NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Methadone and buprenorphine for the management of opioid misuse

Response to consultee and commentator comments on the ACD

CONSULTEE	COMMENTS	RESPONSE
RCN	Nurses working in this area of health have reviewed the Appraisal Consultation Document for the use of methadone and buprenorphine for the management of opiod dependence. They consider the document very comprehensive and have nothing further to add on behalf of the Royal College of Nursing at this stage.	Comment noted.
WAG	Thank you for giving the Welsh Assembly Government the opportunity to comment on the above appraisal consultation document. We are content with the technical detail of the evidence supporting the provisional recommendations and have no further comments to make at this stage.	Comment noted.
Schering-Plough	Schering-Plough welcomes this opportunity to respond to the Appraisal Consultation Document. Overall we are pleased with the preliminary guidance, and are confident that the ACD reflects the best interests of patients and the NHS in ensuring treatment choice and appropriate use of methadone and buprenorphine. On this basis, it is our view that the provisional recommendations are sound and constitute a suitable basis for the preparation of guidance to the NHS.	Comment noted.

NHS QIS (reviewer 2)	This a comprehensive and complete (as far as I am aware) report of the evidence for the cost effectiveness of both methadone and buprenorphine in the management of opioid dependence and the conclusions appear fully supported and justified. In the current climate, some comment about the needs to keep both agents out of inappropriate hands (particularly of children) might be helpful. The advice will be equally valid in Scotland as in England and Wales if the final appraisal reached the same conclusions.	Comments noted. The issue of diversion was considered, see sections 4.3.2, 4.3.5 and 4.3.6.
Department of Health, Social Services and Public Safety	The preliminary recommendations and document provide an excellent guidance on the management of Opiate Substitution. However, I have **very significant concerns about the preliminary recommendation 1.2 particularly the statement that Methadone should be prescribed as first choice**. This statement in an era of major pre-occupation with safety and serious adverse incidents and fatalities does not take account of the very significant and major intrinsic safety features and differences between Methadone and Buprenorphine. There is a particular duty to take this into account when introducing Opiate Substitutes into new populations and new services as in the Northern Ireland context. I disagree due to the major differential regarding safety between the two drugs. I disagree with the committee recommending that Methadone should be prescribed as first choice as this prejudices and discriminates against establishing the equally effective and much safer medication. This statement is contrary to many ethical and philosophical considerations in the clinical practice of medicine. I also wish to draw the committees attention to the concern that in making this statement they have not given sufficient consideration to the risk to more chaotic high risk individuals, children of addicts, and the wider community from diversion of Methadone in particular. Regarding recommendation 1.3, I disagree with the wording, in that it	Comments noted. The Committee carefully considered the safety of methadone and buprenorphine (see FAD section 4.3.2, 4.3.5 and 4.3.6). It concluded that new prescriptions of both drugs should be administered under supervision and that the risks and benefits of treatment specific to each individual (and their family) should be considered when initiating treatment. Recommendations 1.2 and 1.3 have been revised to clarify this. The Committee further concluded that, after taking these considerations into account, where there is little difference between the two drugs, methadone was the cost effective treatment and should be prescribed as first-choice (see FAD Sections 1.2 and 4.3.8).

	fails to emphasise the greater risk and greater need for adequate supervision of Methadone due to its greater toxicity. The consequences of these recommendations is that the progressively increasing number of individuals on opiate substitution will inevitably lead to increasing numbers unsupervised due to capacity limitations. While services strive to implement the ideal of "adequate supervision" the limits of capacity results in more and more unsupervised prescribing. The safety of buprenorphine in these situations is increasingly important and should influence choice. The following facts regarding the two medications is crucial and pivotal when considering recommending choice in prescribing. These facts have been insufficiently highlighted in the draft document: 1. The **intrinsic dangerousness of Methadone** as illustrated by the fact that in England and Wales during the mid 1990's (1994-97) the Office for National Statistics ONS recorded twice the number of drug related deaths due to Methadone compared to heroin. The "Reducing Drug Related Deaths Report" notes there were 674 Methadone related deaths in 1997. This dangerousness is heightened in those addicts in poor physical health, engaging in polydrug abuse and with other diseases. This intrinsic dangerousness is also well illustrated in the Australian literature by Caplehorn and Drummer MJA 1999 . This Australian literature especially highlights the dangerousness of Methadone in new, inexperienced or rapidly expanding services. 2. The **inherent safety of Buprenorphine** even in overdose or when diverted to others is a marked contrast to the dangerousness of Methadone. This is illustrated by the French field experience Auriacombe M. et al. It is also	

evidenced at the conclusion of Ling's Review. The contrast in safety profile between the two medications is striking.

The rationale for prescribing Buprenorphine as a first choice treatment especially in a new service and in a new population is as follows:

The rationale in a new service for using buprenorphine as the first line opiate substitute treatment, is safety, for the individuals, for any young children they may have and the community they reside in. This safety benefit is most realised in the event of overdose on opiates, or diversion to individuals not on opiate substitution. This enhanced safety is based on the following;

- The intrinsic safety of buprenorphine in overdose compared to the inherent dangerousness of methadone. This is increasingly acknowledged by all the literature.
- If buprenorphine is diverted, its risks to the community are significantly less than methadone due to its relative inherent safety.
- The opiate receptor blocking effect of buprenorphine reduces the motivation and impulse to use other opiates "on top" as euphoria is not experienced. This reduces the associated risks of additional intravenous or oral consumption.
- The less addictive quality of buprenorphine compared to methadone with consequent ease of detoxification of patients who decide eventually to abstain. It is therefore less likely to promote an ever increasing cohort of individuals with little realistic option but to be retained in opiate substitution.

- The ‘clearer consciousness’ afforded by buprenorphine thereby increasing likelihood of normalising social and occupational functioning.

