

BMJ Open Paramedic-supplied 'Take Home' Naloxone: protocol for cluster randomised feasibility study

Chris Moore,¹ Gregory Lloyd,² Rossana Oretti,³ Ian Russell,⁴ Helen Snooks⁵

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ABSTRACT

Introduction: 'Take Home' Naloxone (THN) kits for use by peers in the event of an opioid overdose may reduce further overdose and deaths, but distribution through Drugs Services may not reach those at highest risk. Attendance by paramedics at emergency calls for patients who have suffered an overdose presents an opportunity to distribute THN kits. In this feasibility study we will assess the acceptability of this intervention, and gather data to inform definitive trial planning.

Methods and analysis: Cluster randomised trial with staggered allocation of paramedics (clusters) to groups. We will invite paramedics in an urban area of south Wales, UK to take part. We will randomly allocate those that accept to training sessions during the first 4 months of the trial. Patients attended by paramedics who have been trained and issued THN kits will fall into the intervention group. Patients attended by paramedics following usual practice (until they receive their training and THN kits) will fall into the control group. We will gather data about processes and outcomes of care: numbers of patients eligible for intervention, offered and accepted THN, attended emergency department, suffered further overdose, died within 3 months and about follow-up rates: numbers of patients consented, completed (postal or telephone) questionnaire. We will gather qualitative data about acceptability to patients and paramedics through interviews and focus groups.

Ethics and dissemination: Ethical approval for this study was granted on 7 December 2011, by South East Wales Research Ethics Committee, Panel C. Results of this study will be reported through peer-reviewed scientific journals, conference presentations and internal organisational report. We will also seek to report our findings through local and national substance misuse networks and publications.

Trial registration number: ISRCTN98216498.

INTRODUCTION

Background and rationale

Deaths in the UK from opioid overdose are among the highest in Europe,¹ accounting for 37% of all poisoning deaths in young people aged 15–19 in England between 1985

Strengths and limitations of this study

- Providing 'Take Home' Naloxone (THN) to opioid users in the prehospital setting provides a considerable opportunity to intervene and engage with this high-risk group at a time of high personal significance.
- The popularity of providing THN as an intervention is growing internationally, yet there is little published evidence to support its effectiveness or acceptability among opioid users.
- It is acknowledged that there will be challenges in recruitment and follow-up of this user group.

and 1995.² In England and Wales approximately 1200 men and 400 women die per year from drug poisoning related to drug misuse. Since 2010, the number of male deaths related to drug misuse has begun to show a decline, but female deaths continue to rise. Heroin and morphine remain the substances most commonly involved in drug-poisoning deaths,³ with 83% of drug-induced deaths in the UK showing the presence of opioids.¹ In 2011, the highest mortality rate from drug misuse was in 30–39-year-olds.³ The UK government target, set in 1999 to reduce drug-related deaths by 20% by 2004, was not met.

Death from heroin/morphine misuse made up nearly half of male deaths from poisoning and more than a quarter of female deaths and increased between 2003 and 2004. It is estimated that as many as one million people take class A drugs each year, and a quarter of these will be 'problematic' drug users.⁴ There is a lack of UK data on fatal and non-fatal poisonings and this has led to calls for collating standardised ambulance call-out statistics.⁵

Typically, deaths attributed to opioid overdose are older, heroin-dependent men not in drug treatment at the time of death.⁶ Risk of death from overdose is also increased by use of more than one drug, injecting



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For numbered affiliations see end of article.

Correspondence to

Chris Moore;
Chris.moore@wales.nhs.uk

behaviour, homelessness and changes in tolerance especially after periods in prison.^{1 7–12} Research indicates that a high proportion of drug misusers who die will have attended an emergency department within the previous 12 months.^{13 14}

The Wales and UK Substance Misuse Strategies (2008–2018) make reference to reducing harm by the introduction of naloxone protocols and guidelines.^{15 16}

Naloxone is a very safe and effective antidote to opioid overdose. It has no abuse potential¹⁷ and virtually no side effects, though it may precipitate acute withdrawal symptoms in opioid-dependent individuals, if given in large doses.¹⁸ It is administered routinely by emergency personnel in the prehospital setting, and physicians in the A&E department.¹⁹ Naloxone is usually administered either intravenously or intramuscularly when intravenous access is not possible.²⁰

