3 THE LITERATURE SEARCH IS SUFFICIENTLY RIGOROUS TO IDENTIFY ALL THE RELEVANT STUDIES

A systematic review based on a limited literature search – for example, one limited to MEDLINE only – is likely to be heavily biased. A well-conducted review should at a minimum look at EMBASE and MEDLINE and, from the late 1990s onward, the Cochrane Library. Any indication that hand searching of key journals, or follow-up of reference lists of included studies, were carried out in addition to electronic database searches can normally be taken as evidence of a well-conducted review.

1.4 STUDY QUALITY IS ASSESSED AND TAKEN INTO ACCOUNT

A well-conducted systematic review should have used clear criteria to assess whether individual studies had been well conducted before deciding whether to include or exclude them. If there is no indication of such an assessment, the review should be rejected as a source of level-1 evidence. If details of the assessment are poor, or the methods are considered to be inadequate, the quality of the review should be downgraded. In either case, it may be worthwhile obtaining and evaluating the individual studies as part of the review being conducted for this guideline.

1.5 THERE ARE ENOUGH SIMILARITIES BETWEEN THE STUDIES SELECTED TO MAKE COMBINING THEM REASONABLE

Studies covered by a systematic review should be selected using clear inclusion criteria (see question 1.4 above). These criteria should include, either implicitly or explicitly, the question of whether the selected studies can legitimately be compared. It should be clearly ascertained, for example, that the populations covered by the studies are comparable, that the methods used in the investigations are the same, that the outcome measures are comparable and the variability in effect sizes between studies is not greater than would be expected by chance alone.

Section 2 relates to the overall assessment of the paper. It starts by rating the methodological quality of the study, based on the responses in Section 1 and using the following coding system:

++	All or most of the criteria have been fulfilled. Where they have not been fulfilled, the conclusions of the study or review are thought **very unlikely** to alter.
+	Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought **unlikely** to alter the conclusions.
–	Few or no criteria fulfilled. The conclusions of the study are thought **likely or very likely** to alter.

Appendix 10

Quality Checklist for an RCT			
Study ID:			
Guideline topic:		**Key question no:**	
Checklist completed by:			
SECTION 1: INTERNAL VALIDITY			
In a well-conducted RCT study:		**In this study this criterion is: (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
1.2	The assignment of subjects to treatment groups is randomised.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.3	An adequate concealment method is used.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.4	Subjects and investigators are kept 'blind' about treatment allocation.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.5	The treatment and control groups are similar at the start of the trial.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.6	The only difference between groups is the treatment under investigation.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.7	All relevant outcomes are measured in a standard, valid and reliable way.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.8	What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?		
1.9	All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis).	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.10	Where the study is carried out at more than one site, results are comparable for all sites.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
SECTION 2: OVERALL ASSESSMENT OF THE STUDY			
2.1	How well was the study done to minimise bias? *Code ++, + or –*		

NOTES ON THE USE OF THE METHODOLOGY CHECKLIST: RCTs

Section 1 identifies the study and asks a series of questions aimed at establishing the internal validity of the study under review – that is, making sure that it has been carried out carefully and that the outcomes are likely to be attributable to the intervention being investigated. Each question covers an aspect of methodology that research has shown makes a significant difference to the conclusions of a study.

For each question in this section, one of the following should be used to indicate how well it has been addressed in the review:

- well covered
- adequately addressed
- poorly addressed
- not addressed (that is, not mentioned or indicates that this aspect of study design was ignored)
- not reported (that is, mentioned but 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 to be answered on the basis of its conclusions.

1.2 THE ASSIGNMENT OF SUBJECTS TO TREATMENT GROUPS IS RANDOMISED

Random allocation of patients to receive one or other of the treatments under investigation, or to receive either treatment or placebo, is fundamental to this type of study. If there is no indication of randomisation, the study should be rejected. If the description of randomisation is poor, or the process used is not truly random (for example, allocation by date or alternating between one group and another) or can otherwise be seen as flawed, the study should be given a lower quality rating.

1.3 AN ADEQUATE CONCEALMENT METHOD IS USED

Research has shown that where allocation concealment is inadequate, investigators can overestimate the effect of interventions by up to 40%. Centralised allocation, computerised allocation systems or the use of coded identical containers would all be regarded as adequate methods of concealment and may be taken as indicators of

a well-conducted study. If the method of concealment used is regarded as poor, or relatively easy to subvert, the study must be given a lower quality rating, and can be rejected if the concealment method is seen as inadequate.

1.4 SUBJECTS AND INVESTIGATORS ARE KEPT 'BLIND' ABOUT TREATMENT ALLOCATION

Blinding can be carried out up to three levels. In single-blind studies, patients are unaware of which treatment they are receiving; in double-blind studies, the doctor and the patient are unaware of which treatment the patient is receiving; in triple-blind studies, patients, healthcare providers and those conducting the analysis are unaware of which patients received which treatment. The higher the level of blinding, the lower the risk of bias in the study.

1.5 THE TREATMENT AND CONTROL GROUPS ARE SIMILAR AT THE START OF THE TRIAL

Patients selected for inclusion in a trial should be as similar as possible, in order to eliminate any possible bias. The study should report any significant differences in the composition of the study groups in relation to gender mix, age, stage of disease (if appropriate), social background, ethnic origin or comorbid conditions. These factors may be covered by inclusion and exclusion criteria, rather than being reported directly. Failure to address this question, or the use of inappropriate groups, should lead to the study being downgraded.

1.6 THE ONLY DIFFERENCE BETWEEN GROUPS IS THE TREATMENT UNDER INVESTIGATION

If some patients received additional treatment, even if of a minor nature or consisting of advice and counselling rather than a physical intervention, this treatment is a potential confounding factor that may invalidate the results. If groups were not treated equally, the study should be rejected unless no other evidence is available. If the study is used as evidence, it should be treated with caution and given a low quality rating.

1.7 ALL RELEVANT OUTCOMES ARE MEASURED IN A STANDARD, VALID AND RELIABLE WAY

If some significant clinical outcomes have been ignored, or not adequately taken into account, the study should be downgraded. It should also be downgraded if the measures used are regarded as being doubtful in any way or applied inconsistently.

1.8 WHAT PERCENTAGE OF THE INDIVIDUALS OR CLUSTERS RECRUITED INTO EACH TREATMENT ARM OF THE STUDY DROPPED OUT BEFORE THE STUDY WAS COMPLETED?

The number of patients that drop out of a study should give concern if the number is very high. Conventionally, a 20% drop-out rate is regarded as acceptable, but this may vary. Some regard should be paid to why patients dropped out, as well as how many. It should be noted that the drop-out rate may be expected to be higher in studies conducted over a long period of time. A higher drop-out rate will normally lead to downgrading, rather than rejection of a study.