In contrast the risk to the community of using methadone first line is the accumulation of an increasing cohort of patients on methadone substitution who will only with considerable motivation and determination be able to detoxify and rehabilitate themselves, even if they wish to. This accumulating cohort is also a potential source of diversion, of the inherently dangerous and marketable methadone to the rest of the community. This negative potential is illustrated by the widespread availability of Methadone throughout all centres in the UK where it is used for Opiate Substitution.
The mortality figures for Methadone related deaths in these areas highlight this concern.
Even with active supervised consumption of Methadone, more and more patients progress to weekly or fortnightly take home Methadone.

The choice of buprenorphine first line may be a departure from current practice in most of the UK, however in addition to its pharmacological benefits there are clear justifications for adopting this first line choice in the context of developing new services, as is the experience in N.I. These are as follows:

- New services are establishing, fortunately at a time when an equally effective and much safer medication is available.
- A new service where methadone use is not widespread or entrenched does not have to overcome resistance to change among large numbers of current patients.
- The duty to avoid the introduction of a potentially lethal

opiate, to a methadone naïve population, when a much safer one is now available.

- Realising the safety advantages of a safer medication while developing and training a new opiate substitution team and service.
- In practice, the first line choice of buprenorphine is a reality in three of the five new services in Northern Ireland, where a historical reliance on methadone prescribing is not established. The other two services are prescribing in excess of 40% buprenorphine. In France buprenorphine is also first line for opiate substitution with well recognised mortality benefits. In other parts of the UK where there are new services the prescription of buprenorphine is rapidly rising despite the traditional reliance and enthusiasm for methadone. This is illustrated in the research report "The Rise of Buprenorphine Prescribing in England: Analysis of NHS Regional Data, 2001-03 (Addiction 100, 495-499)".

The preliminary recommendations do not sufficiently highlight and illustrate some of the characteristics of buprenorphine which significantly influences its appeal as a first line treatment for opiate substitution. These were usefully articulated in the research report "The Rise of Buprenorphine in England: Analysis of NHS Regional Data, 2001-2003". Cornelis J. de Wet (Addiction 100, 495 – 499. 2005)

"It is safer in overdose, and as such is more suitable for prescription outside specialist drug treatment centres, particularly in primary care. Preliminary studies suggest that Buprenorphine has fewer side effects than Methadone at therapeutic doses, and adverse reactions are rare. Owing to its long half life patients can be maintained on alternate day dosing, and following tapered withdrawal treatment patients

can be transferred to Naltrexone almost immediately. Like Methadone, Buprenorphine can be diverted but its slow onset and propensity to precipitate withdrawal make it a less attractive drug of misuse to use out of treatment. When it has been implicated in overdose deaths, it is usually in the context of polysubstance misuse. It is relatively safe during pregnancy and breastfeeding, and neonatal withdrawal may be less frequent, less severe and of shorter duration. Buprenorphine may also have a more positive reputation among drug users and attract more into treatment than traditional Methadone treatment."

Additional characteristics of note are that buprenorphine is less addictive with a lower addictive potential compared to methadone. There is greater ease and speed of detoxification from buprenorphine compared to methadone which is highly addictive and requires a prolonged and highly motivated process for detoxification and withdrawal. The incentive to use other opiates "on top" of buprenorphine is lower as it blocks the opiate receptors and prevents euphoria. Methadone by contrast particularly in low or moderate dosage allows the addict to experience euphoria when other opiates are used "on top" of the methadone. This characteristic of methadone increases the possibility of the continued or intermittent abuse of **heroin**.

The draft guidelines also fail to make explicit the high risk associated with fatalities from the combined misuse of methadone, illicit opiates, high dose benzodiazepines and alcohol. The high risk of overdose and drug related mortality associated with this pattern of drug misuse is singled out for special concern and advice in the ACMD "Reducing Drug Related Death" 2000 publication. There is no acknowledgement, that in chaotic individuals the risk of death by

	overdose will be reduced by the choice of the safer buprenorphine. The pharmacological basis of this is the inherent safety of buprenorphine and the opiate receptor blocking effect it has. This will be protective if other illicit opiates are consumed. In addition this opiate receptor blocking effect and the lack of euphoria will discourage continued use of other opiates "on top" of the buprenorphine. The problem and the dangers of continued use of illicit opiates "on top" of opiate substitution is illustrated in the South London studies where the problem of continued daily use of heroin occurs in 31% of patients on methadone maintenance. This continued daily or monthly use of heroin while on methadone is one of the most salient reasons for choice of buprenorphine rather than methadone. Safety is a major consideration, especially in the more chaotic individuals engaging in multiple and combined drug and alcohol misuse. The recommendation that methadone rather than buprenorphine should be prescribed first choice is contrary to the natural history and progression of medicine, in that medicines with more risk and side effects are gradually superseded, when equally effective and safer ones become available. A recent example of this is the withdrawal of the analgesic Co-proxamol by The Chairman of the Committee on Safety of Medicines. This widely used analgesic has been recently withdrawn from use due to its unacceptable toxicity in overdose and especially in combination with alcohol (Ref CEM/CMO/2005/2). Although patient preference has an important place in prescribing decisions, considerations of risk should be the paramount factor. In the draft document there appears to be very little emphasis placed on individual assessment of risk, as is considered an urgent duty by the ACMD report (para 8.23 – 8.27 Para 10.8 and 10.11)	

