

Consideration of naloxone

May 2012

ACMD

Advisory Council on the Misuse of Drugs

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Anne Milton MP
Parliamentary Under-Secretary of State for Public Health
Department of Health
Richmond House
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Dear Minister,

The Advisory Council on the Misuse of Drugs (ACMD) has undertaken a review of naloxone availability in the UK, presented in the attached report. The purpose of the report is to provide Government with advice on whether naloxone should be made more widely available, in order to prevent future drug-related deaths, and help engage and educate those most vulnerable of suffering an opioid overdose.

The evidence we present in the report shows that naloxone provision reduces rates of drug-related death. Evidence also shows that training in all aspects of overdose response is important alongside naloxone provision, and benefits both service users and carers. Naloxone is already available on prescription to people at risk of opioid overdose, such as heroin users. However, maximum impact on drug-related death rates will only be achieved if naloxone is given to people with the greatest opportunity to use it, and to those who can best engage with heroin users.

The efficacy of naloxone is not in dispute. Naloxone is a WHO-recommended medicine, and efficacy has been proven in several published studies and pilots. Naloxone is a safe, effective drug, with no dependence-forming potential. Its only action is to reverse the effects of opioid overdoses, and it is already used by emergency services personnel in the UK for this purpose. Despite recent falls in the number of deaths attributable to heroin overdose, we find that many of these fatalities are preventable by the use of naloxone as an intervention.

Naloxone provision is aligned with the Drug Strategy aim of preventing drug-related deaths, which is one of eight key outcomes for delivery in a recovery-orientated drug treatment system. Continued use of local public health interventions like overdose prevention training and naloxone provision is important to improve people's health, and maximise their chances of recovery from drug dependence. In this context we find it positive that naloxone provision can increase people's engagement with drug treatment services.

Critics have suggested that naloxone provision in the community could encourage people to use drugs more dangerously, if they know naloxone is available. The ACMD is not aware of any significant body of evidence that naloxone provision encourages increased heroin use.

Naloxone has been provided locally to service users and carers for some years in the UK. In Scotland and Wales, recent successful pilots have led to national programmes. The NTA in England ran a naloxone and overdose programme for families and carers, but there has been no similar roll-out. Last year, the Scottish Lord Advocate allowed naloxone to be provided to some services without prescription, for use in an emergency. This is commendable because Scottish drug treatment and homeless hostel staff can now hold it ready for use, and that Scottish medical professionals supplying naloxone are protected in cases of liability.

The ACMD concludes that naloxone provision is an evidence-based intervention, which can save lives. Naloxone provision fits with other measures to promote recovery by encouraging drug users to engage with treatment services, and ultimately, keep them alive until they are in recovery. This report recommends actions for government to take to consider naloxone's role in steps to make an impact on drug-related death rates.

The production of this report has been aided by valuable contributions from several organisations and experts. The ACMD is particularly grateful to those experts who provided written and oral evidence.

We welcome an opportunity to discuss this report with you in due course.

Yours sincerely,



Professor Les Iversen
Chair, ACMD
ACMD



Professor Raymond Hill
Chair, Technical Committee
ACMD

cc: Rt. Hon. Theresa May MP – Home Secretary
Lord Henley – Minister of State for Crime Prevention and Antisocial Behaviour Reduction

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1. Executive Summary

- 1.1. The ACMD has been considering the issue of naloxone availability and provision, as an intervention to prevent drug-related deaths, since 2009 and has previously written to the Medicines and Healthcare products Regulatory Agency (MHRA) concerning provision.
- 1.2. Naloxone is a safe, efficacious drug for reversing the effects of opioid overdoses. This report provides advice to the Government concerning the evidence and issue of making naloxone more widely available.
- 1.3. In the UK, there are hundreds of deaths related to heroin use every year and a lesser number due to the abuse of other opioids.¹ Preventing drug-related deaths has been, and continues to be a priority for the Government. Naloxone is already used by emergency services personnel to reverse heroin and other opioid overdoses. In 2005, naloxone was made available under UK law to be administered by anyone for the purpose of saving a life. However, naloxone remains a prescription-only drug, and is only licensed for use in injectable form. This means that at present it is not able to be distributed to anyone without a named prescription.
- 1.4. Because it is prescription-only, non-medical services which may experience frequent opiate-related overdoses are not able to legally hold stocks of naloxone to use in an emergency.
- 1.5. There is evidence that take-home naloxone, given to service users and training carers or peers in how to administer naloxone, can be effective at reversing heroin overdoses. Wider provision of naloxone could result in a reduction in overall drug-related deaths in the UK.
- 1.6. The ACMD believe that the single intervention of wider provision of naloxone is not sufficient in efforts to prevent future drug-related deaths. The Council considers itself aligned with UK and worldwide research that indicates that training service users, peers and carers in all aspects of how to respond to an overdose is important alongside naloxone provision.
- 1.7. Scotland has already made provisions to make naloxone more widely available, through its 2011 Lord Advocate's Guideline. This promotes the availability of naloxone to approved services without prescription, for use in an emergency. It also protects medical professionals supplying naloxone in cases of liability.

¹ The Office for National Statistics has reported at least 800 deaths due to drug poisoning with heroin mentioned on the death certificate in each year since 2000.

Recommendations are listed in brief below. For more details see section 11.

- 1.8. Recommendation 1: Naloxone should be made more widely available, to tackle the high numbers of fatal opioid overdoses in the UK.
- 1.9. Recommendation 2: Government should ease the restrictions on who can be supplied with naloxone
- 1.10. Recommendation 3: Government should investigate how people supplied with naloxone can be suitably trained to administer it in an emergency and respond to overdoses

2. Background

- 2.1. The ACMD is established under the Misuse of Drugs Act 1971 (hereafter termed the 'Act'). Its purpose is to keep under review the drugs situation in the UK and provide advice to ministers. That advice may be concerned with; restricting availability, facilities and treatment (recovery), promoting co-operation between professional and community services, educating the public and promoting research.
- 2.2. This report is concerned with advice on the supply and administration of the opioid antagonist naloxone. Naloxone rapidly, but temporarily, reverses the effects of heroin and other opioids. Naloxone has been distributed as part of emergency kits to heroin users worldwide for some years. This includes in England, Scotland, and Wales in the UK; and New York State, Los Angeles and Chicago in the USA. It has been distributed over the counter in pharmacies in Italy.
- 2.3. International and UK research has found that naloxone provision may be effective at preventing opiate-related deaths. Wider benefits around engaging with drug users and empowering family members and carers is also reported.