1.9 ALL THE SUBJECTS ARE ANALYSED IN THE GROUPS TO WHICH THEY WERE RANDOMLY ALLOCATED (OFTEN REFERRED TO AS INTENTION-TO-TREAT ANALYSIS)

In practice, it is rarely the case that all patients allocated to the intervention group receive the intervention throughout the trial, or that all those in the comparison group do not. Patients may refuse treatment, or contra-indications arise that lead them to be switched to the other group. If the comparability of groups through randomisation is to be maintained, however, patient outcomes must be analysed according to the group to which they were originally allocated, irrespective of the treatment they actually received. (This is known as intention-to-treat analysis.) If it is clear that analysis was not on an intention-to-treat basis, the study may be rejected. If there is little other evidence available, the study may be included but should be evaluated as if it were a non-randomised cohort study.

1.10 WHERE THE STUDY IS CARRIED OUT AT MORE THAN ONE SITE, RESULTS ARE COMPARABLE FOR ALL SITES

In multi-site studies, confidence in the results should be increased if it can be shown that similar results were obtained at the different participating centres.

Section 2 relates to the overall assessment of the paper. It starts by rating the methodological quality of the study, based on the responses in Section 1 and using the following coding system:

++	All or most of the criteria have been fulfilled. Where they have not been fulfilled, the conclusions of the study or review are thought **very unlikely** to alter.
+	Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought **unlikely** to alter the conclusions.
−	Few or no criteria fulfilled. The conclusions of the study are thought **likely or very likely** to alter.

Appendix 10

Quality Checklist for a Cohort Study*			
Study ID:		Relevant questions:	
Guideline topic:			
Checklist completed by:			
SECTION 1: INTERNAL VALIDITY			
In a well-conducted cohort study:		**In this study the criterion is:** *(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 SUBJECTS			
1.2	The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.3	The study indicates how many of the people asked to take part did so, in each of the groups being studied.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.4	The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.5	What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed?		
1.6	Comparison is made between full participants and those lost to follow-up, by exposure status.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
ASSESSMENT			
1.7	The outcomes are clearly defined.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.8	The assessment of outcome is made blind to exposure status.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.9	Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.10	The measure of assessment of exposure is reliable.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.11	Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable

1.12	Exposure level or prognostic factor is assessed more than once.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
CONFOUNDING			
1.13	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			
1.14	Have confidence intervals been provided?		
SECTION 2: OVERALL ASSESSMENT OF THE STUDY			
2.1	How well was the study done to minimise the risk of bias or confounding, and to establish a causal relationship between exposure and effect? *Code ++, + or –*		

*A cohort study can be defined as a retrospective or prospective follow-up study. Groups of individuals are defined on the basis of the presence or absence of exposure to a suspected risk factor or intervention. This checklist is not appropriate for assessing uncontrolled studies (for example, a case series where there is no comparison [control] group of patients).

NOTES ON THE USE OF THE METHODOLOGY CHECKLIST: COHORT STUDIES

The studies covered by this checklist are designed to answer questions of the type 'What are the effects of this exposure?' It relates to studies that compare a group of people with a particular exposure with another group who either have not had the exposure or have a different level of exposure. Cohort studies may be prospective (where the exposure is defined and subjects selected before outcomes occur) or retrospective (where exposure is assessed after the outcome is known, usually by the examination of medical records). Retrospective studies are generally regarded as a weaker design, and should not receive a 2++ rating.

Section 1 identifies the study and asks a series of questions aimed at establishing the internal validity of the study under review – that is, making sure that it has been carried out carefully, and that the outcomes are likely to be attributable to the intervention being investigated. Each question covers an aspect of methodology that has been shown to make a significant difference to the conclusions of a study.

Because of the potential complexity and subtleties of the design of this type of study, there are comparatively few criteria that automatically rule out use of a study as evidence. It is more a matter of increasing confidence in the likelihood of a causal relationship existing between exposure and outcome by identifying how many aspects of good study design are present and how well they have been tackled. A study that fails to address or report on more than one or two of the questions considered below should almost certainly be rejected.

For each question in this section, one of the following should be used to indicate how well it has been addressed in the review:

- well covered
- adequately addressed
- poorly addressed
- not addressed (that is, not mentioned or indicates that this aspect of study design was ignored)
- not reported (that is, mentioned but 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 to be answered on the basis of its conclusions.

1.2 THE TWO GROUPS BEING STUDIED ARE SELECTED FROM SOURCE POPULATIONS THAT ARE COMPARABLE IN ALL RESPECTS OTHER THAN THE FACTOR UNDER INVESTIGATION

Study participants may be selected from the target population (all individuals to which the results of the study could be applied), the source population (a defined subset of the target population from which participants are selected) or from a pool of eligible subjects (a clearly defined and counted group selected from the source population). It is important that the two groups selected for comparison are as similar as possible in all characteristics except for their exposure status or the presence of specific prognostic factors or prognostic markers relevant to the study in question. If the study does not include clear definitions of the source populations and eligibility criteria for participants, it should be rejected.

1.3 THE STUDY INDICATES HOW MANY OF THE PEOPLE ASKED TO TAKE PART DID SO IN EACH OF THE GROUPS BEING STUDIED

This question relates to what is known as the participation rate, defined as the number of study participants divided by the number of eligible subjects. This should be calculated separately for each branch of the study. A large difference in participation rate between the two arms of the study indicates that a significant degree of selection bias may be present, and the study results should be treated with considerable caution.

1.4 THE LIKELIHOOD THAT SOME ELIGIBLE SUBJECTS MIGHT HAVE THE OUTCOME AT THE TIME OF ENROLMENT IS ASSESSED AND TAKEN INTO ACCOUNT IN THE ANALYSIS

If some of the eligible subjects, particularly those in the unexposed group, already have the outcome at the start of the trial, the final result will be biased. A well-conducted study will attempt to estimate the likelihood of this occurring and take it into account in the analysis through the use of sensitivity studies or other methods.

1.5 WHAT PERCENTAGE OF INDIVIDUALS OR CLUSTERS RECRUITED INTO EACH ARM OF THE STUDY DROPPED OUT BEFORE THE STUDY WAS COMPLETED?

The number of patients that drop out of a study should give concern if the number is very high. Conventionally, a 20% drop-out rate is regarded as acceptable, but in observational studies conducted over a lengthy period of time a higher drop-out rate is to be expected. A decision on whether to downgrade or reject a study because of a high drop-out rate is a matter of judgement based on the reasons why people dropped out and whether drop-out rates were comparable in the exposed and unexposed groups. Reporting of efforts to follow up participants that dropped out may be regarded as an indicator of a well-conducted study.

1.6 COMPARISON IS MADE BETWEEN FULL PARTICIPANTS AND THOSE LOST TO FOLLOW-UP BY EXPOSURE STATUS

For valid study results, it is essential that the study participants are truly representative of the source population. It is always possible that participants who dropped out of the study will differ in some significant way from those who remained part of the study throughout. A well-conducted study will attempt to identify any such differences between full and partial participants in both the exposed and unexposed groups. Any indication that differences exist should lead to the study results being treated with caution.

