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

Final Protocol (4 AUG 2005) AMENDED[A] 11 AUGUST 2005

1. Title of the project:

Methadone and buprenorphine for the management of opioid dependence.

2. Name of TAR team and 'lead'

West Midlands Health Technology Assessment Collaboration

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3. Plain English Summary

Heroin and other opioids are powerful drugs that can induce a sense of well-being, deliver a boost to self esteem and make a person less able to feel pain. People taking opioids for recreational use or for their medical condition may eventually become dependent on the drug. Getting their next dose can then become an important part of each day. Such drug dependence is likely to have many negative effects, for example overdose, getting an infection (e.g. HIV or hepatitis), causing family distress or disruption at work, or involvement in criminal activities.

It is difficult to stop using drugs and remain a non-user because of craving, unpleasant withdrawal symptoms, and continued or worsening personal circumstances that led to illicit drug use in the first place. Even when a drug user manages to overcome the unpleasant withdrawal symptoms and become drug-free it is likely he or she will return to using drugs within a short time.

Several treatment approaches are currently used to help opioid dependent people. One common element of these approaches is to try to replace the illicit opioid with a prescribed opioid that has more favourable properties than heroin. Two examples are methadone and buprenorphine, both of which can be taken by mouth. The aim of prescribing these drugs is to help users through the initial phase of withdrawal towards abstinence from opioid drugs, or to provide a stable long-term legal source as an alternative to using illicit drugs.

This report will look at the scientific research to assess how well methadone and buprenorphine work and whether they provide good value for money.

4. Decision Problem

4.1 Purpose of the decision to be made

[A] Amendments to the protocol as the result of the consultee meeting of 10th August 2006 are flagged by footnotes.

Physical and psychological dependence can occur with any opioid drug, but illicit or 'street' heroin presents the greatest problems due in part to its potency and illegality. Opioid dependence is a chronic, relapsing-remitting condition with physical, psychological and social dimensions. It is typically characterised by a loss of control over one's drug use, and is usually associated with unsuccessful attempts to cut down or control use. Opioids are taken in larger amounts or over a longer period than was intended, and considerable time is spent in obtaining, using, or recovering from the effects of the drugs. This leads to a reduction in other social, occupational, or recreational activities, but use continues despite the drug-related problems. Physical tolerance to opioids and a withdrawal syndrome on reduction or cessation of use are usually present.

The natural history of heroin users attending treatment services suggests that most individuals develop dependence in their early twenties, several years after their first use of heroin, and continue use over the next 10 to 20 years. There are considerable harms associated with illicit heroin use, including increased mortality (approximately 10 to 20 times greater than age and gender matched non-users); increased infection with blood-borne viruses (HIV, HCV, HBV); high levels of depression and anxiety disorders; social problems such as disrupted parenting, employment and accommodation; and increased participation in income-generating crime. Even when users become drug free there is a high probability of their returning to drug use within a few months.

The chronic-relapsing nature of drug dependence makes it desirable that interventions help achieve appreciable periods of abstinence or long term maintenance to help reduce use of illicit opioid. Methadone and buprenorphine are each licensed as an adjunctive treatment for opioid dependence.

This report looks at how effective and cost-effective maintenance therapy with sublingual buprenorphine and oral methadone are in comparison to other treatments when used as an adjunct intervention for opioid dependence The report also tries to identify whether there are particular subgroups of opiate users in whom these drugs are likely to be more effective or cost effective and what doses and delivery settings are optimum.

4.2 Definition of the intervention

Methadone and buprenorphine are synthetic opioids. Methadone is an opioid agonist and buprenorphine is an opioid partial agonist and partial antagonist. The Summary Product Characteristics (SPC) for methadone states that it is indicated for "use in the treatment of opioid drug addictions (as a narcotic abstinence syndrome suppressant)". The SPC for buprenorphine states that it is indicated for "substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment". Methadone[‡] is used in opioid dependence at a dose of 10-40mg daily, increased by up to 10mg daily until no signs of withdrawal or intoxification; the usual dose range is 60-120 mg daily however larger doses may be employed. Only oral methadone will be considered. Buprenorphine[‡] is used in opioid dependence by sublingual tablet administration at an initial dose of 0.8-4mg as a single daily dose, adjusted according to response; however in practice a starting dose is often > 4 mg/day. The maximum is 32mg in any one day.

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

Each drug is used as an adjunct in the treatment of opioid dependence and can be used in strategies aimed at both maintenance/harm reduction and detoxification/abstinence. Strategies may employ other treatments, such as psychosocial interventions.