Heroin-related deaths in the UK

- 2.4. Heroin has been the most widely-used opiate drug in the UK for some time (Home Office, 2011). It is estimated that there are approximately 380,000 problematic drug users (including heroin users) in the UK (Department of Health, 2011). Figures for the UK are unknown, but latest figures for England suggest there are 264,072 opiate users (Hay *et al.*, 2011).
- 2.5. Heroin users are far more likely to die than peers of the same age and gender. Opiate overdoses are usually accidental, and most opiate users have experienced at least one non-fatal overdose. The risk of overdose is increased further in those recently released from prison (Bird *et al.*, 2003; Farrell *et al.*, 2007).
- 2.6. Those who inject heroin are at increased risk of overdose and death (Gaston *et al.*, 2009). Latest prevalence estimates for England indicate there are approximately 103,185 injectors (including those who inject other drugs such as cocaine).
- 2.7. Heroin has contributed to over one thousand deaths in the UK in each of the last ten years. Deaths where heroin was mentioned on the death certificate represent a significant proportion (between a third and a half) of all deaths due to drug poisoning in the UK (Office for National Statistics, 2011; National Records of Scotland, 2011; Northern Ireland Statistics and Research Agency, 2011).

- 2.8. Preventing drug-related deaths has been a Government priority over the last ten years. Numbers of drug-related deaths have significantly failed to reduce, and the English, Scottish, and Welsh governments have all implemented national naloxone pilots or implementation programmes, as part of measures to address the high rates.

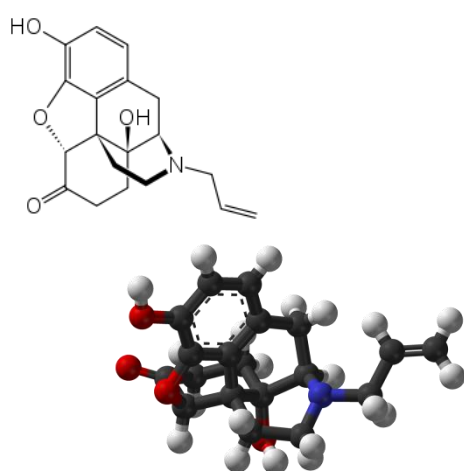
Naloxone availability

- 2.9. The ACMD wrote to the MHRA in October 2009 welcoming the National Treatment Agency's (NTA) naloxone programme announced earlier in 2009, which provided family members and carers overdose and naloxone training, and supplies of naloxone to heroin users (Annex A).
- 2.10. This review, of the ACMD's own volition, has been prompted by the growing body of evidence on the effectiveness of naloxone as a life saving provision to heroin users and carers, and also the benefits of engaging with the heroin using population, with regards to recovery.

3. Introduction and scope

- 3.1. This review seeks to provide advice on making naloxone as widely available as possible in the UK, in order that it might have maximum impact on preventing opiate-related deaths.
- 3.2. This review is not intended to address the efficacy of naloxone as a drug for reversing the effects of an opioid overdose – its efficacy is unquestionable: naloxone is recommended as an intervention to prevent overdose by the World Health Organisation as an essential medicine. The Global Fund to Fight AIDS, Tuberculosis, and Malaria recommends naloxone distribution as a component of comprehensive services for drug users (The Global Fund to Fight AIDS, Tuberculosis and Malaria, 2011).
- 3.3. Naloxone (see Figure 1) is an opioid antagonist which rapidly, but temporarily, reverses the effects of heroin and other opioids. Importantly, amongst the effects of heroin that can be reversed is respiratory depression. Naloxone has no intoxicating effects or misuse potential.

Figure 1: 17-allyl- 4,5 α -epoxy- 3,14-dihydroxymorphinan- 6-one



- 3.4. When injected intravenously naloxone acts very quickly, usually within a minute of administration, and its effects can last up to 45 minutes. Its half-life is between 1 and 1.5 hours. Alternatively it can be injected subcutaneously or intramuscularly. It is available in intranasal formulations in the USA, but these are not licensed in the UK. Naloxone is marketed under a number of trademarks including Narcanti, Narcan and Nalone. Naloxone has a high affinity for μ -opioid receptors in the central nervous system.
- 3.5. Naloxone is a prescription-only medicine in the UK. It can be supplied to named individuals at risk of opioid overdose, via a prescription or a Patient Group Direction (PGD) or Patient Specific

Direction (PSD). Since naloxone has been allowed to be used by anyone for the purpose of saving a life under UK law in 2005, it has been provided via take-home programmes. It is reasonable for services to pilot take-home naloxone locally, with suitable training for its users – and for relatives and carers, if appropriate (Department of Health (England) and the devolved administrations, 2007).