1.7 THE OUTCOMES ARE CLEARLY DEFINED

Once enrolled in the study, participants should be followed until specified end points or outcomes are reached. In a study of the effect of exercise on the death rates from heart disease in middle-aged men, for example, participants might be followed up until death, reaching a predefined age or until completion of the study. If outcomes and the criteria used for measuring them are not clearly defined, the study should be rejected.

1.8 THE ASSESSMENT OF OUTCOME IS MADE BLIND TO EXPOSURE STATUS

If the assessor is blinded to which participants received the exposure, and which did not, the prospects of unbiased results are significantly increased. Studies in which this is done should be rated more highly than those where it is not done or not done adequately.

1.9 WHERE BLINDING WAS NOT POSSIBLE, THERE IS SOME RECOGNITION THAT KNOWLEDGE OF EXPOSURE STATUS COULD HAVE INFLUENCED THE ASSESSMENT OF OUTCOME

Blinding is not possible in many cohort studies. In order to assess the extent of any bias that may be present, it may be helpful to compare process measures used on the participant groups – for example, frequency of observations, who carried out the observations, the degree of detail and completeness of observations. If these process measures are comparable between the groups, the results may be regarded with more confidence.

1.10 THE MEASURE OF ASSESSMENT OF EXPOSURE IS RELIABLE

A well-conducted study should indicate how the degree of exposure or presence of prognostic factors or markers was assessed. Whatever measures are used must be sufficient to establish clearly that participants have or have not received the exposure under investigation and the extent of such exposure, or that they do or do not possess a particular prognostic marker or factor. Clearly described, reliable measures should increase the confidence in the quality of the study.

1.11 EVIDENCE FROM OTHER SOURCES IS USED TO DEMONSTRATE THAT THE METHOD OF OUTCOME ASSESSMENT IS VALID AND RELIABLE

The inclusion of evidence from other sources or previous studies that demonstrate the validity and reliability of the assessment methods used should further increase the confidence in the quality of the study.

1.12 EXPOSURE LEVEL OR PROGNOSTIC FACTOR IS ASSESSED MORE THAN ONCE

Confidence in data quality should be increased if exposure level or the presence of prognostic factors is measured more than once. Independent assessment by more than one investigator is preferable.

1.13 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 allowed for in the analysis. Clinical judgement should be applied to consider whether all likely confounders have been considered. If the measures used to address confounding 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.

1.14 HAVE CONFIDENCE INTERVALS BEEN PROVIDED?

Confidence limits 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 relates to the overall assessment of the paper. It starts by rating the methodological quality of the study, based on the responses in Section 1 and using the following coding system:

++	All or most of the criteria have been fulfilled. Where they have not been fulfilled, the conclusions of the study or review are thought **very unlikely** to alter.
+	Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought **unlikely** to alter the conclusions.
–	Few or no criteria fulfilled. The conclusions of the study are thought **likely or very likely** to alter.

APPENDIX 11: SEARCH STRATEGIES FOR THE IDENTIFICATION OF HEALTH ECONOMICS EVIDENCE

1. GENERAL SEARCH FILTERS

Drug misuse

a. CINAHL, HMIC, EMBASE, MEDLINE, PsycINFO – OVID interface

1 exp narcotic dependence/ or exp opioid-related disorders/
2 (addiction or analgesic agent abuse or drug abuse or drug abuse pattern or drug dependenc$ or drug misuse or intravenous drug abuse or psychoses, substance-induced or substance abuse, intravenous or substance abuse, perinatal or substance abuse or substance dependence or substance withdrawal syndrome or substance-related disorders).sh.
3 "substance use disorders"/
4 ((drug$1 or substance$) adj3 (abstain$ or abstinen$ or abus$ or addict$ or dependen$ or disorder$ or intoxicat$ or misus$ or over dos$ or overdos$ or use$2 or using or withdraw$)).tw.
5 or/1-4
6 diamorphine/ or exp heroin/ or morphine/
7 exp narcotic agent/ or exp narcotics/ or exp narcotic drugs/
8 (acetomorphine or diacephine or diacetylmorphine or diamorphine or diaphorin or heroin$ or morphacetin or morphine).mp. or 1502-95-0, 561-27-3.rn.
9 (anpec or duromorph or epimorph or morfin$ or morphia or morphin$ or morphinium or morphium or opso$1 or skenan).mp. or 57-27-2.rn.
10 opiate$.mp. or 8008-60-4.rn.
11 (opioid$ or opium or narcotic$).tw.
12 (abstain$ or abstinen$ or abus$ or addict$ or (excessive adj use$) or dependen$ or (inject$ adj2 drug$) or intoxicat$ or misus$ or over dos$ or overdos$ or (use$ adj (disorder$ or illicit)) or withdraw$).mp.
13 (or/6-11) and 12
14 or/5,13

b. NHS Economic Evaluation Database (NHS EED), Health Technology Assessment Database (HTA) – Wiley Interscience interface

1 MeSH descriptor Opioid-Related Disorders explode all trees
2 MeSH descriptor Substance-Related Disorders, this term only
3 MeSH descriptor Substance Abuse, Intravenous, this term only
4 MeSH descriptor Substance Withdrawal Syndrome, this term only
5 MeSH descriptor Psychoses, Substance-Induced, this term only

6 (drug* or substance*) near (abstain* or abstinen* or abus* or addict* or dependen* or disorder* or intoxicat* or misuse* or over dos* or overdos* or use or user* or using or withdraw*):ti or (drug* or substance*) near (abstain* or abstinen* or abus* or addict* or dependen* or disorder* or intoxicat* or misuse* or over dos* or overdos* or use or user* or using or withdraw*):ab or (drug* or substance*) near (abstain* or abstinen* or abus* or addict* or dependen* or disorder* or intoxicat* or misuse* or over dos* or overdos* or use or user* or using or withdraw*):kw

7 (#1 OR #2 OR #3 OR #4 OR #5 OR #6)

8 MeSH descriptor Heroin, this term only

9 MeSH descriptor Morphine explode all trees

10 MeSH descriptor Narcotics explode all trees

11 (acetomorphine or diacephine or diacetylmorphine or diamorphine or diaphorin or heroin* or morphacetin or morphin*):ti or (acetomorphine or diacephine or diacetylmorphine or diamorphine or diaphorin or heroin* or morphacetin or morphin*):ab or (acetomorphine or diacephine or diacetylmorphine or diamorphine or diaphorin or heroin* or morphacetin or morphin*):kw

12 (anpec or duromorph or epimorph or morfin* or morphia or morphin* or morphinium or morphium or opso* or skenan):ti or (anpec or duromorph or epimorph or morfin* or morphia or morphin* or morphinium or morphium or opso* or skenan):ab or (anpec or duromorph or epimorph or morfin* or morphia or morphin* or morphinium or morphium or opso* or skenan):kw