	Paragraphs 10.8 and 10.11 call for a change in culture of services, with complacency unacceptable The report condemns as deeply unsatisfactory the lax system which permits the prescribing and dispensing of methadone so that it spills to the illicit market, and the too generous prescribing of benzodiazepines. Deaths due to methadone may fairly be described as a cause for national reproach. Prescribers must acknowledge a responsibility towards their communities as well as toward the individual drug user. Actively motivating and educating patients to accept the safest and least addictive medication should be a priority. The avoidance and prevention of methadone deaths in the community, is the motivation for the adoption of buprenorphine as first line opiate substitute and not explicitly stating as in this draft, that methadone should be prescribed first choice. The risk of methadone and buprenorphine to children is another important consideration. Again the marked contrast in the literature and incident reports regarding these two medications and risk of children, needs to be taken into account. *All the key policy documents draw attention to the annual occurrence of accidental poisoning of children who swallow methadone prescribed for their parents or carers.* • *ACMD para 7.12* • *NTA Guidance or treatment providers* • *NTA Guidance for Commissioners para 3.1* *By contrast Gaulier in a case report to Clinical Toxicology Vol 42, No. 7, 2004 concludes that a 4 year old child's accidental swallowing 4 mg of buprenorphine, suffered only mild consequences.*	

	Eastwood, (London England 1998); gives a description of 13 children poisoned with methadone syrup prescribed to a parent, 5 died. Methadone serum concentrations in children who died overlapped that in children who survived. Although this draft report recommends that methadone should be prescribed as first choice, alternative and contrary opinions are being clearly and urgently expressed in the leading UK medical literature. BMJ editorial 10th December 2005 **Is methadone too dangerous for opiate addiction? The case for using a safer alternative, buprenorphine, is strong.** This editorial concludes "*Nevertheless, the safety of buprenorphine in overdose is a significant advantage over methadone, especially considering the continued failure to prevent diversion of these agents on to the black market*." Ref . de Wet, Reed and Bearn (2005) Addiction 100 **The rise of buprenorphine prescribing in England: analysis of NHS regional data, 2001-03.** This research paper concludes: *"Buprenorphine prescribing has increased dramatically and represents a disproportionately large fraction of community opiate prescribing costs. The marked regional variation suggests the need for further research and the development of national guidelines to support rational prescribing and equitable access to treatment."* It seems rational and logical that buprenorphine should be the mainstay of opiate substitution especially in new services for very sound reasons of safety and avoidance of any methadone related mortality.	

	Outside the UK, in the USA, the US Department of Health and Human Services has published a detailed Treatment Improvement Protocol "Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction (Ref www.samhsa.gov). **The rise of buprenorphine prescribing is clearly evident in the new services in Northern Ireland. It is also evident in the newer services in England and especially where problems with Methadone mortality are encountered. This rise is set to continue with the increasing realisation of its safety benefits. Recommending methadone first choice is contrary to the growing concerns re safety.**	
Clinical expert	1.2 Don't agree, would remove 'whether the patient's aim is to become abstinent,…'	Comment noted. Recommendation 1.2 has been revised.
Clinical expert	1.3 Important to state supervision if for 'When commencing treatment, Methadone and buprenorphine should be administered under adequate supervision. Also the care programme should also include physical health care.	Comments noted. Recommendation 1.3 has been revised. No evidence on interventions to promote physical care were presented or discussed at the Committee meeting.
SCAN	2.1 – It is not correct to say that opiate dependence causes spread of blood borne viruses or overdose – better to say 'may be associated with'.	Comment noted. Section 2.1 has been revised.
Clinical expert	2.1 Would add 'depression' to comorbidity conditions - Reference Dean EUROPEAN Psychiatry 2004 19 (8) 510-513	Comment noted. Depression is included within affective disorders.
Clinical expert	2.2 Important to add most drug users would not be criminals.	Comment noted. Section 2.2 has

		been revised.
BAPS	2.3 –Could NICE quote ICD-10 criteria as well DSM criteria which would be more familiar to the UK audience? We do understand that most studies will have employed DSM criteria so does have to be described.	Comment noted. Section 2.3 has been revised to include ICD-10 criteria.
Department of Health, Social Services and Public Safety	2.3 The phrase "opioid use quickly escalates to misuse" may give the misleading impression the illicit opioid use in the initial stages is not perceived to be 'misuse'.	Comment noted. Section 2.3 has been revised.
BAPS	2.4 – The first sentence is not clear since if a patient is relapsing, they are no longer abstinent. An alternative would be to say that 'when an opioid dependent person manages to become abstinent, there *have been usually previously "repeated cycles of cessation and relapse, with extensive treatment history spanning decades".*	Comment noted. Section 2.4 has been revised.
Clinical expert	2.4 Add after illicit opioid misuse, allowing health and social circumstances to improve.	Comment noted. Section 2.4 has been revised.
SCAN	2.5, line 6 – it is not correct to say most people in treatment are there because of the availability of substitute medications. It would be more accurate to say that psychosocial treatments are poorly developed and delivered for illicit substances but contrast this to services for people who misuse alcohol where there are huge numbers in treatment but no substitution therapy.	Comment noted. Section 2.5 has been revised. The purpose of this sentence is to highlight that of those people in drug treatment services most are dependent on opioids.
Clinical expert	2.5 'Because of the lack of substitute medications for other drugs'. This is extremely simplistic about treatment (and many working in alcohol services would be really unhappy with you! – treatment is much more than substitute medication. I would remove and change to something like 'Secondary treatment services were set up when there was an explosive of heroin use first in 60s and again in 80s when there was little cocaine and other drugs around. Most treatment services have been slow to adapt to the changing drug scene.	Comment noted. Section 2.5 has been revised. The purpose of this sentence is to highlight that of those people in drug treatment services most are dependent on opioids.