- 3.6. The main aim of take-home naloxone programmes is to prevent and reduce opioid-related deaths. Such interventions are commonly associated with a wider spectrum of ‘harm reduction’ initiatives which have developed in the UK over the last decade.
- 3.7. The UK drug treatment landscape has undergone recent changes, with the introduction of a new Drug Strategy. The Drug Strategy 2010 notes that a fundamental difference between the strategy and those that have gone before, is that instead of focusing primarily on reducing the harms caused by drug misuse, the approach goes much further and offers every support for people to choose recovery as an achievable way out of dependency (HM Government, 2010).
- 3.8. Preventing drug-related deaths (and blood-borne viruses) is the second of eight outcomes noted in the Drug Strategy, as key to successful delivery in a recovery-oriented treatment system. Preventing harm from drug use is a key public health issue, and preventing drug-related deaths remains a vital aspect of drug treatment provision. Interventions to support people as they move through treatment and recovery, including support if they relapse, remain important in the context of the Drug Strategy (HM Government, 2010).
- 3.9. New NTA guidance to commissioners aims to help them develop local Joint Strategic Needs Assessments (JSNAs). It includes advice on preventing drug-related deaths in local areas, in support of the Drug Strategy outcomes. The guidance contains specific questions for commissioners when considering what success might look like in a recovery-oriented treatment system around drug-related death prevention. A support pack promotes the benefits of continued investment; specifically including harm reduction.
- 3.10. The ACMD has been considering naloxone provision for some time. The ACMD wrote to the MHRA in 2009, with the view that wider provision of naloxone to those likely to come into contact with, or caring for drug misusers, which is a specific and safe chemical, could provide benefits. The MHRA responded by stating it had no objections in principle to proposing changes to medicines legislations along these lines (Annex B). The MHRA sought the views of the Department of Health to establish if they supported a change in the law, to allow persons who may be in contact with

drug misusers to obtain supplies for use in an emergency, and to seek views on how such persons could be defined.

- 3.11. The ACMD understands that the Department of Health were supportive, in principle, with optimising suitable access to naloxone supplies in an emergency. They stated that further consideration needed to be informed by the outcomes of the NTA overdose and naloxone programme for families and carers.
- 3.12. The results of the NTA programme are now available. This report's purpose is to provide consideration of this report, and other recent UK and international evidence on the effectiveness of naloxone provision. The report will provide recommendations on making naloxone more widely available to those who would be best placed to help people who have overdosed, in an attempt to prevent drug-related deaths.

4. Current regulatory framework for prescribing naloxone

- 4.1. Under the Medicines Act (1968), no-one, except individual patients with a prescription and appropriate medical practitioners (or those acting under medical instructions, including nurses), is allowed to administer parenteral (injectable) prescription-only medicines
- 4.2. There is a limited list of exceptions to the restrictions of Section 7 of the Medicines Act. These include a number of injectable medicines that can be given by injection by anyone for the purpose of saving life in an emergency. The list includes adrenaline, atropine, glucagon, glucose and snake-venom antiserum.
- 4.3. In June 2005, in the Medicines for Human Use (Prescribing) (Miscellaneous Amendments) Order, the United Kingdom added naloxone to that limited list of medicines. This means that currently:
 - i. naloxone is an injectable, and therefore prescription-only, medicine that may be used by anyone for the purpose of saving life in an emergency;
 - ii. naloxone can be prescribed directly to a patient, or supplied via a Patient Group Direction (PGD) or Patient Specific Direction (PSD);
 - iii. prescribers should only prescribe and supply naloxone to a known patient with a medical condition that requires the medication, and with the patient's informed consent; and,
 - iv. naloxone cannot currently be prescribed (or supplied using a PGD/PSD) to a carer, peer, or member of staff on behalf of a drug user, and cannot be given to anyone without the drug user's informed consent.
- 4.4. These conditions mean that naloxone is restricted under prescription-only supply, and that supplies are not able to be held for general use on people in settings such as homeless hostels, or carried by outreach workers, for example.

5. Methods of administration

- 5.1. Naloxone is most commonly administered intravenously or intramuscularly. It is common for users and carers to be trained to administer it intramuscularly (Galea, 2006; Tobin, 2009)². Naloxone can also be given intranasally, using an atomizer spray, but this preparation is not currently licensed for use or available in the UK, and there may not be robust evidence as to its efficacy (see 5.3).
- 5.2. There is US evidence that intranasal naloxone administration is safe and effective at reversing opioid overdose in the community (Doe-Simkins *et al.*, 2009). Intranasal naloxone may be an attractive option in the UK as it would not fall under the same regulations as an injectable medicine. It would also eliminate the risk of needle-stick injuries from the injectable naloxone preparation, needle disposal, and blood-borne virus transmission in a population already at greater risk (Doe-Simkins *et al.*, 2009; Kerr *et al.*, 2008).
- 5.3. Other evidence suggests that intranasal naloxone has poor bioavailability (the degree and rate at which a drug is absorbed) compared with intramuscular naloxone (Dowling *et al.*, 2008). Intranasal naloxone may not be as effective as injectable naloxone and further research on the efficacy of this route of administration is needed (Kerr *et al.*, 2008; Clarke *et al.*, 2005).
- 5.4. The ACMD recognises that intranasal naloxone may be an attractive option for some people because it does not require the use of needles. The ACMD will continue to monitor any development of intranasal naloxone manufacture and licensing in the UK, and will review evidence to suggest it is a proven effective alternative to injectable naloxone. However, it is not thought to be a suitable alternative to injectable naloxone at this time.

² The NTA overdose and naloxone training programme for families and carers, the Scottish national naloxone programme, and the Welsh Government's Take-Home Naloxone programme all trained people in how to inject intramuscularly.

6. Naloxone provision in the UK

England

- 6.1. The National Treatment Agency (NTA) was tasked to oversee the overdose and naloxone training programme for families and carers by the Department of Health in 2009, and a report on this was published in August 2011 (NTA, 2001a; NTA, 2011b).
- 6.2. The programme did not focus on the efficacy of giving naloxone as a treatment intervention to drug users who have overdosed. The pilots aimed to demonstrate how training family members to respond to overdoses, including using naloxone, can be implemented locally. The NTA programme also did not set out to make recommendations on increasing the availability of naloxone, or amending current regulations on naloxone's prescription-only status.
- 6.3. The aims of the NTA programme were to show the benefits of training carers to respond to overdoses, and to administer naloxone; and to provide a set of practice recommendations for any local area wanting to run its own training programme.
- 6.4. The evaluation had quantitative and qualitative components. The quantitative elements comprised data from two questionnaires devised by the National Addiction Centre, which the NTA adapted. Carers completed questionnaires before training and again three months afterwards. The main aim was to see if they had witnessed further overdoses and had used naloxone. As there was low compliance with carers repeating questionnaires, more useful information was captured during interviews with the pilot leads and the focus groups.
- 6.5. Training was provided to 495 people across 16 pilot sites. These were a mixture of service user-carers, or as a carer for a service user.³
- 6.6. The main findings from the NTA report were:
 - i. Naloxone was used 18 times in an opiate overdose situation. In two other instances, carers used the training they received while taking part in the pilot to successfully revive someone who had overdosed, without using naloxone.
 - ii. There were difficulties in recruiting carers, especially in prison and inpatient detox settings. This was for a variety of reasons,

³ The NTA report states that several pilot sites trained pairs of mutual carers (partners, close friends, or housemates), who both received a naloxone supply. Some were former service users no longer at risk of overdose themselves, but who cared for somebody at risk. Some carers did not use drugs, but cared for a drug using family member.

including stigma around drug use and fear of impact on the length of a prison sentence.