13 (opiate*):ti or (opiate*):ab or (opiate*):kw

14 (opioid* or opium or narcotic*):ti or (opioid* or opium or narcotic*):ab or (opioid* or opium or narcotic*):kw

15 (abstain* or abstinen* or abus* or addict* or (drug near use*) or (excessive* near use*) or dependen* or (inject* near drug*) or intoxicat* or misus* or over dos* or overdos* or (use* near (disorder* or illicit)) or withdraw*):ti or (abstain* or abstinen* or abus* or addict* or (drug near use*) or (excessive* near use*) or dependen* or (inject* near drug*) or intoxicat* or misus* or over dos* or overdos* or (use* near (disorder* or illicit)) or withdraw*):ab or (abstain* or abstinen* or abus* or addict* or (drug near use*) or (excessive* near use*) or dependen* or (inject* near drug*) or intoxicat* or misus* or over dos* or overdos* or (use* near (disorder* or illicit)) or withdraw*):kw

16 ((#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14) AND #15)

17 (#7 OR #16)

c. Health Economic Evaluations Database (OHE HEED) – Wiley interface

1 AX = (stimulant* or drug* or substance) and (abstain* or abstinen* or abus* or addict* or dependen* or detox* or disorder* or intoxicat* or misuse* or overdos* or use* or using* or withdraw*)

2 AX = acetomorphine or diacephine or diacetylmorphine or diamorphine or diaphorin or heroin or morphacetin or morphine
3 AX = anpec or duromorph or epimorph or morfin* or morphia or morphin or morphinium or morphium or opso* or skenan
4 AX = opioid* or opium or narcotic* or opiate*
5 AX = abstain* or abstinen* or abus* or addict* or dependen* or intoxicat* or misus* or overdos* or withdraw* or 'disorder within 1 use' or 'disorder within 1 user' or 'disorder within 1 using' or 'disorders within 1 use' or 'disorders within 1 user' or 'disorders within 1 using' or 'drug within 2 use' or 'drug within 2 user' or 'excessive within 2 use' or 'excessive within 2 user' or 'excessively within 2 use' or 'excessively within 2 user' or 'illicit within 1 use' or 'illicit within 1 user' or 'illicit within 1 using' or 'illicitly within 1 use' 'illicitly within 1 user' or 'illicitly within 1 using' or 'inject drug' or 'inject drugs' or 'injecting drug' or 'injecting drugs'
6 CS = 2 OR 3 OR 4
7 CS = 5 AND 6
8 CS = 1 OR 7

2. HEALTH ECONOMIC AND QUALITY OF LIFE FILTERS

a. MEDLINE, EMBASE, PsycINFO, CINAHL – OVID interface

1 exp "costs and cost analysis"/ or "health care costs"/
2 exp health resource allocation/ or exp health resource utilization/
3 exp economics/ or exp economic aspect/ or exp health economics/
4 exp value of life/
5 (burden adj5 (disease or illness)).tw.
6 (cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$ or expenditure$ or economic$).tw.
7 (fiscal or funding or financial or finance or budget).tw.
8 (resource adj5 (allocation$ or utility$)).tw.
9 or/1-8
10 (value adj5 money).tw.
11 exp quality of life/
12 (qualit$3 adj5 (life or survival)).tw.
13 (wellbeing or health status or QOL).tw.
14 or/9-13

APPENDIX 12:
QUALITY CHECKLISTS FOR ECONOMIC STUDIES

1.1 FULL ECONOMIC EVALUATIONS

Author: **Date:**
Title:

	Study design	Yes	No	NA
1	The research question is stated	❑	❑	
2	The viewpoint(s) of the analysis are clearly stated	❑	❑	
3	The alternatives being compared are relevant	❑	❑	
4	The rationale for choosing the alternative programmes or interventions compared is stated	❑	❑	
5	The alternatives being compared are clearly described	❑	❑	
6	The form of economic evaluation used is justified in relation to the question addressed	❑	❑	
	Data collection			
1	The source of effectiveness data used is stated	❑	❑	
2	Details of the design and results of the effectiveness study are given	❑	❑	❑
3	The primary outcome measure(s) for the economic evaluation are clearly stated	❑	❑	
4	Methods to value health states and other benefits are stated	❑	❑	
5	Details of the subjects from whom valuations were obtained are given	❑	❑	
6	Indirect costs (if included) are reported separately	❑	❑	❑
7	Quantities of resources are reported separately from their unit costs	❑	❑	

8	Methods for the estimation of quantities and unit costs are described	❑	❑	
9	Currency and price data are recorded	❑	❑	
10	Details of currency of price adjustments for inflation or currency conversion are given	❑	❑	❑
11	Details of any models used are given	❑	❑	❑
12	The choice of model used and the key parameters on which it is based are justified	❑	❑	❑
	Analysis and interpretation of results			
1	Time horizon of costs and benefits is stated	❑	❑	
2	The discount rate(s) is stated	❑	❑	❑
3	The choice of rate(s) is justified	❑	❑	❑
4	An explanation is given if costs or benefits are not discounted	❑	❑	❑
5	Details of statistical tests and confidence intervals are given for stochastic data	❑	❑	❑
6	The approach to sensitivity analysis is given	❑	❑	
7	The choice of variables for sensitivity analysis is given	❑	❑	
8	The ranges over which the variables are varied are stated	❑	❑	
9	Relevant alternatives are compared	❑	❑	
10	Incremental analysis is reported	❑	❑	❑
11	Major outcomes are presented in a disaggregated as well as aggregated form	❑	❑	
12	The answer to the study question is given	❑	❑	
13	Conclusions follow from the data reported	❑	❑	
14	Conclusions are accompanied by the appropriate caveats	❑	❑	

1.2 PARTIAL ECONOMIC EVALUATIONS

Author: **Date:**
Title:

	Study design	Yes	No	NA
1	The research question is stated	❑	❑	
2	The viewpoint(s) of the analysis is clearly stated and justified	❑	❑	
	Data collection			
1	Details of the subjects from whom valuations were obtained are given	❑	❑	
2	Indirect costs (if included) are reported separately	❑	❑	❑
3	Quantities of resources are reported separately from their unit costs	❑	❑	
4	Methods for the estimation of quantities and unit costs are described	❑	❑	
5	Currency and price data are recorded	❑	❑	
6	Details of currency of price adjustments for inflation or currency conversion are given	❑	❑	❑
7	Details of any model used are given	❑	❑	❑
8	The choice of model used and the key parameters on which it is based are justified	❑	❑	❑
	Analysis and interpretation of results			
1	Time horizon of costs is stated	❑	❑	
2	The discount rate(s) is stated	❑	❑	❑

