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

Date: 8th August 2005

1. Title of the project:

Naltrexone as a treatment for relapse prevention in drug misusers.

2. Name of TAR team and 'lead'

TAR Team:

West Midlands Health Technology Assessment Collaboration (WMHTAC)
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3. Plain English Summary

Heroin, and other similar drugs, known as “opioids”, are powerful drugs that can induce a temporary sense of well-being, deliver a boost to self-esteem and make people less sensitive to pain. As people get used to taking such drugs they tend to need more of them to get the same positive feelings. Those taking opioids, whether for recreational use or for a medical condition, may become dependent on them. For people who are dependent on drugs, getting their next dose can become a main focus of their lives.

Drug dependence can have many harmful consequences both for the users and for their families and society. Harms include: an increased risk of infection (e.g. with HIV or hepatitis); a risk of overdose; financial problems; disruption at work; involvement in criminal activities.

It is difficult to stop using drugs because of cravings, unpleasant withdrawal symptoms and the personal circumstances that led to drug use in the first place. Even when a drug user manages to overcome the unpleasant withdrawal symptoms and become drug-free there is a high probability that he or she will return to using drugs within months.

The drug naltrexone works by blocking the effects of heroin and other opioids. It therefore reduces the pleasurable consequences of taking these drugs. It is licensed for use in people who were dependent on drugs and who have become drug free to help them stay off drugs. The blocking effect of naltrexone wears off within days and thus it needs to be taken every day. The idea behind the treatment is that individuals can take naltrexone when they are feeling strong and this will protect them from the effects of using drugs should they have a momentary relapse when they are feeling weak or vulnerable, thereby helping prevent them from becoming addicted again.

This report will look at the scientific research to see how effective naltrexone is at helping people stay off drugs. It will also look at the costs and savings to the National Health Service of giving people naltrexone, to see whether it is a good use of money.

4. Decision problem

4.1 Purpose of the decision to be made

Physical and psychological dependence can occur with any opioid drug, but illicit or ‘street’ heroin presents the greatest problems due to its 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 in treatment 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.

This chronic relapsing nature of drug dependence makes interventions that can help prevent relapse desirable. Naltrexone (Nalorex®, Bristol-Myers Squibb Pharmaceuticals Ltd) is licensed as an adjunctive prophylactic therapy in the maintenance of detoxified, formerly opioid-dependent patients. This report looks at how effective and cost effective naltrexone is when used for this purpose compared to no or other adjunctive treatments. The report also tries to identify whether there are particular subgroups of opioid users and particular settings or care packages in which naltrexone is likely to be more effective or cost effective.

4.2 Definition of the intervention

Naltrexone is an opioid antagonist with a high affinity for opioid receptors. It competitively displaces opioid agonists (e.g. heroin or methadone), blocking the euphoric and other effects of opioid use and thereby minimising the positive rewards of heroin or opioid use. It is taken orally at a dose of 50mg per day.

Naltrexone is used to help the patient prevent a relapse back to opioid use following detoxification. The patients know that if they take the therapeutic dose of naltrexone on a daily basis, using heroin or other opioid drugs will have no effect. Therefore naltrexone can be seen as a form of 'insurance' and a protection against a sudden temptation to use opioids. It will not stop them wanting to use heroin or maintain their motivation to remain abstinent.

Those who take naltrexone regularly after detoxification have high abstinence rates from heroin use. However, the blockade wears off within 48 to 72 hours of discontinuing naltrexone after which heroin will produce its normal physiological and psychological consequences. Issues concerning concordance with the naltrexone regimen are therefore very important.

One problem associated with naltrexone treatment is the increased risk of death from heroin overdose in patients who return to opioid use after being treated with naltrexone. An increase in the risk of death by overdose occurs in recently detoxified, formerly physically dependent, opioid patients. After discontinuing naltrexone, a dose of heroin that the user had been accustomed to inject during their last period of addiction may now prove fatal. Furthermore there is a serious risk of overdose if a patient who has taken naltrexone in the previous few days tries to take larger doses of heroin in order to overcome the blockade and achieve a pleasurable effect.