[‡] BNF 49 March 2005 http://www.bnf.org/bnf/bnf/current/openat/ (accessed 4 Aug 2005)

Detoxification may be the first stage of an opiate withdrawal programme. It aims to reduce or eliminate withdrawal symptoms and help the patient reach a drug-free state in a safe and humane way. Prior to maintenance approaches detoxification was the only treatment available to those dependent on opioids. The last 25 years have seen the introduction of new medications to assist withdrawal including alpha-2-agonists (such as clonidine or lofexidine).

An alternative to attempting to stop opiate use altogether is the maintenance approach, the focus of this report. In this approach methadone is prescribed in doses higher than that required merely to prevent withdrawal symptoms. By doing so, it becomes harder for the patient to experience euphoria if they use heroin in addition to their prescription, and craving for opiates is reduced. By exchanging an expensive illicit drug of unkown purity and quality for a pharmaceutically produced drug of more certain dose, the user may begin to achieve some stability in their life. The prescription of methadone, or latterly buprenorphine, can act as an inducement for the patient to attend a treatment programme where other problems that originally led to drug use may be addressed (e.g. housing, relationship or employment difficulties).

Various medications can be provided in a range of different settings within the community and the criminal justice system, including inpatient or residential, day patient or outpatient settings. Ultimately the selection of which type of maintenance programme and setting is appropriate depends on complex factors including: available methods and funding, the severity of dependence, the degree of multiple drug use, physician or patient preference or the local legal framework.

4.4 Relevant comparators

The interventions are adjuncts to current treatment strategies and therefore the comparator will be treatment strategies without methadone (oral) or buprenorphine (sublingual), but may include an alternative pharmacological treatment or alternative non-pharmacological treatment in place of methadone or buprenorphine. Comparator regimens will also include methadone or buprenorphine used for detoxification / withdrawal.[B]

4.5 Population and relevant sub-groups

Opioid dependent adults (16-years and over) are the target population for this assessment, although data for younger persons will be considered if it is available[C]. It is possible that maintenance therapies with methadone or buprenorphine are more successful amongst particular groups of patients or when administered in particular settings. We will examine these subgroups where the evidence allows (see section 5.3).

4.6 Key factors to be addressed

The primary focus of this assessment will be clinical and cost outcomes from the perspective of the healthcare system (NHS) and Personal Social Services. The wider societal implications including public health and safety, and costs to the criminal justice system will be considered.

5. Report methods for synthesis of evidence of clinical effectiveness

5.1 Search strategy

A scoping search has already been undertaken to identify existing systematic reviews and to

[B] Amendment: new comparison of use in maintenance relative to withdrawal.
[C] Amendment: coverage extended (n.b. methadone licence specifies not in children; BNF defines child as 12 years old and younger).

estimate the volume and nature of primary studies. Nine published Cochrane systematic reviews (2001-2004) have been identified that assess the use of methadone or buprenorphine in the management of opioid dependence.[1-9] It is proposed that this report will update these Cochrane systematic reviews . Searches for new primary studies will be restricted to RCTs (these will date from the earliest search amongst these reviews: i.e. from January 2000). In addition, a full search (with no date restriction) for systematic reviews (of RCT and/or observational studies) will be carried out to particularly address outcomes related to harms and adverse effects of treatment. The search for systematic reviews will follow the ARIF search protocol (Appendix 1).

The following resources will be searched for relevant primary studies:

- Bibliographic databases: Cochrane Library, MEDLINE(Ovid), MEDLINE In-Process & Other Non-Indexed Citations (Ovid), EMBASE(Ovid), PsycINFO, IBSS, Sociolological AbstractsSearches will be based on index and text words that encompass methadone, buprenorphine; opioid misuse, dependence and withdrawal (see Appendix 1). Depending on the yield of references a filter to identify particular study designs will be included.
- Citations of relevant studies will be examined.
- Further information will be sought from contacts with experts.
- Research registries of ongoing trials including National Research Register, Current Controlled Trials, Clinical Trials.gov
- Relevant internet resources
- Industry submissions

5.2 Types of studies included

Systematic reviews, meta-analyses and primary studies suitable for inclusion will be selected from those identified as potentially relevant by the search strategy, using the criteria listed below:

Inclusion criteria

Study Design:

- Reviews: systematic reviews of RCTs or systematic reviews of observational studies (either with or without meta-analyses);
- Primary studies: RCTs only;

Based on the volume and nature of observational evidence identified, a suitable cut-off for inclusion will be chosen.

Population:

- Persons[D] who are dependent on opioids.