3	Details of statistical tests and confidence intervals are given for stochastic data	❑	❑	❑
4	The choice of variables for sensitivity analysis is given	❑	❑	
5	The ranges over which the variables are varied are stated	❑	❑	
6	Appropriate sensitivity analysis is performed	❑	❑	
7	The answer to the study question is given	❑	❑	
8	Conclusions follow from the data reported	❑	❑	
9	Conclusions are accompanied by the appropriate caveats	❑	❑	

APPENDIX 13:
DATA EXTRACTION FORM FOR ECONOMIC STUDIES

Reviewer: **Date of Review:**

Authors:

Publication Date:

Title:

Country:

Language:

Economic study design:

- ❑ CEA
- ❑ CBA
- ❑ CUA
- ❑ CMA
- ❑ CCA
- ❑ CA

Modelling:

- ❑ No
- ❑ Yes

Source of data for effect size measure(s):

- ❑ Meta-analysis
- ❑ RCT
- ❑ Quasi experimental study
- ❑ Cohort study
- ❑ Mirror image (before-after) study
- ❑ Expert opinion

Comments _____

Primary outcome measure(s) (please list):

_____

Interventions compared (please describe):

Treatment: _____

Comparator: _____

Setting (please describe):

_____

Patient population characteristics (please describe):

_____

_____

_____

Perspective of analysis:

❑ Societal
❑ Patient and family
❑ Healthcare system
❑ Healthcare provider
❑ Third party payer
❑ Other: _____

Time frame of analysis: _____

Cost data:

❑ Primary ❑ Secondary

If secondary please specify: _____

Costs included:

Direct medical	Direct non-medical	Lost productivity
❑ direct treatment	❑ social care	❑ income forgone due to illness
❑ inpatient	❑ social benefits	❑ income forgone due to death
❑ outpatient	❑ travel costs	❑ income forgone by caregiver
❑ day care	❑ caregiver out-of-pocket	
❑ community healthcare	❑ criminal justice	
❑ medication	❑ training of staff	

Or

❑ staff
❑ medication
❑ consumables
❑ overhead
❑ capital equipment
❑ real estate

Others: _____

Currency: _____ **Year of costing:** _____

Was discounting used?
❑ Yes, for benefits and costs ❑ Yes, but only for costs ❑ No

Discount rate used for costs: _____

Discount rate used for benefits:_____

Result(s):

Comments, limitations of the study:

Quality checklist score (Yes/NA/All): ……/……/……

APPENDIX 14:
EVIDENCE TABLES FOR ECONOMIC STUDIES

Study, year and country	Intervention details	Study population setting study design – data source	Study type	Costs: description and values outcomes: description and values	Results: cost-effectiveness	Comments internal validity (Yes/No/NA) industry support
SHANA-HAN *et al.*, 2006	Intervention: Various detoxification methods (buprenor-phine outpatient, conventional inpatient, rapid detoxification) Comparator: conventional outpatient detoxification	Heroin users 18 years and over, seeking treatment Data source: four trials of heroin detoxification N = 365 Perspective: healthcare provider Australian quasi-experimental cohort study	Cost-effectiveness analysis	Costs (AUD$, 1999 prices): $491-buprenorphine outpatient, $605-conventional outpatient, $1404-conventional inpatient, $1990-rapid detoxification Outcomes: 7-day period of abstinence: RODA-58%, RODS-60%, conventional inpatient-24%, buprenorphine outpatient-12%, conventional outpatient-4%. Entry into post-detoxification treatment: RODA-42%, RODS-68%, conventional inpatient-12%, buprenorphine outpatient-65%, conventional outpatient-27%	Buprenorphine outpatient detoxification more cost effective overall. Rapid detoxification under sedation most cost effective inpatient treatment.	Sensitivity analysis: one-way Results were robust Discounting: not needed since time horizon for all analyses is less than 12 months. Internal validity:26/3/6
HARTZ *et al.*, 1999	Intervention: 180-day methadone detoxification enhanced with	Opioid dependent patients (N = 102) Participants were stabilised to a 80 mg methadone dose for	Cost effectiveness & cost-benefit analysis	Costs: cash credits can start from 35 cents and accumulate to a maximum of $755 at the end of treatment Cost of treatment was calculated for each participant individually	An incremental cost of $17.27 produced an additional 1% increase of abstinent	Failure to collect healthcare cost data for the full sample Small sample, extreme variance didn't provide

Continued

Study, year and country	Intervention details	Study population setting Study design – data source	Study type	Costs: description and values Outcomes: description and values	Results: cost effectiveness	Comments Internal validity (Yes/No/NA) Industry support
	contingency management Comparator: 180-day methadone detoxification	the first 4 months, followed by a 2-month taper		Total healthcare costs based on Medicare DRGs. Contingency management average cost: $3,278 (SD = 1003.29), STD average cost: $3,041 (SD = $1072.86)-not statistically significant difference Outcomes: continuous abstinence from drugs and alcohol during 4-month treatment	participants. For every additional $ spent there was a healthcare saving of $4.87. These are statistically insignificant differences.	enough power to achieve statistical significance. Discounting: not needed since time horizon was 4 months Internal validity: 20/5/10

GOSSOP, 2000	Detoxification of people who misuse opioids	People who misuse opioids Settings: 1. inpatient drug-dependence unit (DDU) 2. outpatient DD clinic 3. specialist inpatient unit 4. general psychiatric ward Outcome data from Gossop *et al.*, 1986	Cost and cost-effectiveness analysis	Costs: were taken from the NTORS study. Cost per week, per episode, per abstinence case were calculated for all four options Cost per abstinence case: £1,636 inpatient, £1,840 outpatient, £12,189 DDU, £6,421 general psychiatric ward Outcomes: successful detoxification completion rates 1.81% inpatient DDU 2.17% outpatient DD clinic 3.75% specialist inpatient unit 4.43% general psychiatric ward	The cost ratio for inpatient compared with outpatient is almost 2:1, adjusted for achievement of abstinence (for 10-day inpatient treatment costs are almost the same). The cost ratio for specialist DDU compared with general psychiatric ward is 1.9:1, adjusted for successful detoxification.	No sensitivity analysis was performed Discounting: not needed since time horizon for all analyses is less than 12 months Crude cost estimations used Internal validity: 4/9/10

10. GLOSSARY

12-step group: A non-profit fellowship of people who meet regularly to help each other remain abstinent. The core of the 12-step programme is a series of 12 stages that include admitting to a drug problem, seeking help, self-appraisal, confidential self-disclosure, making amends (when possible) where harm has been done, achieving a spiritual awakening and supporting other people who misuse drugs who want to recover.

Abstinence: Abstinence-oriented treatments aim to reduce an individual's level of drug use, with the ultimate goal of refraining from use altogether.