Naltrexone has been used in the management of opioid dependence since the 1980s to assist relapse prevention following detoxification. More recently, naltrexone has been used as a detoxification medication, for 'precipitated' or 'rapid' detoxification, and in the management of alcohol dependence. This review is only concerned with naltrexone as a relapse prevention agent for opioid dependence.

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

Naltrexone is licensed for use in formerly opioid-dependent drug users.

Since naltrexone competitively binds to opioid receptors, it can precipitate a severe opioid withdrawal reaction if taken while opioid dependent. Therefore it is recommended that naltrexone only be commenced in individuals at least 5-7 days after the last use of heroin, and 7-14 days after the last methadone use. As a precaution against the inadvertent precipitation of withdrawal symptoms, an intravenous or intramuscular naloxone challenge may precede oral naltrexone administration, as this has a shorter duration of action.

The initial dose of naltrexone should be 25 mg (half a tablet) on day one, followed by 50 mg (one tablet) daily from day two onwards. A three-times-a-week dosing schedule may be considered if it

is likely to result in better compliance e.g. 100 mg on Monday, 100 mg on Wednesday and 150 mg on Friday.[1]

Concomitant administration of naltrexone with an opioid-containing medication should be avoided. Patients should be warned that attempts to overcome the blockade may result in acute opioid intoxication which may be life threatening. In an emergency requiring opioid analgesia an increased dose of opioid may be required to control pain. The patient should be closely monitored for evidence of respiratory depression or other adverse symptoms and signs.

It is usually recommended that patients prescribed naltrexone also engage in psychosocial interventions, such as relapse prevention counselling and attendance at self-help groups.

4.4 Relevant comparators:

Maintenance therapy with methadone is the commonest pharmacological method used currently in the UK to help prevent relapse. However, it is not uncommon for people to want to try and remain drug free with no pharmacological support. This report will consider the effectiveness and cost effectiveness of naltrexone for relapse prevention in detoxified formerly opioid-dependent individuals compared to any strategy that does not use naltrexone, including treatment with placebo, other pharmacological treatments, psychosocial interventions, or no treatment.

4.5 Population and relevant subgroups:

Population: Detoxified, formerly opioid-dependent individuals, including both those previously dependent on heroin alone and those on other or multiple opioid drugs (e.g. heroin and methadone).

Relevant subgroups: Naltrexone's success is dependent on good compliance with the drug regimen and it has been suggested that it may be more effective in those with high motivation, such as professional groups like doctors and lawyers who need to remain drug free to continue in their professions. Effectiveness may also be dependent on treatment setting (e.g. prison or the community). See Section 5.4 for full details of all subgroups we propose to look at if there is sufficient data.

4.6 Key factors to be addressed

The primary focus of this assessment will be clinical and cost outcomes from the perspective of the NHS and Personal Social Services in the reference case. The wider societal implications including public health and safety, and costs to the criminal justice system will be considered in a non-reference case.

5. Report methods for synthesis of evidence of clinical effectiveness

5.1 Search strategy

Search strategy for clinical effectiveness

[1] Summary of Product Characteristics (SPCs), Bristol-Myers Squibb Pharmaceuticals Ltd http://emc.medicines.org.uk/emc/industry/default.asp?page=displaydoc.asp&documentid=9281

Existing systematic reviews will be searched for using the ARIF search protocol given in appendix I. Comprehensive searches will be undertaken to identify relevant primary studies. For the clinical effectiveness review the following sources will be searched:

- Bibliographic databases: Cochrane Library (Wiley), MEDLINE(Ovid) and MEDLINE In-Process (Ovid), EMBASE (Ovid), CINAHL (Ovid), PsycINFO (Ovid), Science Citation Index/Social Science Citation Index (Web of Knowledge)
- Research registries of ongoing trials including National Research Register, Current Controlled Trials *meta*Register and Clinical Trials.gov
- Citations of relevant studies
- Relevant internet sources
- Industry submissions
- Further information will be sought from contacts with experts.
- References in selected papers will be followed up

The search will not be limited by date and no language restrictions will be applied. An example search strategy is found in Appendix I.