Intervention

- Buprenorphine or methadone employed in maintenance therapy irrespective of dose. [*We will employ the following operational definition: Any trial that calls itself "maintenance" OR any trial that does not include a reducing or cessation of methadone / buprenorphine dose as part of its intervention*].

Comparator:

- Any comparative regime used in maintenance therapy (including no therapy or placebo) or the intervention drug used in withdrawal/detoxification therapy.[E]

[D] Amendment: Changed to include any age.
[E] Amendment: Comparators extended to allow buprenorphine maintenance to be compared with buprenorphine withdrawal across common outcome measures, and similarly for methadone.

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

- Drug use
    - Changes in illicit drug use[§]
    - Concordance with, and retention in treatment
- Health of drug user
    - Drug-related mortality[§]
    - Drug-related morbidity (e.g. blood-borne virus infection rates) [§]
    - Health-related quality of life[§]
    - Use of health care system
    - Major adverse effects of treatment (drug interactions, liver disease, cardiac abnormality, exacerbation of comorbidity) [§]
- Social effects
    - Effects on employment
    - Effects on family
- Effects on criminal justice system
    - Rates of crime
    - Recidivism

[§] Primary outcomes for the report

Exclusion criteria [F]

- Case reports

Based on the above inclusion/exclusion criteria, study selection will be made independently by two reviewers. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary.

[F] Amendment: Studies no longer excluded on the basis of age of trial participants.

5.3 Sub-groups to be examined

Related to treatment / setting

1. Setting, e.g. within community, residential, or criminal justice system
2. Treatment regimen:
   - Dose
   - Duration of program
   - Degree of supervision / delivery
3. Adjunctive care

Related to individual

1. Age
2. Sex
3. Ethnicity
4. Profession
5. Employment status
6. Degree of social support
7. Other substance use or dependence
8. Pregnancy[G]

These subgroups will be examined for the outcomes listed above (section 5.2)

5.4 Data extraction strategy

Data will be extracted independently by at least one reviewer using a standardised data extraction form (see Appendix 2) and checked by a second reviewer. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary. Details of study characteristics, study participants, drug and comparative regime and outcome results will be extracted,

5.5 Quality assessment strategy

The quality of the individual studies will be assessed by one reviewer, and independently checked for agreement by a second reviewer. Any disagreements will be resolved by consensus and if necessary a third reviewer will be consulted. The quality of included studies will be assessed according to criteria such as based on NHS CRD Report No.4.[10] and the scoring system developed by Gowing and Bornemann.[4]

5.6 Methods of analysis/synthesis

Based on the nature of the outcome (binary, continuous or time-related) an estimate of effect size will be calculated for each individual study. Where possible, and appropriate, effect sizes will be pooled across studies using meta-analytic methods. Analysis of subgroups will be explored should evidence allow.

5.7 Methods for estimating quality of life

[G] Amendment: subgroup added

See following section (Section 6.)

6. Report methods for synthesising evidence of cost-effectiveness

6.1 Systematic review of literature relevant to economic evaluation

A comprehensive search for literature on the cost and cost-effectiveness of Methadone and Buprenorphine as substitute opiates for opioid dependent drug misusers will be conducted.

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

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

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

Standard approaches to applying inclusion/ exclusion criteria will be employed. Quality assessment for assessments of cost-effectiveness will be done using standard criteria. [11,12] Papers may be excluded at this stage on the basis of quality assessment. Justification for the exclusion of papers will be presented. The papers that remain in the review will be summarised on the basis of key items of information, an example of which is listed below.

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

6.2 Economic Evaluation

In order to explore both the effectiveness and the cost-effectiveness of Methadone and Buprenorphine as substitute opiates for opioid dependent drug misuse programmes, and depending on the results of our literature reviews, we may expand existing decision analytic models or develop our own decision-analytic model. The choice of model will be dependent on both the appropriate structure of the model and the quality of previously published models. If the data allows we will conduct a probabilistic sensitivity analysis, otherwise we will conduct one-way and two-way sensitivity analyses.

The cost-effectiveness analysis for the reference case will be expressed in terms of incremental cost per quality adjusted life year. The perspective for the reference case model will be NHS/PSS. The time horizon of our reference case analysis will be one year. Subject to the availability of suitable data, the costs and benefits of different service strategies and optimum care package (e.g. setting, dosage, supervision, monitoring, etc) will be explored in sensitivity analysis. In particular, the costs and benefits in different settings (community and criminal justice system settings) and among different patient subgroups (identified in clinical effectiveness evidence synthesis) will be explored.