Agonist: An agonist is a substance that mimics the actions of a **neurotransmitter** or hormone to produce a response when it binds to a specific receptor in the brain. **Opioid** drugs, for example heroin and **methadone**, are agonists that produce responses such as 'liking', analgesia and respiratory depression.

Alpha$_2$ adrenergic agonist: An adrenergic **agonist** has an adrenaline-like action upon adrenergic receptors in the brain. Stimulation of the alpha adrenergic receptors leads to constriction of the bronchi and blood vessels, and dilation of the pupils of the eyes. Consequently, alpha$_2$ adrenergic agonists are useful in improving **opioid withdrawal symptoms** associated with the **noradrenaline system**, including sweating, shivering, and runny nose and eyes. Clonidine and lofexidine are examples of adrenergic agonists used as adjunctive medication in opioid detoxification.

Antagonist: In contrast to the action of an **agonist**, an antagonist, such as **naltrexone**, binds to a specific receptor in the brain but does not activate it. Therefore, if an agonist, for example heroin or **methadone**, is present and activating the receptor, taking naltrexone will counteract the activation, resulting in withdrawal.

Buprenorphine: An analgesic **opioid** substitute used in **maintenance**-oriented treatment, buprenorphine has both **agonist** and **antagonist** properties.

Cannabis: Cannabis is a generic term denoting the various psychoactive preparations of the hemp plant, including marijuana leaves, hashish resin and oil (WHO, 2006). It is the most commonly used illicit drug in the UK.

Cognitive behavioural therapy (CBT): Cognitive behavioural therapy encompasses a range of behavioural and cognitive behavioural therapies, in part derived from the cognitive behavioural model of affective disorders, in which the patient works collaboratively with a therapist using a shared formulation to achieve specific treatment goals. Such goals may include recognising the impact of behavioural and/or thinking patterns on feeling states and encouraging alternative cognitive and/or behavioural

coping skills to reduce the severity of target symptoms and problems. Therapies relevant to the field of drug misuse include **standard cognitive behavioural therapy** and **relapse-prevention cognitive behavioural therapy**.

Community reinforcement approach: In community reinforcement, emphasis is placed on environmental contingencies in aspects of life such as work, recreation, family involvement, and so on, to promote a lifestyle that is more rewarding than drug misuse (Roozen *et al.*, 2004).

Confidence interval (CI): The range within which the 'true' values (for example, size of effect of an intervention) are expected to lie with a given degree of certainty (for example, 95% or 99%). (Note: confidence intervals represent the probability of random errors, but not systematic errors or bias.)

Contingency management (CM): Contingency management provides a system of incentives and disincentives designed to make continual drug use less attractive and abstinence more attractive (Griffith *et al.*, 2000). The three main methods of providing incentives are voucher-based, whereby vouchers representing monetary values are provided upon receipt of biological samples (usually urine) that are negative for the tested drugs, prize-based (whereby participants receive prize-draw entries upon presentation of a negative biological sample) and privilege-based (whereby participants receive privileges such as take home methadone doses upon presentation of a negative biological sample).

Deep/heavy sedation: A high level of sedation, where the subject may not be easily aroused or purposefully respond to verbal commands and may only respond minimally to very significant stimuli (such as high levels of pain). He or she may experience partial or complete loss of protective reflexes, including the ability to independently and continuously maintain an open airway. The individual may therefore require assistance in maintaining an open airway, and spontaneous ventilation may be inadequate. Cardiovascular function is usually maintained.

Dependence: Dependence is defined by the WHO as a strong desire or sense of compulsion to take a substance, a difficulty in controlling its use, the presence of a physiological withdrawal state, tolerance of the use of the drug, neglect of alternative pleasures and interests and persistent use of the drug, despite harm to oneself and others (WHO, 2006).

Detoxification: Detoxification is the process by which an individual is withdrawn from the effects of a psychoactive substance. As a clinical procedure, the withdrawal process should be supervised and carried out in a safe and effective manner, such that withdrawal symptoms are minimised. Typically, the individual is clinically intoxicated or already in withdrawal at the outset of detoxification. Detoxification may involve the administration of medication, the dose of which is calculated to relieve withdrawal symptoms without inducing intoxication, and is gradually tapered off as the individual recovers.

Drug misuse/problem drug use: Drug misuse is the use of a substance for a purpose not consistent with legal or medical guidelines (WHO, 2006). The ACMD defines problem drug use as a condition that may cause an individual to experience social, psychological, physical or legal problems related to intoxication and/or regular excessive consumption, and/or dependence; any injection drug use also constitutes misuse (ACMD, 1998).

False negative: A test result that fails to detect an effect, condition or drug when it is in fact present.

False positive: A test result that incorrectly shows an effect, condition or drug to be present when it is not.

Family intervention: A psychological intervention derived from a model of the interactional processes in families. Interventions are aimed to help participants understand the effects of their interactions on each other as factors in the development and/or maintenance of drug misuse. Additionally, the aim is to change the nature of the interactions so that they may develop relationships that are more supportive and have less conflict (NICE, 2004).

General anaesthesia: Under general anaesthesia, an individual is unconscious and unresponsive, even in the face of significant stimuli. The ability to independently maintain ventilatory function is often impaired and assistance is frequently required in maintaining an open airway. Cardiovascular function may be impaired.

Harm reduction: Measures aiming to prevent or reduce negative health or other consequences associated with drug misuse, whether to the drug-using individual or to society. Attempts are not necessarily made to reduce the drug use itself.

Incremental cost-effectiveness ratio (ICER): The difference in the mean costs in the population of interest divided by the differences in the main outcomes in the population of interest.

Individual drug counselling: The assessment of an individual's needs, provision of information and referral to services to meet these needs (including psychosocial interventions, methadone and residential rehabilitation). No attempt is made to engage in any specific formal psychological intervention. Sessions are normally weekly and last 15–20 minutes (Rawson *et al.*, 1983). This to some extent resembles keyworking as used in the UK drug treatment field.

Interpersonal therapy (IPT): A discrete, time-limited, structured psychological intervention that focuses on interpersonal issues and where therapist and service user: a) work collaboratively to identify the effects of key problematic areas related to interpersonal conflicts, role transitions, grief and loss, and social skills, and their effects on current drug misuse, feelings states and/or problems; and b) seek to reduce

drug misuse problems by learning to cope with or resolve interpersonal problem areas (Weissman *et al.*, 2000).

Legally coerced (drug) treatment: This requires that the person who misuses drugs enter into treatment as an alternative or adjunct to criminal sanctions (Wild *et al.*, 2002). Such treatment can either be legally ordered by the court or through diversion away from the judicial process, usually following arrest and charge for drug-related and other offences.

Lofexidine: An **alpha$_2$ adrenergic agonist** currently licensed and used widely in the UK to ameliorate a cluster of **opioid withdrawal symptoms** (those associated with the **noradrenaline system**, including sweating, shivering, and runny nose and eyes).