5.2 Types of studies included

All primary studies of controlled trials of naltrexone use in prevention of relapse in formerly opioid-dependent adults and systematic reviews of analytical observational studies.

5.3 Inclusion and exclusion criteria

5.3.1 Inclusion criteria:

Design:
- Controlled trials of naltrexone
- Systematic reviews of analytical observational studies

Population:
- Detoxified, formerly opioid-dependent individuals

Intervention
- Oral naltrexone

Comparator:
Any (validated or) relevant relapse prevention strategy (pharmacological, psychosocial, etc) without naltrexone used in detoxified formerly opioid-dependent individuals.

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

- **Drug use:**
    - Changes in illicit drug use
    - Proportion of individuals being maintained opioid-free
    - Concordance with and retention to treatment
- **Health of drug user:**
    - Drug-related mortality
    - Drug-related morbidity (e.g. infection rates)

  - Psychological health of drug users
  - Health-related quality of life
  - Use of health care system
  - Adverse effects of treatment
- **Social effects:**
  - Effects on employment
  - Effects on family
- **Effects on criminal justice system:**
  - Rates of crime
  - Recidivism

5.3.2 Exclusion criteria

- Studies of naltrexone treatment outside the licensed indications , subcutaneous implants or parenteral depot preparations.
- Studies of use in alcohol dependence
- Studies looking only at surrogates for any of the above outcomes
- Case reports, case series not included in systematic reviews

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.

5.4 Subgroups to be examined

5.4.1 Related to treatment/setting:

1.Setting, e.g. community, residential, prison
2.Type of prescriber e.g. GP (shared care) or specialist clinic
3.Treatment regimen:

- Dose
- Duration of programme
- Method of induction (e.g. rapid detoxification with naltrexone)
- Supervised/unsupervised

4. Country in which the study was carried out
5. Adjunctive care

5.4.2.Related to individual

1. Age
2. Sex
3. Ethnicity
4. Profession

5. Type of illicit drug use before detox
6. Level of abstinence during detox
7. Psychosocial function at baseline
8. Demographic considerations
9. Co-morbidity or previous treatment
10. Other substance use or dependence (e.g. cocaine, alcohol)
11. Severity and nature of addiction

5.5 Outcomes to be examined

Primary outcomes

- Changes in illicit drug use
- Drug-related morbidity
- Drug-related mortality
- Health-related quality of life

Secondary outcomes

- Proportion of individuals being maintained opioid-free
- Concordance with and retention to treatment
- Adherence to treatment, treatment drop out
- Societal function
- Criminal activity, (Re-) Incarcerations
- Utilisation of health care system.
- Mean duration of treatment
- Serious adverse effects of treatment (e.g. severe depression, abnormal liver function tests, thrombocytopaenia, heroin overdose)

5.6 Data extraction strategy

Data will be extracted independently by one reviewer using a standardised data extraction form (see Appendix II) 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.

5.7 Quality assessment strategy

The quality of the individual studies will be assessed by one reviewer and checked by a second reviewer. Any disagreements will be resolved by consensus and if necessary a third reviewer will be consulted.

The quality of the clinical effectiveness studies will be assessed according to criteria based on NHS CRD Report No.4[2] and the scoring system developed by Gowing and Bornemann.[3]

[2] CRD's Guidance for those Carrying out or Commissioning Reviews. Undertaking Systematic Reviews of Research on Effectiveness. *CRD Report 4 (2'nd edition)* 2001 http://www.york.ac.uk/inst/crd/report4

5.8 Methods of analysis/synthesis

The main results will be reported in tables. Studies will be grouped according to outcome and comparison groups. Where possible the results will be summarised, calculating relative risks and risk differences with 95% confidence intervals for dichotomous outcomes and weighted mean differences and 95% confidence intervals for continuous outcomes. Meta-analysis will be carried out where appropriate. Analysis by subgroups (e.g. settings, patient characteristics) will be explored if evidence allows.

5.9 Methods for estimating qualify of life

The time horizon of our reference case analysis will one year. 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 discount rates of 6% for costs and 1.5% for benefits will be applied in the reference case. A discount rate of 3% for both will be explored in a sensitivity analysis.