A longer-term time horizon will be explored depending on the evidence available and this will be referred to as a non-reference case. The appropriate discount rate will be applied [‡]. In a further non-reference case analysis the NHS/PSS perspective may be widened to include costs and benefits relevant to a societal perspective. The terms the analysis will be expressed in will depend on availability and appropriateness of suitable data, as data restrictions may require us to use measures such as cost per Major Outcome Averted (MOA). From our scoping work we anticipate that the direct evidence linking drug misuse and outcomes such as the societal function, criminal activity, and public health and safety will be weak. It will probably not be appropriate nor feasible to explore the effect on public health and safety of infectious disease transmission associated with drug misuse. However, if the literature reports direct links between drug misuse and these outcomes they will be included as part of the sensitivity analysis.

7. Handling the company submission(s)

Company submissions by the manufacturers/sponsors will be considered if received by the TAR team no later than **21st October 2005**. Data arriving after this date will not be considered.

If the clinical data meet the inclusion criteria for the review they will be extracted and quality assessed in accordance with the procedures outlined in this protocol. Any economic evaluations included in the company submission, provided it complies with NICE's advice on presentation, will be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used in the economic model. If the TAR team judge that the existing economic evidence is not robust, then further work will be undertaken, either by adapting what already exists or developing *de-novo* modeling.

Any 'commercial in confidence' data taken from a company submission will be underlined in the assessment report.

8. Competing interests of authors

Personal specific	**Non-personal specific**
Esther Albon - None	Esther Albon - None
Martin Connock - None	Martin Connock - None
Ed Day - None	Ed Day - None
Emma Frew – None	Emma Frew - None
Anne Fry-Smith - None	Anne Fry-Smith - None
Sue Jowett - None	Sue Jowett - None
Ariadna Juarez-Garcia - None	Ariadna Juarez-Garcia - None
Nick Lintzeris - Dr Nicholas Lintzeris has been supported to attend an international conference, and has been paid to deliver educational programs for health professionals by Schering Plough, the marketing agents of buprenorphine (Subutex®) in Europe.	Nick Lintzeris - None

[‡] discounting at 6% costs, 1.5% benefits. Sensitivity analysis at 3.5% discounting for both costs and benefits will be undertaken.

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Tracy Roberts - None	Tracy Roberts - None
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Rod Taylor - None	Rod Taylor - None
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9. Appendices

Appendix 1 DRAFT Search Strategy

Draft MEDLINE search strategy

1 methadone.mp.
2 buprenorphine.mp.
3 or/1-2
4 Exp Opioid-Related Disorders/
5 Substance Withdrawal Syndrome/
6 Substance related disorders/
7 Heroin dependence/
8 (substance abuse OR substance misuse OR substance dependen$).mp.
9 (opioid abuse OR opioid misuse OR opioid dependen$).mp.
10 (heroin abuse OR heroin misuse OR heroin dependen$).mp.
11 (opiate abuse OR opiate misuse OR opioid dependen$).mp.
12 or/4-11
13 3 and 12

Example of a filter for randomized controlled trials

1 randomized controlled trial.pt.
2 controlled clinical trial.pt.
3 randomized controlled trials.sh.
4 random allocation.sh.
5 double blind method.sh.
6 single blind method.sh.
7 or/1-6
8 (animals not human).sh.
9 7 not 8
10 clinical trial.pt.
11 exp clinical trials/
12 (clin$ adj25 trial$).ti,ab.
13 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
14 placebo$.ti,ab.
15 random$.ti,ab.
16 placebos.sh.
17 research design.sh.
18 or/10-17
19 18 not 8
20 19 not 9
21 9 or 20

ARIF search protocol

1) Cochrane Library
- Cochrane Reviews
- Database of Abstracts of Reviews of Effectiveness (DARE)
- Cochrane Central Register of Controlled Trials (CENTRAL)
- Health Technology Assessment (HTA) database

2) ARIF Database
An in-house database of reviews compiled by scanning current journals and appropriate WWW sites. Many reviews produced by the organisations listed below are included.

3) NHSCRD (WW Web access)
- DARE
- Health Technology Assessment Database
- Completed and ongoing CRD reviews

4) Health Technology Assessments and evidence based guidelines (WW Web access)
- NICE appraisals and work plans for TARs, Interventional Procedures and Guidelines programmes (NCCHTA work pages:www.ncchta.org/nice/) Public Health excellence
- Office of Technology Assessment
- NHS Coordinating Centre for Health Technology Assessments
- Canadian Co-ordinating Office for Health Technology Assessment
- New Zealand Health Technology Assessment
- Wessex STEER Reports
- Agency for Healthcare Research and Quality (AHRQ)
- National Horizon Scanning Centre
- SIGN (Scottish Intercollegiate Guidelines Network)

5) Clinical Evidence

6) Bandolier

7) TRIP Database

8) Bibliographic databases
- Medline - systematic reviews
- Embase - systematic reviews
- Other specialist databases.