Maintenance: In the UK context this refers primarily to the pharmacological maintenance of people who are **opioid** dependent; that is, prescription of opioid substitutes (**methadone** or **buprenorphine**). This aims to reduce illicit drug use and its consequent harms.

Meta-analysis: The use of statistical techniques to integrate the results of several independent studies.

Metabolite: A chemical product derived from breakdown (metabolism) of another chemical.

Methadone: A synthetic, psychoactive **opioid** substitute used in **maintenance**-oriented treatment, particularly heroin dependence. Methadone has **agonist** properties.

Minimal/light sedation: This involves the administration of medication in order to deal with anxiety, insomnia or agitation. The defining characteristic of this type of sedation is that the individual still appears relatively awake and is able to communicate clearly at all times. Although cognitive function and coordination may be impaired, ventilatory and cardiovascular functions are unaffected.

Moderate sedation: This occurs where the individual appears obviously sedated but, importantly, is able to independently maintain an open airway and respond to stimuli purposefully (such as verbal questioning).

Naloxone: A short-acting **antagonist** that blocks the effects of **opioid** drugs on receptors in the brain, naloxone is used to detect the presence of opioid effects (in what is known as a naloxone challenge test) and also in emergency situations to reverse opioid overdose.

Naltrexone: An **antagonist** that blocks the effects of **opioid** drugs on receptors in the brain, naltrexone is used in **maintenance** treatment to prevent detoxified service users from relapsing to opioid use.

National Collaborating Centre for Mental Health (NCCMH): One of seven centres established by the **National Institute for Health and Clinical Excellence (NICE)** to develop guidance on the appropriate treatment and care of people with specific diseases and conditions within the NHS in England and Wales. Established in 2001, the NCCMH is responsible for developing mental health guidelines, and is a partnership between the Royal College of Psychiatrists and the British Psychological Society.

National Institute for Health and Clinical Excellence (NICE): An independent organisation responsible for providing national guidance on the promotion of good health and the prevention and treatment of ill health. It provides guidance on three areas of health: clinical practice, public health and health technologies.

National Treatment Agency for Substance Misuse (NTA): The NTA is a special health authority, which was established by the government in 2001. It is tasked with increasing the availability, capacity and effectiveness of treatment for drug misuse in England and embraces user involvement as a core component of its strategy.

Near-patient testing: This refers to the process of obtaining a biological sample from a service user and using a drug-testing kit to immediately detect the presence of any of a variety of substances (for example, **opioids**, amphetamines, cocaine metabolite, benzodiazepines, methadone and cannabis) on site. This process eliminates the need for external laboratory support and provides rapid results.

Needle and syringe exchange: A service aiming to reduce transmission of blood-borne viruses through the promotion of safer drug injection behaviour, primarily via the distribution of sterile needles, but often also by offering education and other psychosocial interventions.

Neurotransmitter: A chemical messenger (for example, dopamine or **noradrenaline**) used by nerve cells to transmit nerve impulses from one nerve cell (neuron) to another, or between neurons and other tissues, such as muscles or glands.

Noradrenaline system: A neuronal system that is responsible for the synthesis, storage and release of the neurotransmitter noradrenaline, which exists in both the central and peripheral nervous systems. It is the primary neurotransmitter released by the sympathetic nervous system, which mediates the 'fight or flight' reaction, preparing the body for action by affecting cardiovascular function, gastrointestinal motility and secretion, bronchiole dilation, glucose metabolism, and so on.

Odds ratio (OR): A measure of the relative benefit of the experimental treatment that can be obtained by dividing the experimental odds by the control odds.

Opioid: A class of psychoactive substances derived from the poppy plant, including opium, morphine and codeine, as well as their semi-synthetic counterparts, including heroin (WHO, 2004). In this guideline, the term 'opioid' is used more broadly to

incorporate synthetic compounds (including **methadone**) with similar properties, also commonly known as opioids.

Psychosocial intervention: Any formal, structured psychological or social intervention with assessment, clearly defined treatment plans and treatment goals, and regular reviews (NTA, 2006), as opposed to advice and information, drop-in support or informal keyworking.

Quality adjusted life years (QALY): A form of utility measure calculated by estimating the total life years gained from a treatment and weighting each year with a quality-of-life score in that year.

Randomised controlled trial (RCT): An experiment in which investigators randomly allocate eligible people into groups to receive or not to receive one or more interventions that are being compared. The results are assessed by comparing outcomes in the different groups. Through randomisation, the groups should be similar in all aspects, apart from the treatment they receive during the study.

Rapid/ultra-rapid detoxification: Approaches for detoxifying those dependent upon **opioids** whereby opioid **antagonists**, such as **naloxone**, **naltrexone** or nalmefene, are used under **general anaesthesia** or **deep sedation**. The aim is to flood the brain with an opioid antagonist to remove all agonists while the sedation (for rapid detoxification) or anaesthesia (ultra-rapid detoxification) minimises discomfort. The individual is then maintained on naltrexone.

Relapse-prevention cognitive behavioural therapy: This differs from **standard cognitive behavioural therapy** in the emphasis on training drug users to develop skills to identify situations or states where they are most vulnerable to drug use, to avoid high-risk situations, and to use a range of cognitive and behavioural strategies to cope effectively with these situations (Carroll & Onken, 2005).

Relative risk (RR): The ratio of risk in the intervention group to the risk in the control group. The risk (proportion, probability or rate) is the ratio of people with an event in a group to the total in the group. An RR of 1 indicates no difference between comparison groups. For undesirable outcomes, an RR that is less than 1 indicates that the intervention was effective in reducing the risk of that outcome.

Residential rehabilitation programme: Residential rehabilitation centres provide accommodation in a drug-free environment and a range of structured interventions to address drug misuse, including, but not limited to, abstinence-oriented interventions (NTA, 2006). Services vary and are based on a number of different treatment philosophies.

Screening: The systematic application of a test or enquiry to identify individuals at high risk of developing a specific disorder who may benefit from further investigation

or preventative action (Peckham & Dezateux, 1998). Routine screening for drug misuse in the UK is largely restricted to criminal justice settings, including police custody and prisons (Matrix Research and Consultancy & NACRO, 2004).

Self-help group: A group of people who misuse drugs meet regularly to provide help and support for one another. The group is typically community-based, peer-led and non-professional.

Sensitivity: A term used to assess **screening** tools, sensitivity refers to the proportion of people with disease who test positive for that disease.

Short-term psychodynamic intervention: A psychological intervention, derived from a psychodynamic/psychoanalytic model in which: a) therapist and service user explore and gain insight into conflicts and how these are represented in current situations and relationships, including the therapy relationship; b) service users are given an opportunity to explore feelings and conscious and unconscious conflicts originating in the past, with the technical focus on interpreting and working through conflicts; c) therapy is non-directive and service users are not taught specific skills such as thought monitoring, re-evaluation or problem solving. Treatment typically consists of 16–30 sessions (Leichsenring *et al.*, 2004).