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 naltrexone as a treatment for relapse prevention for 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 (Wiley internet version) (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.

Quality assessment for assessments of cost effectiveness will be done using standard criteria.[4,5] 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.

- form of economic analysis
- comparator/s
- perspective

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[3] Gowing L , Farrell M , Bornemann R , Ali R Substitution treatment of injecting opioid users for prevention of HIV infection. The Cochrane Database of Systematic Reviews: Reviews 2004 Issue 4. John Wiley & Sons , Ltd Chichester, UK DOI : 10 1002 /14651858 2004.

[4] Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R, *et al*. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. *Health Technology Assessment* 2004; **8**(36):1-188.

[5] Drummond MF, O'Brien B, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes. 2nd edition. Oxford: Oxford University Press, 1997.

- time horizon
- modelling
- effectiveness data
- health state valuations
- resource use data
- unit cost data
- price year
- discounting

6.2 Economic Evaluation

In order to explore both the effectiveness and the cost-effectiveness of naltrexone as a treatment for relapse prevention for drug misuse programmes, and depending on the results of the 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 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, method of detox, etc) will be explored in sensitivity analysis. In particular, the costs and benefits in different settings (community and prison 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 **26th October 2005**. It will not be possible to consider data arriving after this date.

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.

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

8. Competing interests of authors

None.

9. Appendices

9.1. Appendix I Naltrexone search strategies

a) Systematic reviews

Database: Ovid MEDLINE(R) 1966 to present
Sample Search Strategy:

1 naltrexone.mp. or exp NALTREXONE/
2 nalorex.mp.
3 revia.mp.
4 naloxone.mp.
5 or/1-4
6 substance abuse$.mp. or exp Substance-Related Disorders/
7 exp Opioid-Related Disorders/ or opioid$ abuse$.mp.
8 (opioid$ or opiate$) dependence.mp.
9 (opioid or opiate$) addict$.mp.
10 (opioid or opiate$) abuse$.mp.
11 exp Heroin Dependence/ or heroin addict$.mp.
12 (maintenance adj2 abstinence).mp.
13 (relapse adj2 prevent$).mp.
14 exp Substance Withdrawal Syndrome/ or substance withdrawal$.mp.
15 or/6-14
16 5 and 15
17 (systematic adj review$).tw.
18 (data adj synthesis).tw.
19 (published adj studies).ab.
20 (data adj extraction).ab.
21 meta-analysis/
22 meta-analysis.ti.
23 comment.pt.
24 letter.pt.
25 editorial.pt.
26 animal/
27 human/
28 26 not (26 and 27)
29 16 not (23 or 24 or 25 or 28)
30 or/17-22
31 29 and 30

b) Example of a filter for randomised 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$.ti,ab.
16 placebos.sh.
17 research design.sh.
18 or/10-17
19 18 not 8
20 19 not 9
21 comparative study.sh.
22 exp evaluation studies/
23 follow up studies.sh.
24 prospective studies.sh.
25 (control$ or prospective$ or volunteer$).ti,ab.
26 or/21-25
27 26 not 8
28 27 not (9 or 20)
29 9 or 20 or 28

c) 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 guideline**s (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

9.2. Appendix II Data extraction form

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 (ITT only; 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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N.B. **All correspondences should be sent to the senior reviewer, the main reviewer, the project administrator and WMHTAC Senior Manager:**

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Timetable/milestones

Event	**Deadline / Date**
Team submit draft protocol to NCCHTA	18 July 2005
Expected date of NICE comment on draft protocol to team	1 August 2005
Team submit revised/finalised protocol to NCCHTA	8 August 2005
Consultees meeting	10 August 2005
NICE send industry submissions to the team	26 October 2005
Team submit progress report to NCCHTA	2 November 2005
Team send complete-near-final draft assessment report to referees and NICE	7 January 2006
Team submit assessment report to NCCHTA	28 February 2006
Assessment report consultation	March 2006
1st Appraisal committee meeting	7 June 2006
ACD consultation	June 2006
2nd Appraisal Committee meeting	6 September 2006
Anticipated launch	March 2007