- iii. Pilot sites, carers and service users found training beneficial. All felt it made sense to train those people most likely to be present when users were taking drugs and running the risk of an overdose. This was often family members, but also other users.
- 6.7. The NTA concluded that there is limited evidence that carers are the most appropriate people to receive naloxone training. They state that while training carers is beneficial in itself, training service users and providing overdose training and naloxone to as many people as possible may need to be considered to achieve a wider impact on overall fatal and non-fatal overdose rates. This includes service users who do not have a direct carer.

Scotland

- 6.8. The Scottish national naloxone programme has been funded centrally since June 2011, although some local areas, for example Glasgow, have been providing naloxone for some time already. After March 2012, the first statistics regarding the amount of naloxone distributed and the numbers trained in using it will be available. Findings will be reported to the national naloxone advisory group to identify potential barriers to the future of the programme.
- 6.9. Naloxone is now available in almost all Scottish Alcohol & Drug Partnerships (ADPs). Anecdotally, uptake of naloxone training and provision has not been as high as expected. These are similar to findings from the NTA report, especially concerns from prisoners who do not want to be recognised as drug users, or who believe they will not use drugs again following release. Delays in use have occurred as naloxone kits do not come pre-prepared with a needle inside the naloxone kit, so must be hand-assembled.
- 6.10. Everyone who receives a naloxone supply must have training in how to use it. Family and friends of service users are not offered naloxone, but they can be offered training in how to use it. ADP and health board areas are being trained in how to deliver naloxone training themselves.
- 6.11. In its 2009-10 annual report, the National Forum on Drug-related Deaths included a report from the Short Life Working Group (SLWG) on Naloxone Supply. It stated that there is an apparent anomaly within current regulations that even though naloxone can be given by anyone, it is a prescription-only medicine. Naloxone should be made available in places where staff routinely have contact with large groups of individuals at high risk of overdose. Staff should be trained to provide emergency basic life support and

be provided with naloxone for immediate use before ambulance services arrive. This includes non-health staff in services such as homeless hostels or supported accommodation, outreach services and other non- NHS sites and agencies.

- 6.12. The SLWG requested a 'letter of comfort' from the Scottish Lord Advocate, which would enable supplies to be made to identified groups of staff working with 'at risk' drug users who have completed naloxone and basic life support training programmes to hold stocks of naloxone for use in emergencies (Scottish Government, 2010).
- 6.13. The Lord Advocate considered that naloxone should be widely available in order for the Scottish national naloxone programme to be run efficiently. In March 2011, the Scottish Lord Advocate issued a guideline that approves authorised prescribers to supply naloxone to individuals likely to come into contact with those at risk of opiate overdose (Annex C).
- 6.14. Supporting the national naloxone programme and the Lord Advocate's Guideline is guidance from the Scottish Care Inspectorate (Rees *et al.*, 2011). This guidance states that services in contact with drug users, with no other means of holding stocks of naloxone, are allowed to hold naloxone, such as homeless hostels which would not normally be allowed to stock prescription-only medicines. In services which have seen overdoses and staff have experience of managing overdoses until emergency services arrive, staff can use naloxone to aid their response to overdoses.
- 6.15. This means the national naloxone programme is able to be run in appropriate services based a needs assessment. All staff who might use naloxone must undertake appropriate basic life support training, as specified by the Scottish Government's Drugs Policy Unit. This does not mean naloxone is a personal supply to a named worker. Workers receive the naloxone and training in how to use it on behalf of the service for storage, and use within the service. Naloxone can be used within the range of service provision that a service might undertake, including outreach work or residential services.
- 6.16. Glasgow Addiction Services, in conjunction with the Care Inspectorate, has produced guidance for non-NHS services in contact with people at risk of opiate overdose (Glasgow Addiction Services, 2011). This provides background information on the national naloxone programme, and has points for consideration by service managers in developing a policy regarding take home naloxone within their service. It can be adapted for different local areas, and has practical advice around auditing naloxone use.
- 6.17. A range of services have been supplied under the national naloxone programme, but the majority are residential as this is where the majority of overdoses occur. These include a housing

support project where outreach workers already carried a first aid pack, and where they had recent experience of having to manage overdoses and call the ambulance.

- 6.18. The implications of the Lord Advocate's Guideline and Care Inspectorate guidance are that naloxone is being distributed to a greater number of people, who are in a position to assist someone who has overdosed. Naloxone remains a prescription-only medicine. Authorised prescribers who supply naloxone to service workers, rather than named patients, are also immune from prosecution under the Lord Advocate's Guideline.
- 6.19. The Scottish government do not consider that over-the-counter provision would be an appropriate option within the context of its national naloxone programme. It considers there would be no assurance that someone had been appropriately trained in how to use it. A prescription requirement, and provisions under the Lord Advocate's guideline, allows the government to evaluate the programme, monitor the amount distributed and whether it is used, and the impact on drug-related death rates.

Wales

- 6.20. The Welsh Government launched the Take Home Naloxone (THN) demonstration project in selected areas in September 2009. This was to test the feasibility of expanding the scheme nationwide (Annex D). The evaluation recommended a national naloxone programme be rolled out with further delay (Bennett *et al.*, 2011).
- 6.21. As a result of the evaluation findings, the Welsh Government's strategy for tackling substance misuse "Working together to reduce harm" has a commitment to take actions which focus on reducing the number of drug related deaths and near fatal drug poisonings. On the back of the recommendations from the evaluation, one of the key actions contained in the strategy's 3 year implementation plan is the development of guidance and protocols to introduce take home naloxone. Nine Welsh areas are taking part in the programme.