Clinical expert	2.5 Add although the percentage of woman presenting to treatment in primary care is greater	Comment noted. Section 2.5 has been revised to not be specific regarding treatment settings.
SCAN	2.6 Can we have dependence throughout the document – a dependency is a small country.	Comments noted. Medical editors have advised that the term dependency can be used.
BAPS	2.7 – This section is quite muddled. Abstinence **is not** also known as detoxification and withdrawal. In order to become abstinent an individual usually undergoes a process of detoxification and withdrawal. In addition for opiate dependence, we suggest separating abstinence from detoxification since they are different stages of treatment / addiction. Interventions can be different for abstinence and withdrawal and detoxification. Lastly, in opiate dependence, substitution is generally followed by detoxification and then abstinence. We would suggest the following amendment: 'Pharmacological treatments are broadly characterised as substitution or maintenance (also know as harm reduction and involves a substitution regimen), detoxification or abstinence. Abstinence means that a person has stopped taking that drug. Whilst abstinence generally refers to an individual stopping all drugs, ie. Including their substitute drug, abstinence may be used when the person is now abstinent from their 'street' or illicit drugs. Therefore when talking about abstinence one may need to qualify whether it is total abstinence from all drugs or from their 'street' drugs. The total abstinence definition is preferred. The following sentence which starts: 'In abstinence strategies, a person…' needs to be changed since abstinence strategies are to maintain abstinence not to stop taking a drug, this is the definition of detoxification. We would suggest the following rewording:	Comments noted. Section 2.7 has been revised.

	'In order to become abstinent a person must undergo detoxification or withdrawal from the drug. Once abstinent, there are several strategies available to prevent relapse.'	
Department of Health, Social Services and Public Safety	2.7 The ease of eventual progression to abstinence therapy is an important factor in the initial choice of opiate substitute. The flexibility, shorter time scale for withdrawal, and reduced withdrawal effects of buprenorphine are all clinically crucial factors for choice of buprenorphine in patients who eventually wish to progress to abstinence. These factors in the midterm and long-term will also have economic cost effective benefits.	Comments noted.
Clinical expert	2.7 Add in definition of maintenance as: (a fixed dose to reduce and stop illicit use), or abstinence (also known as detoxification and withdrawal). Also add in 'All need relapse prevention strategies and psychological support after detox as relapse rate (and hence mortality) is high.'	Comments noted. Section 2.7 has been revised.
SCAN	**2.8** – the term 'maintenance' seems to be used as if synonymous with substitute prescribing. I think the use of terminology is somewhat lax in the UK. My personal preference is to refer to reducing substitution therapy where there is an intention, albeit long term, to effect stepwise reductions of medication and ultimately achieve abstinence. Maintenance on the other hand suggests that there is no intention to reduce and that substitute prescribing is indefinite. The practical implication is that those on reducing regimens will continue to receive active psychosocial interventions, broadly aimed at changing lifestyles and dealing with psychological problems, while those on maintenance regimens will be seen infrequently and not receive active psychosocial interventions. The cost implications will be significant.	Comment noted.
Clinical expert	2.8 '…enabling the person to make use of psychosocial interventions.' Not sure if this is true.	Comment noted. Section 2.8 has been revised.

Clinical expert	2.8 Add in 'Maintenance is also safer than detoxification and the death rate is lower.	Comment noted. This appraisal did not consider the safety of maintenance versus detoxification.
Department of Health, Social Services and Public Safety	2.9 The recommendation regarding supervision of the first three months only, acknowledges that many or most patients rapidly progress to being unsupervised. This practice is an important reason for the choice of the much safer substitute buprenorphine, especially in community and primary care settings.	Comments noted. Section 2.9 has been revised to more fully reflect the Department of Health guidelines for the UK.
Clinical expert	2.11 'average dose of methadone 50mg/day'. This is not a maintenance dose! Good Maintenance is between 60-120 Patients on <60 are twice as likely to leave treatment as those on 60-80 and 4x as likely as those on >80	Comment noted. Section 2.11 has been revised.
Clinical expert	2.11 'average dose of buprenorphine 10mg/day'. Either is this! At this level almost no blockage effect	Comment noted. Section 2.11 has been revised.
Department of Health, Social Services and Public Safety	2.11 The approximate 5:1 ratio of Methadone to buprenorphine use relates to historical factors such as the timing of licensing of the opiates substitutes and established clinical habits and practice, rather than the effectiveness of the respective medication. The rapidly growing use of buprenorphine is related to the increasing recognition of its superior safety profile and ease of clinical manourverability.	Comments noted.
Department of Health, Social Services and Public Safety	3.2 The statement that the usual maintenance dose range is 60-120mg daily is not consistent with the assumption of an average dose of 50mg per day in paragraph 2.11 above.	Comments noted. Section 2.11 has been revised.
Clinical expert	3.2 Need to explain why Methadone increased by up to 10 mg daily (with a maximum weekly increase of 30mg *because of the delay to reach steady state)*. Also need to add. Methadone is also available as concentrated solution, tablets and injectable ampoules. Only the oral form of	Comment noted. Section 3.1.2 is taken directly from the British National Formulary.

	methadone is considered in this appraisal.	Section 3.1.3 has been revised accordingly.
Clinical expert	3.3 Add length half-life(usually 20-37 hours),	Comment noted. Section 3.1.3 has been revised.
Clinical expert	3.4 Would remove 'The risk of death during methadone initiation has been calculated as nearly seven times greater than the risk of death before entering maintenance treatment.' And replace with 'The risk of methadone deaths in early treatment due to excessive initial doses, failure to recognise cumulative effects, effects of chronic hepatitis and / or failure to inform patients of dangers of overdose, especially when using other drugs as well'.	Comments noted. Section 3.1.4 has been revised.
Clinical expert	3.7 Never use starting doses of 0.8 – usually 4-8 mg, adjusted according to response. Also need to add explanation that nitiation of buprenorphine is very different than methadone and can be done swiftly and safer.	Comment noted. Section 3.2.2 is taken from the SPC for buprenorphine. No change.
Clinical expert	3.8 Add in about injecting ''One important problem is its abuse potential from injecting, which is currently running at about 30% in France where there is very little supervision. Suboxone (buprenorphine and naltrexone) has been used in US and will be introduced in UK to help prevent this.	Comment noted. Section 3.2.3 has been revised. The remit for this appraisal was for methadone and buprenorphine. Suboxone does not have a marketing authorisation for use in the UK.
Royal College of Psychiatrists	No comment is made regarding the possible crushing and illicit injection of oral buprenorphine, which has been described in the literature.	Comment noted. Section 3.2.3 has been revised.
Clinical expert	3.8 Not sure there is the evidence for this statement 'For this reason buprenorphine may be better suited to people who wish to cease using illicit diamorphine completely'.	Comment noted. Section 3.2.3 has been revised.
Clinical expert	3.8 'buprenorphine may precipitate symptoms of withdrawal because…' IMPORTANT ONLY COMMENCING DOSE	Comment noted. Section 3.2.3 has been revised.