In addition to engaging with service users themselves, the National Treatment Agency and Department of Health has identified carers as one of the key groups to be targeted to reduce the risks of opioid overdose.²¹ Research has shown that a high proportion of overdoses are witnessed,^{19 22} yet medical help is often not sought or is sought too late. Witnesses at an overdose event are however, often willing to intervene so providing training in cardiopulmonary resuscitation, recognition of overdose and the use of naloxone by service users and carers, can improve chances of an individual surviving an opioid overdose.⁶

Since the 1990s, interest has grown in providing 'Take-Home' Naloxone (THN) to users, families and drug services.^{23–25} A Welsh Government-supported initiative saw an introduction of THN in Wales through demonstration sites in 2009. National roll-out was achieved in October 2011. The THN initiative is consistent with the Welsh Assembly Government's 10-year strategy,¹⁶ which aims to take forward actions which focus on reducing the number of drug poisonings in Wales. Uptake of this innovative intervention is however, currently limited to those already accessing community-based substance misuse services.

Data from the Welsh Regional Confidential Review Panels into drug-related deaths (since 2006) have shown that the highest number of drug-related deaths is in individuals who have either never accessed substance-misuse treatment, or have dropped out of such treatment. Early release from incarceration is also linked with increased risk of fatal overdose.¹³ Accessing these high-risk individuals requires an innovative approach that takes the intervention direct to the point of care.

Studies indicate that at least 50% of opiate users will have experienced a non-fatal overdose at some point in their lives,²⁶ and are at increased risk of suffering a fatal overdose, as 60% of those who died, had accessed A&E services in the previous 12 months.

This study builds on the review of 999 callers and A&E attendees presenting with non-fatal self-poisoning in Wales,²⁷ which was commissioned by the Welsh Assembly

Government. This study highlighted that 999 calls relating to heroin poisoning were concentrated within urban centres in South Wales with Cardiff having the highest number (n=27), within the 3-month study period. In addition, the majority of such 999 calls tended to be from 16:00 until midnight and on Saturdays. This is when the majority of substance misuse treatment agencies are closed. While paramedics could signpost such individuals to community THN projects, it is likely that a number would not attend. In the intervening time interval, before acquiring THN, these individuals theoretically remain at high risk of further non-fatal and possibly fatal overdoses. Research would therefore suggest that providing THN in the prehospital setting provides a considerable opportunity to intervene and engage with this high-risk group at a time of high personal significance.

As THN kits are now widely distributed through community-based Drugs Services in Wales, it is not possible to conduct a randomised trial to test the effectiveness of this model of care; however, the 999 route offers a new model of care that is as yet untested. This study is therefore timely in order to develop this complex intervention and the methods for a definitive trial, if indicated, following the Medical Research Council Framework for the Development and Evaluation of complex interventions.²⁸ The rationale for employing a cluster randomised design is so that all paramedics will have the opportunity to participate in the trial in the intervention group, but we will be able to thoroughly test the trial methods, by retaining a comparator group for a significant portion of the trial period.

Aim

To assess the feasibility of carrying out a randomised controlled trial to determine the safety, clinical and cost-effectiveness of THN distribution by paramedics

Objectives

1. To assess acceptability of and compliance with a new intervention: paramedics supplying THN kits to 999 patients they attend for an opioid overdose.
2. To assess the feasibility of paramedic and patient recruitment and follow-up in order to determine whether a definitive trial is indicated.
3. If so, to provide data to inform trial planning.

METHODS

Study design

Cluster randomised multiple interrupted time series feasibility study, with paramedics as the unit of clustering and randomisation stratified by station and shift. We will invite paramedics in the Cardiff and Vale of Glamorgan areas to take part in this feasibility study. We will randomly allocate those that accept to training sessions which will be scheduled during the first 4 months of the trial. Patients attended by paramedics who have been trained and issued THN kits for distribution will fall into

the intervention group. Patients attended by paramedics following usual practice (until they receive their training and THN kits) will fall into the control group.