Social network interventions: Professionals seek to promote change by helping the person who misuses drugs to engage with a close network of family members or friends who provide positive social support for attempting or maintaining abstinence (Copello *et al.*, 2005).

Specificity: A term used to assess **screening** tools, specificity refers to the proportion of people without disease who test negative for that disease.

Standard cognitive behavioural therapy: A discrete, time-limited, structured psychological intervention, derived from a cognitive model of drug misuse (Beck *et al.*, 1993). There is an emphasis on identifying and modifying irrational thoughts, managing negative mood and intervening after a lapse to prevent a full-blown relapse (Maude-Griffin *et al.*, 1998).

Standard deviation (SD): A statistical measure of variability in a population of individuals or in a set of data. While the average measures the expected middle position of a group of numbers, the standard deviation is a way of expressing how different the numbers are from the average. The standard deviation is (approximately) the amount by which the average person's score differs from the average of all scores.

Standardised mean difference (SMD): In a **meta-analysis**, a way of combining the results of studies that may have measured the same outcome in different ways, using different scales. Statistically, it is calculated by dividing the weighted average effect size by the pooled standard deviation. The SMD is expressed as a standard value with no units.

Stimulant: Broadly any substances that activate, enhance or increase neural activity (WHO, 2006). Illicit stimulants include cocaine, crack cocaine and methamphetamine. Cocaine is one of the most commonly misused stimulants in the UK; crack cocaine refers to the cocaine alkaloid that has been purified from the other components of cocaine powder, and methamphetamine is one of a group of synthetic substances (amphetamines) with broadly similar properties to cocaine.

Systematic review: Research that summarises the evidence on a clearly formulated question according to a predefined protocol using systematic and explicit methods to identify, select and appraise relevant studies, and to extract, collate and report their findings. It may or may not use statistical **meta-analysis**.

Tramadol: A synthetic **opioid**, tramadol is a weak **agonist** which may also have partial **antagonist** properties. More commonly used in the context of pain relief, it is neither licensed nor routinely used in the UK for the treatment of opioid dependence.

Weighted mean difference (WMD): A method of meta-analysis used to combine measures on continuous scales, where the mean, standard deviation and sample size in each group are known. The weight given to each study (for example, how much influence each study has on the overall results of the **meta-analysis**) is determined by the precision of its estimate of effect and, in the statistical software used by the **NCCMH**, is equal to the inverse of the variance. This method assumes that all of the trials have measured the outcome on the same scale.

Withdrawal symptoms: Withdrawal symptoms ensue when a person who has become tolerant to the effects of a drug stops taking it. Such symptoms typically emerge within 6–12 hours for short-acting **opioids** such as heroin and about 24–36 hours after the last dose of methadone or buprenorphine, depending on the dose. Withdrawal can also ensue when an opioid **antagonist**, such as **naloxone** or **naltrexone** is taken; this is called precipitated or abrupt withdrawal. Opioid withdrawal symptoms can include pupil dilation, diarrhoea, low mood, irritability, anxiety, insomnia, muscular and abdominal pains, restlessness and 'craving'. In addition, tachycardia, sweating, runny nose, hair standing on end and shivering are generally experienced.

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12. ABBREVIATIONS

ACMD	Advisory Council on the Misuse of Drugs
AE	adverse event
AGREE	Appraisal of Guidelines for Research and Evaluation Instrument
AIDS	autoimmune deficiency syndrome
AMED	A bibliographic database produced by the Health Care Information Service of the British Library
APA	American Psychiatric Association
ASI	Addiction Severity Index
CA	Cost analysis
CBA	Cost-benefit analysis
CBT	cognitive behavioural therapy
CCA	Cost-consequences analysis
CEA	Cost-effectiveness analysis
CI	confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CMA	Cost-minimisation analysis
COWS	Clinical Opiate Withdrawal Scale
CSAT	Center for Substance Abuse Treatment
CUA	Cost-utility analysis
DD	drug dependence
DDU	drug-dependence unit
DH	Department of Health
DIP	Drug Interventions Programme
DSM	Diagnostic and Statistical Manual of Mental Disorders (versions III-R and IV-TR)
DTTO	Drug Treatment and Testing Order
EMBASE	Excerpta Medica database
EEG	electroencephalogram
F	the statistic calculated by analysis of variance (F ratio)
GDG	Guideline Development Group
GFN	guanfacine
GP	general practitioner
GRADE	Grading of Recommendations: Assessment, Development and Evaluation (Working Group)
GRP	Guideline Review Panel

HIV	human immunodeficiency virus
HMIC	Health management and policy database from the Healthcare Management Information Consortium
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
K	number of studies
LAAM	levo-alpha acetyl methadol
LDQ	Leeds Dependence Questionnaire
LSD	lysergic acid diethylamide
MAP	Maudsley Addiction Profile
MEDLINE	Compiled by the US National Library of Medicine and published on the web by Community of Science, MEDLINE is a source of life sciences and biomedical bibliographic information
MMT	methadone maintenance treatment
n	number of participants in a group
N	total number of participants
NACB	National Academy of Clinical Biochemistry
NACRO	National Association for the Care and Rehabilitation of Offenders
NCCMH	National Collaborating Centre for Mental Health
NDTMS	National Drug Treatment Monitoring System
NHS	National Health Service
NHS EED	National Health Service Economic Evaluation Database
NICE	National Institute for Health and Clinical Excellence
NIDA	National Institute on Drug Abuse
NSF	National Service Framework
NTA	National Treatment Agency for Substance Misuse
NTORS	National Treatment Outcomes Research Study
OHE HEED	Office of Health Economics, Health Economics Evaluation Database
OR	odds ratio
OTI	Opiate Treatment Index
OWS	Opiate Withdrawal Scale
p	probability
PICO	patient, intervention, comparison and outcome
PILOTS	An electronic index to the worldwide literature on post-traumatic stress disorder and other mental-health

	consequences of exposure to traumatic events, produced by the US National Center for PTSD
PSS	Personal Social Services
PsycINFO	An abstract (not full text) database of psychological literature from the 1800s to the present
QALY	quality adjusted life year
qid	four times a day
r	correlation
RCT	randomised controlled trial
RD	rapid detoxification (-GA, with general anaesthesia)
RODA	rapid opioid detoxification under anaesthetic
RODS	rapid opioid detoxification under sedation
RR	relative risk
SCAN	Specialist Clinical Addiction Network
SDS	Severity of Dependence Scale
SIGLE	System for Information on Grey Literature in Europe database
SIGN	Scottish Intercollegiate Guidelines Network
SMD	standardised mean difference
SODQ	Severity of Opiate Dependence Questionnaire
t	t-statistic
tid	three times a day
WHO	World Health Organization
WMD	weighted mean difference
χ	chi