9) Contacts
- Cochrane Collaboration (via Cochrane Library)
- Regional experts, especially Pharmacy Prescribing Unit, Keele University (&MTRAC) and West Midlands Drug Information Service (url: www.ukmicentral.nhs.uk) for any enquiry involving drug products

Appendix 2 DRAFT Data Extraction Form Methadone and buprenorphine TAR

Trial details	*Trial ID*	
	Intervention / Control	
	Target maintenance dose / duration	
	Patient condition-type	
	Type of trial design	
	Co-therapy elements	
	Setting	
	Study start and end dates	
	Centres (n) / Country	
Trial design	*Run-in phase*	
	Titration phase (including details of schedule & frequency of doses)	
	Maintenance phase dose/ duration	
	Withdrawal phase dose/ duration	
	Comments on design	
Quality assessment for RCTs	*Was assignment of treatment described as random?*	
	Was method of randomisation described?	
	Was the method really random?	
	Was allocation of treatment concealed?	
	Who was blinded to treatment?	
	Was method of blinding adequately described?	
	Were eligibility criteria described?	
	Were groups comparable at study entry?	
	Were groups treated identically apart from the intervention?	
	Was ITT used?	
	Were withdrawals stated?	
	Were reasons for withdrawals stated?	
	Was a power calculation done?	
	Comments	

Quality assessment for observational studies	*Was the population base described?*			
	Were recruitment / eligibility criteria reported?			
	Was there consideration of possible confounding factors?			
	Were losses to follow up reported?			
	Were losses to follow up > 20%?			
	Were other interventions received differentially during follow up?			
	Was missing data (group or time point data) accounted for?			
	Comments			
Eligibility criteria	*Inclusion criteria (pre and post randomization)*			
	Exclusion criteria			
Baseline characteristics			***[control]***	***[study drug]***
	Number randomised			
	Number analysed			
	Age (wks, mos, yrs) (mean, SD; median, range)			
	Male:female n : n			
	Duration of dependence (wks, mos, yrs) (mean, SD; median, range)			
	Age at diagnosis (wks, mos, yrs) (mean, SD; median, range)			
	Newly treated with study intervention, n (%)			
	Previously treated with study intervention, n (%)			
	Frequency of opioid use (/dy, wk, mo) (mean, SD; median, range)			
	N[o: (1,2,3 etc)] concomitant drugs, n (%)			
	Concomitant non-drug treatments, n (%)			
	Previous treatments, n (%) (please specify)			
	Alcohol, n (%) / additional illicit drug use, n (%)			
	HIV positive n (%) / Hepatitis positive n (%)			

	Ethnicity (%)			
	Professional /employment			
	Employed (%)			
	Educational level			
	Marital / other status			
	Comments			
Monitoring and outcomes	*Urinalysis conducted (including study drug)?*			
	Were arrangements to blind urinalysis mentioned?			
	Who recorded outcome?			
	How often outcome measured?			
	Frequency / type of health-care contacts			
	Primary outcome(s) reported including timepoints if repeated			
	Secondary outcome(s) reported excluding Adverse Events			
	Ad hoc' outcomes reported (if emphasised and not in methods)			
	Comments			
Results unadjusted where available			***[control]***	***[study drug]***
	Median follow-up			
	Maintenance dose achieved			
	Withdrawals including reasons where specified study withdrawals and not outcome of opioid withdrawal	*reasons*		
			Results (diff, or by arm)	***CI for difference; p-value***
	outcome(s)	*details to be clarified*		
	outcomes	*details to be clarified*		
	outcomes	*details to be clarified*		
	Comments (including whether unadjusted results reported)			
Adverse Events	*Criteria for reporting*		***[control]***	***[study drug]***

	Events n/N			
	Comments			
Conclusions	*Author's conclusions*			
	Our conclusions			

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11. Timetable/milestones

20 th October 2005 - Progress report (to NCCHTA)
28 th February 2006 - Assessment Report submitted simultaneously to NICE and NCCHTA[H]

[H] Amendment: changed from 10 th February 2006 according to the latest information from NICE (10 AUG 2005)