We are not aware of any sources of bias in this study, but will monitor recruitment, follow-up rates and compare characteristics of patients between groups at baseline to check for any unexpected differences that may indicate bias.

Inclusion criteria

Patients will be eligible for inclusion in the trial if:

- ▶ Attended by a participating paramedic;
- ▶ 18 years of age or older;
- ▶ Regained full consciousness Glasgow Coma Scale 15 (GCS 15) and demonstrated full mental capacity following treatment for a suspected opioid overdose.

Exclusion criteria

- ▶ Attended by an ambulance that does not include a participating paramedic.
- ▶ Patient is aged 17 years or younger.
- ▶ Failure to regain consciousness (GCS 15) or full mental capacity following treatment by paramedic for suspected opioid overdose.
- ▶ Patient whose proficiency of the English language is not sufficient to carry out consent on scene.

Settings and locations for data collection

All patient clinical records completed by ambulance clinicians (paramedics and emergency medical technicians) who operate in the study area, during the 1-year patient recruitment phase of the study, will be scrutinised to identify any that indicate attendance at an opioid overdose. These data will be used to determine an accurate estimate on the number of opioid-related 999 calls that occur during the study period. A simple data collection form (see online supplementary appendix 1) has been designed to support this and copies will be available on all ambulance vehicles operating in the area. A supply of uniquely coloured envelopes addressed to the study team will also be available on ambulance vehicles, to facilitate easy identification and submission of relevant clinical records. Data will be collated by the chief investigator (CI), who is based at the main ambulance station in the study area.

Standard care by paramedics treating opioid overdose

Standard paramedic care of patients suspected of opioid overdose includes managing airway, breathing and circulation problems in priority order. Naloxone will then be administered to effect, either intravenously, or intramuscularly if the intravenous route is not available. Patients who fail to demonstrate full recovery are always transferred to hospital for further assessment and/or treatment. Those who regain full consciousness at the scene may or may not choose to attend hospital. Those that choose not to attend hospital will be provided call back advice and administered an 800 µg intramuscular dose

of naloxone, aimed at preventing secondary opioid overdose onset.

Intervention

Following a 999 call and resuscitation for an opioid poisoning, paramedics trained to provide the intervention will offer THN kits to fully recovered, consenting patients. Paramedics will supply this intervention under the auspices of a patient group direction. The intervention may be provided at the scene of the opioid overdose, or while en route to hospital.

This complex intervention has the following components:

- ▶ Training for participating paramedics;
- ▶ Protocol for the supply of THN to patients who have suffered and recovered from an opioid poisoning;
- ▶ Issue of an individual THN kit to trained paramedics which will be replaced each time they issue their kit to a patient;
- ▶ Supply of THN and education related to its use, and resuscitation techniques and procedures, to patients.

Provision of the intervention is dependent on the patient remaining engaged and their health status remaining stable during the training and consent process. Patients who do not complete the training or consent process for whatever reason will not be supplied a THN kit. To improve adherence to the study protocol, paramedics will be provided with individually assigned THN kits, to promote a sense of value and ownership. We will provide regular newsletter updates on progress of the study to participating ambulance stations, to maintain awareness of participating paramedics.

Outcome measures

Outcomes listed below will be measured, for both groups except where specified:

1. Processes and outcomes of care for patients attended by participating paramedics, at index call and up to 12 months.

Numbers and proportions of patients:

- ▶ Eligible and not eligible for inclusion in trial;
- ▶ Offered and not offered THN;
- ▶ THN protocol followed and not followed by crew (compliance);
- ▶ Accepted and did not accept THN;
- ▶ Attended emergency department (ED) and did not attend ED;
- ▶ Suffered further overdose(s) and attended by ambulance;
- ▶ Death (from any cause/opioid poisoning).

Time:

- ▶ From 999 call to ambulance free for next call (job cycle time);
- ▶ On scene at index call;
- ▶ To next overdose
 - Patient reported (intervention group only);
 - 999 call.