Department of Health, Social Services and Public Safety	3.3-3.9 The content of these paragraphs illustrate the striking contrast between the inherent dangerousness of Methadone and the intrinsic safety of buprenorphine especially in unsupervised consumption which most individuals progress to eventually. On consideration of safety the recommendation in 1.2 that Methadone should be prescribed as first choice seems perverse and contrary to patient, child and community safety obligations. Regarding economic considerations the apparently greater cost of buprenorphine will be offset in the middle and long-term by the need for less frequent consumption (3 days per week) and less safety concerned about unsupervised consumption. These middle and longer term economic considerations appear not to have been built into the cost effectiveness assessment.	Comments noted. Recommendations 1.2 and 1.3 have been revised to reflect that there should be a consideration of risk. Also see sections 4.3.2, 4.3.5, 4.3.6 and 4.3.8 for the Committee's consideration of these points. Section 4.2.17 outlines one of the sensitivity analysis that the Assessment Group. Methadone was clinically more effective and cheaper than buprenophine even when buprenorphine was delivered unsupervised on alternate days.
BAPS	3.8 – This section is muddled and not entirely accurate. Buprenorphine has a relatively good safety profile when alone because it is a partial agonist at the mu opioid receptor. It is this subtype that mediates respiratory depression and euphoria. Unlike drugs such as methadone or diamorphine, even when all the receptors are occupied by buprenorphine, respiratory depression does not occur. It is for this reason therefore that taken *alone* it has a better safety profile than methadone or diamorphine. This is not the case when taken with other drugs such as alcohol and benzodiazepines. There is no such thing as a partial antagonist. Buprenorphine has an antagonist action when buprenorphine is given to people already on opioids due to its partial agonist activity. Because buprenorphine only activates the receptor partially, if the receptor has been	Comments noted. Section 3.2.3 has been revised.

	maximally stimulated by another opioid eg. diamorphine and because buprenorphine has a higher affinity with the receptor, the diamorphine will be removed form the receptor thus causing withdrawal. In this section buprenorphine's antagonist activity, the kappa subtype is not described; this is thought to be important in reducing dysphoria. We suggest the following rewording: Buprenorphine also has a relatively good safety profile. Doses many times greater than normal therapeutic doses rarely appear to result in clinically significant respiratory depression due to its partial agonist activity at the receptor (mu) involved. The safety of buprenorphine mixed with high doses of other sedative drugs such as alcohol or benzodiazepines is still unclear, though mortality statistics seem to indicate that it is less harmful than full agonists such as heroin and methadone. In people dependent on high doses of opioids, buprenorphine may precipitate symptoms of withdrawal because it displaces these opioid agonists from the receptor and since it is a partial agonist stimulates the receptor less, resulting in withdrawal. In addition whereas methadone is an agonist , buprenorphine is an antagonist at the subtype involved in mood (kappa) potentially resulting in less dysphoria.	
SCAN	**3.8, line 3** – high doses of methadone also have a receptor blockade effect – that is the point of the high dose. So, both medications work at a psychological level by reducing the positive reinforcement of other opiates. See also pg15, para 2 below.	Comment noted. Section 3.2.3 describes specifically buprenorphine.
SCAN	**3.8, line 11** – better to say using other opioids rather than dependent on high doses.	Comment noted. Section 3.2.3 has been revised.

Department of Health, Social Services and Public Safety	4.0-4.1.24 Regarding the interpretation of Methadone and buprenorphine maintenance outcome research it is important to appreciate that outcome studies and reviews report on the **proxy** measure of the ability of Methadone to **retain patients in Methadone maintenance**. They provide very limited evidence of reduction in mortality and no evidence regarding mortality from Methadone in the overall population or in chaotic high-risk sub groups. This overall mortality from Methadone, and other drugs and alcohol combined with Methadone, was the central concern of the ACMD "Reducing Drug Related Deaths" report in 2000. The over-reliance on the proxy measure of retention in Methadone maintenance is obscuring the overall mortality figures for Methadone relative to buprenorphine. This has heightened significance especially in chaotic high-risk subgroups and particularly in those not retained in treatment or never involved in treatment. It must be considered that the ability of Methadone to retain individuals in treatment partly relates to its more highly addictive properties and the major difficulty and lengthy effort involved if one decides to detoxify or abstain. To summarise with a familiar metaphor; the trees of the proxy measure (retention in Methadone maintenance) is obscuring the wood of mortality risk from Methadone. The relevance of the good safety profile of buprenorphine briefly mentioned in paragraph 3.8 needs more detailed consideration especially in relation to realising its benefits in reducing risk to individual addicts (either in or out of treatment), children and the wider community. When these safety benefits are given due consideration it is very difficult to justify recommending the more toxic and dangerous Methadone as 1st choice as in paragraph 1.2. The French field experience with buprenorphine is particularly relevant to this issue of mortality.	Comments noted. The two main outcome measures as reported by the systematic reviews and RCTs are retention in treatment and illicit opioid use. Issues of mortality were discussed by the Committee see sections 4.3.2, 4.3.5, 4.3.6 and 4.3.8.