The N-ALIVE trial – England

- 6.22. The N-ALIVE (NALoxone InVEstigation) trial is a large prison-based randomized controlled trial, designed to test the effectiveness of giving naloxone-on-release to prisoners with history of heroin use to prevent fatal opiate overdoses.
- 6.23. The N-ALIVE trial is divided into two stages; the pilot randomized trial and the subsequent main randomised trial. The pilot trial aims to demonstrate feasibility by recruiting the first 10% of participants

(5,600 participants). The main N-ALIVE trial will assess the number of lives that could be saved by routine provision of naloxone-on-release to adult prisoners aged 18-44 years with a history of heroin injection who are released after seven or more days in prison (whether post-detoxification, on maintenance treatment, or otherwise). The pilot trial includes an ancillary study in which the participants who give their additional consent will be contacted once by phone. This sub-study will allow collection of further information on opiate use, overdoses, and naloxone use soon after release.

- 6.24. Eligible prisoners who give informed consent will be randomised to receive, on release from custody, either a pack containing a single 'rescue' injection of naloxone or a control pack containing no naloxone. The trial is 'double-blind' prior to the participant's release so that neither the participant nor prison staff will know the allocation until the participant opens his/her assigned pack after release (King's College London, 2012).
- 6.25. The trial has received ethical approval, and has funding from the Medical Research Council (MRC). It will be carried out by the MRC's Clinical Trials Unit and will be run in English prisons only, due to the Scottish and Welsh programmes both operating already in prisons as well as the community.
- 6.26. The investigators have estimated the impact of the N-ALIVE trial as follows. Evidence suggests that in the first four weeks, there is one overdose death out of every 200 injectors released from prison. The following assumptions have been made:
 - i. Assumption 1: someone else is present at 80% of overdoses
 - ii. Assumption 2: there is a 75% chance a prisoner will retain their naloxone in the first four weeks of release
 - iii. Assumption 3: there is a 50% chance a prisoner will retain their naloxone in the proceeding eight weeks following release
 - iv. Assumption 4: there is a 50% chance that naloxone will be administered by someone else at the overdose
 - v. This means the effectiveness of naloxone is estimated to be about 30% in the first four weeks following release from prison. The estimated effectiveness of naloxone falls to 20% in the fifth to twelfth weeks following release
 - vi. This means that the distribution of naloxone in the N-ALIVE trial could prevent 42 drug deaths in first and second fortnight per 28,000 who inject drugs when they are released from prison.
- 6.27. Because deaths in England do not need to be registered in the year they occur, this may affect how soon N-ALIVE can find out about drug-related deaths of ex-prisoners involved in the trial. At the time of writing, prisons were being recruited to take part in the trial. Findings are not expected to be available for some years.

7. Effectiveness of naloxone provision

- 7.1. Naloxone can be used by laypeople with the right training, and there is an easy prescribing system. Because many overdoses are witnessed, there is the potential for people to intervene and try to save lives.
- 7.2. The effectiveness of take-home naloxone programmes on drug-related death rates may be difficult to prove, especially if the majority of overdoses are estimated to be non-fatal. Local areas may be able to make estimates based on local overdose and drug-related death rates.
- 7.3. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) estimate that for every fatal overdose, there are up to 25 non-fatal overdoses that occur in Europe. Available information suggests that there are around 150,000 non-fatal overdoses every year in Europe (EMCDDA, 2010). There are no available estimates for the UK only.
- 7.4. Overdose is a real risk for those who inject opiates, and between half and three-quarters of overdoses are witnessed, by people who are willing to help (Strang *et al.*, 2008). Sometimes these include family members. Periods of increased risk follow imprisonment, and when someone has just begun or stopped receiving opioid substitution treatment or after detoxification.
- 7.5. There is no way to know for sure, in individual cases, what effect naloxone may have on a person's survival. An overdose reversal occurring after receiving naloxone may not be because a person has received naloxone. It may be due to life support interventions, or whether or not they were in an overdose state to begin with. This emphasises the importance of providing basic life support and overdose response training at the same time as naloxone provision and training.

Cost-effectiveness

- 7.6. There is a lack of published research on the cost-effectiveness of naloxone provision (NTA, 2011a). Naloxone provision in local areas would therefore be a local decision including an assessment on its cost-effectiveness.
- 7.7. The N-ALIVE trial investigators have shown that their provision of naloxone to inmates on release would meet NICE clinical effectiveness thresholds. For example, the threshold is £20,000 per life year gained, and if naloxone is able to prevent 42 drug deaths in the first and second fortnight per 28,000 injectors released, then naloxone is cost-effective, as it would cost £30 per naloxone prescription/per inmate.

- 7.8. The Scottish Government reimburses £10.95 per naloxone kit to health boards providing training and naloxone. This includes:
- A plastic box
 - A 2ml pre-filled naloxone 1mg/ml syringe (contains five doses)
 - 2 x 23 gauge 1¼ inch muscle needles
 - Patient Information Leaflet
- 7.9. This does not cover the cost of training, which would vary between different regions and services. The Scottish Government is yet to decide whether its programme will be evaluated for cost-effectiveness. If they do, findings will take some years to produce.

8. Worldwide evidence

- 8.1. Naloxone has been available directly to users, or from training programmes in several countries worldwide, in different forms, for some time.