2. Feasibility of service user follow-up: (intervention group only)
 - ▶ Number and proportion of eligible patients consented to follow-up;
 - ▶ Number and proportion successfully contacted (telephone/post);
 - ▶ Number and proportion that resulted in a completed questionnaire.
3. Patient experience in relation to possession and usage of THN and their views on the initiative.
4. Acceptability to paramedics.

Follow-up

We will follow-up those in the intervention group that consent to follow-up, at 3 months by telephone, or postal questionnaire. All elements of the CONSORT flow chart tracking paramedic and patient recruitment will be kept up to date by the CI and local collaborator, linked to a list and contact details of consented patients. This record will be held securely with all other hard copy documents and will ensure that patients are followed up 3 months after the intervention was provided. The CI or local collaborator will make a maximum of three attempts at telephone contact. Where this fails, a maximum of two patient questionnaires will be sent to the address provided by the patient. To improve the chances of return, stamped addressed envelopes will be included with the questionnaires. All returned questionnaires will be held securely and a record of those who consent to further follow-up (patient focus groups ×2), will be made. If we are unable to recruit sufficient patients to run the focus groups, we will consider running focus groups with non-participant opioid users recruited through local drug service providers.

Data collection, management and analysis

Data related to processes and outcomes of care for patients attended by participating paramedics will be retrieved from ambulance service operational and clinical systems.

- ▶ Patient clinical records completed by crews at the scene of 999 calls.
- ▶ Study data collection forms.
- ▶ Subsequent 999 calls to the same patient, and whether for opioid overdose.

All vehicles operating in the study area will be equipped with a study pack including a study flow chart and training materials. Each pack will also contain simple data collection and patient consent forms (for those who agree to the intervention). Hard copy data will be stored securely in chronological order to support ease and reliability of any relevant follow-up actions. A secure electronic database will be created with the support of the sponsoring organisation's *Informatics* and *Information Governance* departments. Access to the database will be strictly limited to the CI and a member of the sponsoring organisation's *Informatics* team. The CI will be responsible for data entry, but appropriate quality

assurance checks will be undertaken to ensure accurate data capture.

We will analyse outcome measure data on the basis of numbers and proportions. Qualitative data gathered from questionnaires and focus groups will be analysed by an independent and appropriately qualified professional academic with expertise in this area of research.

We will follow-up ED contacts, hospital admissions and mortality at 12 months through anonymised linked data via the SAIL Databank.²⁹

Sample size

Previous work in this area²⁷ identified around 25 opioid overdose cases occurring in the city of Cardiff area per calendar quarter. This study aims to recruit up to 100 patients over the 12-month study period in order to inform sample size of a full trial. To achieve adequate participant enrolment, the geographical area previously studied has been extended to include two additional small towns.

Randomisation, blinding and allocation

Source for the randomisation sequence was The Rand Corporation: *A million random digits*. Freepress, Glencoe, Illinois 1955 and was generated by the CI and IR. Of the 87 volunteer paramedics, we will select five to undertake 'research champion' roles because of their interest and enthusiasm to support the project. Eighty-two paramedic clusters stratified by base station and shift will be randomly allocated to the trial arm; we shall group them for the purpose of training and analysis. Paramedics will be trained at the rate of four per week, following the sequence generated by the randomisation method. Paramedic training will be scheduled to take place over the first 20 weeks of the study. After random allocation, the CI will be the sole custodian. IR will remain blind. Paramedics allocated to weekly training will not be revealed to trainers (research champions), until 1-week before training. This will maintain a practical level of concealment, while allowing for a level of planning to accommodate shift patterns and availability of trainers. Volunteer paramedics and a small number of 'research champions' were enrolled by the CI. On commencement of the study, the CI and 'research champions' will train the paramedics in the sequence identified by the randomisation. Consent was sought from the paramedics prior to their being randomly allocated to trial arms. All but the CI is blinded to allocation and sequence of paramedic training. Clinical practice will remain as standard for the prehospital management of opioid overdose. However, once paramedics have been trained to provide the intervention, they will offer fully recovered patients the opportunity to be given a brief training intervention and THN kit.