Clinical expert	4.1.5 Outcomes reported would suggest adding 'greatly reduced mortality' many refs but 16 times less like to die is one of main reasons we do it!	Comment noted. This refers to the main outcomes as reported in the trials.
Clinical expert	4.1.18 Higher doses of MMT (50 mg or more) – evidence is for 60 mg	Comment noted. Section 4.1.18 has been revised.
Clinical expert	4.1.19 Add MMT and BMT appeared to be similarly effective whether delivered in primary care or in outpatient clinics at the beginning.	Comment noted. Section 4.1.19 has been revised.
Clinical expert	4.1.19 'contingency interventions' There is NO evidence from UK and US drug system is so different I would remove.	Comment noted. This is a summary of the trial outcomes. Discussion of trials not being in UK settings is included in other considerations section 4.3.3.
NHS QIS	I am always intrigued that in such a systematic and thorough piece of work, comments such as 4.1.24 sneak in. For me this simply promotes agendas/myths about these substances and is not helpful.	Comment noted. Section 4.1.24 has been removed.
NHS QIS	I think the broad summaries of clinical findings make sense in light of the evidence covered. I am intrigued by some of the financial models which imply that supervision is not an issue in the long term and also that less than daily dispensing is a realistic option. My own interpretation of the evidence to date suggests that less than daily dispensing is still required in most cases on Buprenorphine. Also, in Scotland, where the introduction of Subutex was delayed considerably because of the concerns around Temgesic misuse in the past, supervision is likely to be a considerable issue – and will have resource implications.	Comments noted. The costs associated with supervision were included in the economic model (see FAD section 4.2.12) Recommendations 1.2 and 1.3 have been revised. Sections 4.3.2, 4.3.5, 4.3.6 and 4.3.8 outline the Committee's consideration of these points.
Department of Health, Social Services and Public Safety	4.2 Cost Effectiveness: Given the committee's comments in 4.3.2, about the uncertainty around the risk of mortality and the potential increased risk of death for people using Methadone compared with buprenorphine, and the	The Committee carefully considered information on the effectiveness and risks associated with the treatments. It concluded that after taking into

	comments in 4.3.7 that Methadone yields only marginally more QALYs, it is contrary to the usual quality and safety standards, and also to good sense, that the committee would seek to reinforce the dominance of Methadone prescribing by stating that it should be 1st choice in paragraphs 4.3.9 and 1.2. The main justification for this expressed choice appears to be "cheapness". The human and economic costs of accumulating large cohorts of patients on highly addictive and potentially lethal Methadone (mostly, realistically unsupervised in practice) has not been given insufficient and appropriate weight.	consideration the individual patient's characteristics, including the estimated risks and benefits, where there is little difference between the two drugs methadone should be first choice on grounds of cost effectiveness. Sections 4.3.2, 4.3.5, 4.3.6 and 4.3.8 outline the Committee's consideration of these points. Recommendations 1.2 and 1.3 have been revised.
SCAN	4.3.2 **pg21, line 8** – the problem of supplementing prescriptions of methadone is likely to be greater than that for buprenorphine simply because individuals who are receiving methadone are likely to be doing so because they seek a drug effect. The question of what is failed substitution therapy is rarely addressed in the UK. There are difficult clinical decisions on what to do when someone on a substitute prescription switches from illicit heroin use to supplementing their prescription with cocaine, alcohol, or benzodiazepines.	Comment noted.
NHS QIS	Generally they're sound and acceptable. 4.3.8/4.3.9 do not I feel reflect an objective analysis of the evidence presented and will give the impression to those lobbying for Subutex that it can be demanded through "patient choice" or some spurious notion of safety. In Scotland we have very limited access to basic methadone programmes. There is an active anti-methadone lobby who are promoting any alternative – Subutex is clearly one on many people's minds. In cost-effectiveness terms on the ground, for services – ie not global overall health economic terms – the introduction of Buprenorphine will reduce the capacity of prescribing services in cost	Comments noted. Recommendations 1.2 and 1.3 have been revised. Sections 4.3.5, 4.3.6 and 4.3.8 outline the Committee's consideration of these points.

	terms alone (drug, dispensing and supervision costs). If this is not aligned with significant additional costs (2-3x increases in drug costs alone) NHS organisations will face considerable pressures on budgets which are already capped in some areas. I feel these statements should be reflected on and the real costs taken into account.	
Department of Health, Social Services and Public Safety	In 4.3.10, it has not been sufficiently highlighted that with buprenorphine there is much less potential risk of death due to diversion or inadequate supervision.	Comment noted. Recommendations 1.2 and 1.3 have been revised. Section 4.3.2, 4.3.5, 4.3.6 and 4.3.8 outline the Committee's consideration of these points.
Department of Health, Social Services and Public Safety	5.0 **Implementation** It is alarming and inappropriate, given the uncertainties regarding mortality that the committee has stated that Methadone should be prescribed 1st choice. Given core standard C5 it is alarming that health care organisations may well interpret this as a duty to ensure the dominance of Methadone, the more toxic, addictive and lethal substitute. The prospect in particular of new opiate substitute services being obliged to ensure that they conform to the recommendation that Methadone should be the treatment of choice raises many ethical, philosophical and legal issues. In setting up new services the justifications for preferring the equally effective and much safer buprenorphine are responsible, prudent and informed by the perspective of hindsight of established services, with high Methadone use and high drug related mortality in various regions of the UK. These justifications include;	Comments noted. Recommendations 1.2 and 1.3 have been revised. Sections 4.3.2, 4.3.5, 4.3.6 and 4.3.8 outline the Committee's consideration of these points.