United States

- 8.2. Naloxone has been provided via training programmes in the United States for the last two decades. Naloxone training programmes have improved participants' ability to recognize and respond to opioid overdoses in the community. Drug users with overdose training and confidence in their abilities to respond may effectively prevent overdose mortality, compared with those who have received no training (Green *et al.*, 2008).
- 8.3. Research into 48 US naloxone trials and programmes has found that distribution of naloxone and training in its administration may have prevented numerous deaths from opioid overdose (CDC, 2012).
- 8.4. Peers are willing to respond in an overdose situation and naloxone distribution may have an impact on overdose mortality rates provided with or within the context of a wider overdose prevention programme (Lagu *et al.*, 2006). In Cook County, Chicago, the introduction of and sustained widespread naloxone distribution coincided with a noticeable decrease in drug-related deaths between 2000 and 2007 (Guteson, 2010).
- 8.5. Some US states have passed laws and changed regulations to provide limited liability for prescribers who work with programs providing naloxone to laypersons. Other states have enacted Good Samaritan laws providing protection from arrest in an effort to encourage bystanders at a drug overdose to phone emergency services and use naloxone when available.

Australia

- 8.6. A recent Australian study concluded that naloxone had the potential to reduce opiate overdose mortality and morbidity among injectors. There was strong support for peer distribution programmes and intranasal formulations. Naloxone can only be prescribed directly to an individual for use on them, as in the UK. Naloxone's prescription-only status could limit access, but there are precedents in prescription medication regulations which are already established, such as glucagon for hypoglycaemia (Kerr *et al.*, 2008).

Italy

- 8.7. Naloxone was made available over-the-counter to heroin users in the Emilia-Romagna region of Italy in 1998 (Simini, 1998; Baca *et al.*, 2005). The ACMD is not aware of published findings on the effectiveness of this programme.

Regulation of naloxone supply

- 8.8. In the US, naloxone is subject to similar legal and medical controls as in the UK and Australia. It is available on prescription to named individuals. There have been calls for the requirement for a prescription to be lifted, as it has no abuse potential, has side effects limited to withdrawal symptoms, and can be used by laypeople without doctor's supervision (Beletsky *et al.*, 2009). The cost of hiring a medical professional to provide prescriptions could be prohibitive for programmes which have limited funding.
- 8.9. Legal concerns, especially to do with malpractice or liability, may have presented barriers to implement naloxone programmes more widely across the US (Beletsky *et al.*, 2009). Other evidence suggests that risks of malpractice are similar to those normally found when providing other forms of healthcare (Burriss *et al.*, 2001).
- 8.10. Naloxone's prescription-only status in the US may have further implications than it does in the UK, but this may relate more to the potentially prohibitive cost of involving medical personnel to assess patients and write prescriptions. There may be different cost implications in the UK due to the provision of publically-funded drug treatment by the NHS.

9. Potential for misuse or abuse of naloxone

- 9.1. Naloxone brings on temporary withdrawal symptoms in an individual who has opioids in their system, but on people who do not have opioids in their system, there are no such withdrawal effects. Naloxone has no intoxicating effects or dependence-forming potential.
- 9.2. Side-effects are rarely reported. When side-effects have occurred, they were mostly associated with pre-existing medical conditions (Bryson, 1996; Sporer *et al.*, 2007). They are also associated with significantly higher dose levels than those used in peer overdose interventions. Peer training programmes do not report side effects, probably because peers are trained to give small doses of naloxone (Burriss *et al.*, 2001).
- 9.3. The ACMD is aware of concerns that naloxone provision could encourage increased or riskier drug use (Travis, 2011), or even malicious administration, to induce withdrawal symptoms on purpose.
- 9.4. While there is a risk that opioid users may increase their use if naloxone is there as a 'safety net', and that concern about the risk of increased harm from drug use is legitimate, there is no published evidence to prove this. Recent US evidence does not support the claim that naloxone provision could encourage increased or riskier drug use (Maxwell *et al.*, 2006; Seal *et al.*, 2005; Wagner *et al.*, 2010). Some studies have in fact have found decreased drug use (Seal *et al.*, 2005; Wagner *et al.*, 2010). Some authors argue it is not useful to focus on the harms of drug use when compared with an opportunity to intervene and potentially save lives (Bazazi *et al.*, 2010).
- 9.5. Expert opinion was supplied to the ACMD by UK naloxone expert Professor John Strang:

“There is merit in the training of family and the peer community in essential steps to be taken in the event of discovering or observing a heroin overdose, including the importance of calling an ambulance and initiating ‘rescue breathing’ if breathing is compromised. In this context, the additional administration of an interim dose of intramuscular naloxone may maintain life support until the arrival of medical or para-medical staff.

Evidence from training of both family and peers is that training in overdose management (including how to administer emergency naloxone) leads to greater likelihood of phoning for an ambulance.”

- 9.6. Professor Strang also notes:
- i. There are concerns that naloxone provision could create a perception of greater safety, and lead to excessive heroin use. The response of emergency services with ambulance call-out might similarly generate a perception of greater safety. Professor Strang is not aware of any significant body of evidence that this leads to excessive heroin use.
 - ii. Furthermore, as with other preventive medicine interventions, these concerns must be balanced against the life-threatening nature of the situation that is being addressed, including whether it is better to supply naloxone in case of overdose rather than not supply it because of these concerns.
 - iii. A well-designed research trial which measures the actual impact on overdose deaths will answer some of these questions, such as the current N-ALIVE trial. It is important for these questions to be answered objectively, and carefully-considered and well-designed trials will contribute to the development of improved policy and practice.
- 9.7. There is a considerable body of published evidence, mostly from the UK and Australia, to suggest people would not use more heroin, if naloxone was available (Darke *et al.*, 1996; Lenton *et al.*, 2000; Gaston *et al.*, 2009; Strang *et al.*, 1996). Participants in naloxone programmes have been found to have an “increase in self efficacy and more insight in relation to personal safety and health”. Users would not wish to induce unpleasant withdrawal symptoms, and the availability of naloxone does not promote a ‘false sense of security’ leading to an increase in heroin use (Gaston *et al.*, 2009).
- 9.8. The ACMD is not aware of evidence to support the claim that a fear of instigating withdrawal would lead to someone being unwilling to give naloxone. Nor is the ACMD aware of published evidence which has found an increased risk of inappropriate or malicious use of naloxone, which could raise issues of liability (Gaston *et al.*, 2009). The ACMD is not aware of evidence to suggest people have administered naloxone maliciously to bring on withdrawal symptoms in someone else.