	• The inherent dangerousness of Methadone compared to the intrinsic safety of buprenorphine regardless of what system of supervision is adopted. • The overall recognition in the literature review is that there is very little difference between the effectiveness of buprenorphine and Methadone in treatment. • The recognition from the French field experience and the clinical pharmacology of buprenorphine, that it is much safer for high-risk subgroups and especially safer in the event of overdose of opiates. • The public health benefit of avoiding the introduction of the problem of diverted Methadone into a Methadone naïve community. • The public health and community benefit of avoiding risk to young families with Methadone especially where both parents or young mothers require opiate substitution. • The inalienable responsibility which lies with the individual prescribing doctor to give all medications responsibly. This is especially pertinent when a safer equally effective medication is now available. This applies to every other branch of medicine where safer treatments supersede and gradually replace more dangerous existing ones. • The observation in the New South Wales Methadone mortality studies (Caplehorn and Drummer), of the increased Methadone related mortality in new, inexperienced or rapidly expanding drug treatment services. There are **philosophical and ethical considerations** that influence clinical choice of opiate substitute which are contrary to the preliminary recommendation to prescribe Methadone 1st choice. They include the following; **Primum non nocere**, “first do no harm” is an important dictum in	

	medicine. The recommendation that a clinician should as 1st choice prescribe the more toxic and lethal Methadone when an equally effective and much safer one is available in buprenorphine is contrary to this ethical principle. This principle has been brought to bear on other prescribing decisions in medicine e.g. the use of the analgesic Co-Proxamal and the prescription of the newer more expensive atypical anti-psychotic. The issues and dilemmas associated with **patient autonomy and choice** are most concisely expressed in John Stuart Mills utilitarian concept of Liberty. The famous principle he enunciates in his work "On Liberty". "The only purpose for which power can be rightfully exercised over any member of a civilised community against his will, is to prevent harm to others. His own good, either physical or moral, is not a sufficient warrant." In the application of this principle, although Doctors also must be accorded the right of autonomy and choice in the context of prescribing, ultimately it is the prevention of harm to others (children and the community) which must apply some check and balance to unfettered patient choice. There is the additional consideration of harm to the professions which inevitably accrues in a context where policy is promoting the choice of prescribing large amounts of the most toxic, addictive and lethal opiate substitute. This is frequently the subject of public concern, political concern and GMC inquiries. When considering the **clinical responsibility for prescribing**	

	choice, the philosophical classification of **responsibility** includes **causal**, **legal** and **moral** responsibility. In the matter of prescribing choice, in the event of death by overdose, the prescribing Doctor will be directly causally responsible if he has prescribed a more dangerous drug, while knowing that a much safer one is available, especially in high-risk cases. Legal responsibility, in the event of death by opiate overdose, is likely to be influenced by whether the clinician is judged under the law to have been responsible and accountable for safe prescribing. This would apply to the choice of opiate substitute. **Moral responsibility**; A Doctor can be held morally responsible for deliberately failing to act. The knowing failure to recommend the significantly safer buprenorphine, in the context of high risk, incurs a moral responsibility in the event of death by overdose. This will particularly be an issue currently, particularly when introducing new patients and new populations to opiate substitution.	
Royal College of Psychiatrists	Many clinicians consider buprenorphine maintenance most appropriate for clients with less severe opioid dependence. This is reflected in a number of local clinical guidelines suggesting caution in the use of buprenorphine for patients using opioid equivalents of greater than 40mg methadone daily. It would be helpful if the appraisal could draw some conclusions about the appropriateness of each drug according to severity of dependence.	Comment noted. Recommendation 1.2 has been revised. Section 4.3.5 and 4.3.8 outline the Committee's consideration of this point.
Royal College of Psychiatrists	Finally, it would be useful if the authors could make reference to both patient and practitioner preference which clinically can be extremely important.	Comment noted. See recommendation 1.2 and section 4.3.5 and 4.3.8.
NHS QIS	The group has certainly been comprehensive in its reviews of the literature. I am comfortable that all relevant clinical evidence has been taken into account. There are huge limitations in this research evidence base – not least in light of the lack of UK-based data. I believe this limits considerably what can be generalised for the UK	Comments noted. Section 6 has been revised.

	from this body of evidence. I am surprised they see no need for ongoing research in this field. Examples: Use of fixed dosing – I know of no services which operate in this way for obvious reasons. While it is helpful in demonstrating that any methadone/buprenorphine is better than nothing (at least with regard to the outcomes used) it does not reflect UK practice.	
Schering-Plough	Commercial in Confidence data removed.	This has been responded to separately due to the CiC nature of the comment.

Royal College of Psychiatrists	The proportion of study subjects receiving reduction versus maintenance treatment is not clear for either drug. This would be helpful in interpreting the data.	Comment noted. This is a comment on the assessment report.

Royal College of Psychiatrists	P87”If we assume that episodes of treatment with methadone and buprenorphine are of similar average duration then these results indicate that the risk of death may be 100 times greater for methadone treatment”. It would be helpful if the authors indicated the robustness of this statement and placed it in the context of the other mortality data. It would also be helpful if the authors clarified how they made the assumptions pertaining to lengths of treatment.	Comment noted. This is a comment on the assessment report.
Web responses		
Consultant pharmacist in D&A working in the public sector, Australia.	The average doses mentioned here are relatively low by Australian standards. It would be interesting to know the percentage of people still using an illicit opioid while on a maintenance programme at these low doses.	Comment noted. Illicit use of opioids was measured in the trials as well as retention.
Consultant pharmacist in D&A working in the public sector, Australia.	Given that it takes methadone about 3 days to reach steady state levels, increasing 10mg/daily in the first week of induction onto maintenance may lead to overdose after a few days. The few deaths due to methadone have usually occurred in that first week during induction to maintenance when clinicians have realised too late that the patient"s has been overshot. An increase of 5-10mg every 3rd day, and review, would be a lot safer.	Comment noted.
Service User Volunteer Organiser	Approve of the preliminary recommendations. The one change I would suggest would be to remove the word ""should"" from line 2, section 1.3 and substitute the word ""must, where required after clinical diagnosis,"" FBC	Comment noted. NICE recommendations use ‘should’.
Service User Volunteer	I agree with this section"s sentiments and generally approve the conclusions drawn. It is very sad, however, to read about "harm minimization" and not see any reference at all to somatic and organic	Comments noted. This is an appraisal and not a guideline, these