10. Liability issues

- 10.1. Naloxone provision has been subject to recent debates and challenges in the UK. These include the question of individual liability if naloxone is used 'unsuccessfully'; that is, if the person on whom it was used is not revived, has been questioned. Also, whether greater naloxone availability, for example in hostel settings, might lead to naloxone over-use due to fear of being held liable if someone died (Flemen, 2011). Furthermore, it has been speculated that people trained in administration of naloxone may not always make a correct judgment as to whether a potentially fatal overdose has occurred before they use naloxone.
- 10.2. The ACMD have identified that issues of liability and negligence may arise both currently, and if provision is extended. If the ACMD's recommendations are accepted, it would be a matter for government policy units to assess the risks and benefits associated with liability, and appropriate advice given to practitioners and individuals trained to administer naloxone.

11. Conclusions and Recommendations

- 11.1. There are more than one thousand fatal opioid overdoses in the UK each year, which could be prevented by naloxone. Evidence shows that providing naloxone has benefits that include, but are not limited to, a reduction in opioid-related deaths.
- 11.2. Opportunities to assist unnamed individuals in an overdose situation with naloxone are limited by its prescription-only status. It cannot be supplied directly to individuals who have a good opportunity to intervene in an overdose, such as hostel staff.
- 11.3. The balance of benefit around providing naloxone, and the opportunities for reversing overdoses and saving lives, is greater than any potential risks. Risks and concerns around malicious use of naloxone, or the potential for users to be more reckless with their drug use, are not supported by evidence.

Recommendation 1: Naloxone should be made more widely available, to tackle the high numbers of fatal opioid overdoses in the UK.

- 11.4. The ACMD commends the Lord Advocate's Guideline, and the Care Inspectorate guidance, which are already allowing wider provision of naloxone in Scotland. It would be timely to review the marketing authorisation of naloxone by the Medicines and Healthcare Products Regulatory Agency as a prescription-only medicine.

Recommendation 2: Government should ease the restrictions on who can be supplied with naloxone

- 11.5. Training carers in naloxone administration may be beneficial, but training all those likely to encounter an overdose would have a greater impact on overdose rates.
- 11.6. Naloxone availability to a wider group of people will further highlight the risks of opioid overdose, and have educational and public health benefits.
- 11.7. Naloxone provision is just one of several tools in a package of interventions to prevent opioid overdose. These include basic life support training. It is important that individuals possessing naloxone are given suitable training in how to respond to an overdose, as well as administer naloxone.

Recommendation 3: Government should investigate how people supplied with naloxone can be suitably trained to administer it in an emergency and respond to overdoses.

ACMD

Advisory Council on the Misuse of Drugs

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12th October 2009

Medicines and Healthcare products Regulatory Agency
Market Towers
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Dear Mr Gallagher

Thank you for your response of 27 May 2009 to the Advisory Council on the Misuse of Drugs (ACMD) Technical Committee's correspondence in relation to the provisions of naloxone.

The ACMD welcomes the National Treatment Agency's (NTA) pilot scheme announced earlier this year; which provides family members and carers training and supplies of naloxone for heroin users in the event of an overdose. The ACMD believe that this represents a step forward in tackling the high numbers of fatal opiate overdoses.

However, although the ACMD believe this to be movement of policy in the right direction we consider that provisions should be extended to cover others who may be in contact with drug users through their work such as hostel managers or outreach drugs workers. We would also recommend that it should be made possible for (suitably trained) drug service providers such as needle exchanges and outreach programmes to be able to hold/carry a stock of naloxone for use in an emergency and to consider allowing such services, for example, pharmacy needle exchanges to be able to issue repeat supplies of naloxone without the need for a prescription or a PGD. It should be noted that many drug services, particularly tier 2 services, may not have a nurse, doctor or pharmacist on their premises or in their employ and there is not a professional qualification of "drug worker".

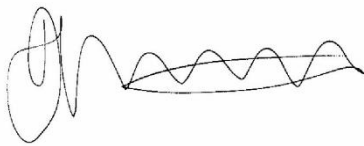
The ACMD acknowledge naloxone's present Prescription Only Medicine (POM) status (and availability through a Patient Group Direction). However, the Committee remains concerned about availability issues. The Technical Committee believes that it would be reasonable for drug service providers to hold supplies of naloxone for unnamed individuals and for it to be administered by trained individuals in the event of an overdose. Further the Technical Committee believes that there is an analogy between naloxone provisions and a House of Lords report recommendation concerning allergies; in which it was recommended that the Government should review the case for schools holding one or two adrenaline autoinjectors to be administered to children with anaphylactic shock in the school environment, the report can be found at <http://www.publications.parliament.uk/pa/ld200607/ldselect/ldsctech/166/166i.pdf> (section 10.26).

Although the NTA identifies that many drug misusers live with family members and that overdoses occur within these environments it is important that other elements of drug misusers' lives are appropriately catered for. Although relatives and carers are an important group to be considered, the ACMD believe that wider provision, of what is a specific and safe chemical, and could provide benefits.

The ACMD also believe that the standard prescription fee should be waived for naloxone when supplied on a NHS prescription or under a PGD as occurs for other certain medicines such as those used for treatment of sexually transmissible infections, for treatment of TB etc.

I would appreciate if you would consider the view of the ACMD in relation to your present work on this issue.

Yours sincerely

A handwritten signature in black ink, appearing to read 'D. Nutt', with a wavy line extending to the right.

Professor David Nutt FMed Sci

Safeguarding public health



Professor Iverson
Chairman
Advisory Council on the Misuse of Drugs
c/o Home Office
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19th March 2010

Dear Professor Iverson

I apologise that the Council has not had a reply to its last letter to Shaun Gallagher. (For your information, Jonathan Mogford has now taken up appointment as the Director of Policy at the MHRA.) This letter updates the Council on their request that the DH/MHRA consider widening the supply of Naloxone to those who care for and work with opioid misusers so it is available to administer in the event of overdose.