Organiser	damage done to individuals, especially where such damage affects patients or service users. I have in mind in particular the impact of hepatitis C, calculated as potentially affecting 80% of the target cohort, especially those from the older "baby-boomer" generation. Ignorance among service users entering treatment is extremely high; it is an exception to find service users (patients) approaching induction or in treatment who are aware of the high level of morbidity and mortality associated with a disease they are exceptionally likely to have acquired. Furthermore there are no guidelines or pathways to mitigate those affected by hepatitis C itself, or undergoing the treatment for this disease.	issues not covered by the remit.
Service User Volunteer Organiser	I would like to see mention of these technologies being used for substance misuse other than opiates. It has become common practice to use Methadone in particular to treat misusers of stimulants (such as amphetamines and cocaine) and even alcohol. It may be entirely appropriate to use the technologies described in this way, but I have yet to see any corroborated, evidenced-based guideline or pathway for the use of substitute medication for these cases.	Comment noted. Remit from DH was to appraise these technologies within their licence indications for opioid dependence.
Member of public	I believe the 1.2 decision is good choice	Comment noted.
Member of public	i believe there should be more help for people drugs and alcohol, more inpatient detox beds and residential rehab`s in the more deprived areas of the country. to meet local demands as it is on the increase the prisons can`t cope with the health of prisoners they have become dumping grounds like the local mental health services.	Comment noted. However this guidance specifically relates to the use of methadone and buprenorphine.
Member of public	I believe Buperenorphine is the best choice, as methadone people i personally know take it then go and use straight afterwards. This drug would help to combat that and get more people stable ready for the other types of treatment once withdrawal was over.	Comment noted. The Committee considered the effectiveness of both drugs. It concluded that clinicians should take into account the

		characteristics of the individual patients (including their history of opioid dependence, commitment to a long-term management strategy and the estimated risks and benefits of the treatment regimen). It also concluded that if there were few differences between the drugs for that individual methadone should be prescribed as first choice.
Member of public	more money for local services separate from different budgets, so that the cost is not take from other local services. provided they use the most up to date details and facts, as it is better to invest money for long term development. than quick and costly methods?	Comment noted. However this guidance specifically relates to the use of methadone and buprenorphine.
Member of public	The sooner the better as people are suffering not just the users, as i bet we all know people personally at one level or another who needs help. to get these guidelines implemented.	Comment noted.
Member of public	I THINK THAT DATE IS TO FAR OFF	Comment noted. The review date has been changed to 2010.
Academic and locum pharmacist	1.1 and 1.2 I agree with and have no further comments. Re. 1.3 - psychosocial therapy enhances outcomes but is not available in all locations and is not required by all patients. Therefore although it can be advocated within treatment, I would suggest that it should not be a requirement of treatment. In some rural areas this requirement may end access to treatment, care is needed in how this is interpreted by practitioners and funders. The primary aim for providers should be access to methadone and buprenorphine as they keep people alive and prevent drug related deaths. Psychosocial interventions improve outcomes so are recommended not essential to save lives. Additionally "adequate supervision" needs to be defined, as the level	Comment noted. Section 1.3 has been revised.

	of supervision varies depending on where the patient is at in terms of length of time in treatment and how stable they are. Supervision of consumption for example should NOT be indefinite and it is constructive to plan for gradual reduced level of supervision/control in order to allow people to regain confidence and self pride.	
Academic and locum pharmacist	This section appears accurate and I have no further comments on it.	Comment noted.
Academic and locum pharmacist	i) technical point -the drugs that are listed as slowing elimination actually don't alter renal clearance they inhibit metabolism through the CYP450 enzyme system in the liver. Elimination is reduced as a consequence of slowed metabolism not as a direct effect on renal function. (ii) cost of medicines in the BNF not very up to date or reliable, better using the drug tariff or pricing catalogues. Also this may be misleading as it does not take into account dispensing and Controlled Drug fees, supervised consumption costs or packaging costs. (iii) Many steps can be taken to reduce overdose risks during induction, the "seven times more risk of death" statistic is misleading as it depends on how risky the person's behaviour is prior to treatment and long term the 12 x greater risk of death is much greater risk if you work on number of opiate using years. (iv) patients do not tend to like 3 x weekly buprenorphine dosing so in practice it is usually daily. This is advocated.	Comments noted. The economic analysis was based on the published list prices of the drugs in accordance with the NICE Guide to methods of technology appraisal. The costs of supervised prescribing were included in the economic analysis, see section 4.2.12 of the FAD.
Academic and locum pharmacist	Most treatment in the UK is delivered in primary care. It needs to be in order to provide adequate levels of treatment, in the person"s own community setting and allowing other health needs to be met. Most of the data, especially the RCTs come from secondary care and treatment models very different from the UK model. The influence of this must be mindful. However, in the absence of data available, the interpretation of the published trials seems accurate to me.	Comments noted. The Committee noted that the RCTs were not based in the UK and considered how generalisable they were to UK practice, see section 4.3.3 of the FAD.

Academic and locum pharmacist	No comments other than to be mindful that primary care results may not be the same as trial data.	Comments noted.
	There is a need to gain data on high dose methadone maintenance versus high dose buprenorphine maintenance long term outcomes. There is a need for more robust research data to show the impact of supervised consumption in terms of overdose prevention and improved health outcomes as this is lacking and based on anecdote. There is little data on the wider family benefits (including costs) of treatment e.g. improved relationships, social interaction, saved sick days, family building etc. There is also a need for further work on MMT and BMT in pregnancy. Better understanding of dosing, which may need to increase in third trimester due to greater volume of distribution, requires clarification through research. As does long term outcomes in pregnant women receiving MMT or BMT.	Comments noted. Section 6 has been revised.
Academic and locum pharmacist	This is a very long time considering that this is an area undergoing substantial research. Perhaps 5 or 6 years would be more realistic in order to try to keep guidance more up to date.	Comments noted. The review date has been changed to 2010.