In reply to the first letter from the Council, the MHRA indicated that we had no objections in principle to proposing changes to medicines legislation to enable those caring for or working with drug misusers to obtain supplies of naloxone to treat opioid overdose. We also said that we would issue the necessary statutory consultation as soon as possible. However as is normal with any consultations, the MHRA, as part of the Department of Health (DH), must first obtain comments and agreement from the relevant policy interests within the DH.

The MHRA therefore sought the views of the DH to establish if they supported a change in the law to allow persons who may be in contact with drug misusers to obtain supplies for use in an emergency, and to seek views on how such persons could be defined. DH were supportive in principle with optimising suitable access to Naloxone supplies in an emergency but felt that any further consideration needed to await until the outcome and evaluation of an NTA Naloxone and Carers' pilot project which is due to report in Autumn 2010.

This is how matters rest at present and the MHRA stand ready to consider the Council's request, if supported by DH, following the evaluation of the project.

Yours sincerely

Anne Thyer

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An executive agency of the Department of Health

**LORD ADVOCATE'S GUIDELINES
ON ALLOWING THE SUPPLY OF NALOXONE TO EXTEND TO STAFF
WORKING FOR SERVICES IN CONTACT WITH PEOPLE AT RISK OF
OPIATE OVERDOSES**

Naloxone is a prescription only medicine (POM) used to temporarily reverse some of the effects of an opiate overdose – primarily respiratory depression.

Essentially, this medication provides extra time for an ambulance to arrive (around 20 minutes) and treatment to be provided. An amendment to the Medicines Act 1968 in 2005 means that now anyone can legally *administer* naloxone to save a life. However the *supply* of this medication by health professionals is restricted to named patients only.

The roll out of a National Naloxone Programme (hereafter 'the Programme') is due to commence in September 2010. The Programme involves services which come into contact with those deemed at risk of an opiate overdose being provided with their own supply of the medication. Those in a position to administer naloxone will receive appropriate training to do so.

It is the view of the Lord Advocate that this medication should be widely available as soon as possible in order for the Programme to be run efficiently. Therefore it is important that authorised persons who are involved in supplying services which come into contact with those vulnerable individuals who may be at risk of opiate overdose, and who possess naloxone for the purpose of administering in emergency situations, are not criminalised for doing so.

The Lord Advocate is aware that the Scottish Government is looking into amending current legislation to allow authorised prescribers to supply such services with the medication. In the meantime the Lord Advocate has approved that authorised prescribers be permitted to supply individuals likely to come into contact with those at risk of opiate overdose with the medication without risk of prosecution. In accordance with this guidance, such authorised prescribers will therefore be immune from prosecution.

This undertaking has been given by the Lord Advocate on the basis that the supplies of the medication by authorised prescribers to such members of staff will only be used for administering in emergency situations. Holders of the medication are required to undertake appropriate basic life support training, as specified by the Scottish Government's Drugs Policy Unit in rolling out the Programme.

Elish Angiolini QC
Lord Advocate
March 2011

To: Ali Mohammed
Advisory Council on the Misuse of
Drugs (Secretariat)
Home Office
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Llywodraeth Cynulliad Cymru
Welsh Assembly Government

CC: Dr Gwyn Roberts, Chair
APoSM

Karen Eveleigh
Welsh Assembly Government
Rhydycar
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CF48 1UZ

Date : 9/March 2011

Dear Ali

RE: ACMD Technical Committee (1) – Tuesday 22nd March 2011

I am pleased to provide below the ACMD technical Committee with the details of how we have taken forward the Naloxone initiative in Wales.

NALOXONE INITIATIVE in WALES

The Welsh Assembly Government's Substance Misuse Strategy, three Year Implementation Plan 2008-11 set an objective to maintain a commitment to reducing Drug Related Deaths. As part of that commitment the Welsh Assembly Government supported the introduction of the use of Naloxone in Wales.

In 2009 a National Working Group was established by The Welsh Assembly Government to oversee the establishment of demonstration sites across Wales to deliver this initiative.

The Demonstration sites were established in Newport, Cardiff, Swansea, North Wales and Swansea, Cardiff, Parc and Usk prisons. This decision was based upon drug related death data showing these areas as particular hotspots. The sites became operational in August 2009. To date 684 Naloxone kits have been issued with 51 being used in an attempt to reverse opiate overdose.

Each site has implemented the initiative in a slightly different way according to local circumstances, but in each area, training is provided in identifying and recognising the symptoms of overdose, exploding the myths around what to do and providing basic first aid training. This is then followed by training in the use of Naloxone and practising injecting. The training has presented a key challenge in terms of ensuring the session length is enough to provide all of the information whilst maintaining interest. Each area targeted existing service users and “hard to reach” groups, their families and carers. The initiative was under-pinned by national guidance which can be accessed at: (<http://wales.gov.uk/topics/housingandcommunity/safety/substancemisuse/publications/naloxone>).

A bespoke Naloxone kit for Wales was developed and purchased centrally for “draw down” at the local level. The bespoke kit was developed via the National Working Group, the basis for this kit was cost effectiveness, current availability of Naloxone and due to the fact that the kit is sealed and childproof.

The initiative has been subjected to an external evaluation by the University of Glamorgan. The researchers worked closely with a wide range of stakeholders across the demonstration sites including service providers and services users to conduct a process and outcome evaluation. The main intention of the evaluation was to identify good practice and “learn lessons” from the demonstration sites to inform the national roll-out of the project. The evaluation has recently be finalised and will be published shortly. Interim results show that service users who had attended the Naloxone training displayed increased knowledge, confidence and a willingness to recognise and respond to overdose situations. The training impacted positively on the confidence of individuals to administer Naloxone, with over 90% of respondents stating that they were ‘very confident’ in carrying out the task.

The next step is to publish the evaluation report and consider roll-out of the project across Wales. If you need further information please do not hesitate to contact me.

Yours sincerely

A handwritten signature in black ink, appearing to read 'Karen Eveleigh', with a long horizontal flourish extending to the right.

Karen Eveleigh
Head of Quality Improvement Programmes – Substance Misuse

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