Monitoring

Data-monitoring functions will be undertaken by an independent statistician from the supporting Clinical

Trials Unit (West Wales Organisation for Rigorous Trials in Health: WWORTH) at a local University, facilitated through the sponsoring organisation's Research and Development Forum. Any reported adverse events or potential harms directly attributable to the study will be assessed by a member of the sponsoring organisations' 'Concerns' team who will be completely independent of the study team. Any decision to stop the study will be made in consultation with an independent member of the Research and Development Forum, the CI and Sponsor. Trial progress will be reported on a quarterly basis to the sponsoring organisations' Research and Development Forum, which includes independent academic and lay members.

Consent

Patients (intervention group)

Following treatment and full recovery of consciousness following their opioid overdose, paramedics in the intervention group (following their training and kit issue) will give patients a standardised brief outline about THN (see online supplementary appendix 1). If the patient wishes to learn more and agrees to participate, the paramedic will provide a standardised training package.

Patients will be guided through a consent form (see online supplementary appendix 2), which confirms their acceptance of the training and receipt of a THN kit and information pack. Patients have the option to accept or decline 3-month follow-up. The information pack includes a withdrawal form and preaddressed envelope, should the patient wish their data to be withdrawn from the study at a later date.

Paramedics

All paramedics who participate will be volunteers. At the conclusion of their training, paramedics will be asked to complete and sign a consent form that confirms they have received all the necessary information and training to make an informed decision to participate in the study itself and any post study (no more than one per paramedic) focus groups they may be invited to attend.

Confidentiality

All clinical records completed by ambulance clinicians in the study area are routinely secured in locked cabinets on return to the base station either during or at the completion of duty. For the duration of the study, this process will continue, with the only modification being that all opioid-related overdose records will be placed in brightly coloured envelopes by ambulance clinicians, to assist in their identification and relevance to the study. All relevant documentation and envelopes will be delivered to the CI and secured in a locked cabinet, in a locked office. Clinical records will be photocopied and then returned to the secure cabinets to ensure routine clinical audit processes continue. Access to all hard copy documents will be strictly limited to the CI. The only exception to this will be for the purposes of data entry

quality assurance checks, which will be performed by an individual normally provided routine access to clinical records. On completion of the trial, all records will be archived securely at the sponsoring organisations' Prehospital Emergency Research Unit.

Criteria for progression to full trial

To assess whether progression to a full trial of the intervention is indicated, we will undertake formal review against the criteria set out below,³⁰ at a meeting of the Trial Management Group approximately 6 months after the operational phase of the study has ended.

- ▶ Feasibility and appropriateness of the trial design
 - Paramedic recruitment within 75% of target;
 - At least 75% of participating paramedics trained.
- ▶ Feasibility and appropriateness of the mechanics, management and safety of the interventions
 - THN kits offered (or reason recorded for not offering) by participating paramedics to at least 50% of eligible patients;
 - Reported adverse events or reactions including malicious administration or death as considered by independent panel.
- ▶ Acceptability and efficiency of implementing the research procedures
 - Retrieval of outcome data for at least 75% of recruited participants;
 - Completed questionnaire returned by 30% of recruited participants.

CONCLUSION

THN has been provided in various forms (ampoules/prefilled syringes) to opioid users registered with drug services since the 1990s. To the best of our knowledge, this is the first study to test the feasibility of the involvement of paramedics in the supply of THN during an emergency care episode where environmental and interpersonal challenges are even higher. Evidence about feasibility, clinical and cost-effectiveness of THN provision by paramedics is urgently needed to inform the development of policy and practice for this high-risk population.

Author affiliations

¹Medical and Clinical Services Directorate, Welsh Ambulance Services NHS Trust, Blackweir Ambulance Station, Cardiff, UK

²Operational Services, Welsh Ambulance Services NHS Trust, Blackweir Ambulance Station, Cardiff, UK

³Cardiff Addictions Unit, Cardiff & Vale University Health Board, Cardiff Royal Infirmary, Cardiff, UK

⁴West Wales Organisation for Rigorous Trials in Health (WWORTH), Institute of Life Science, College of Medicine, Singleton Park, Swansea, UK

⁵Thematic Research Network for Emergency, Unscheduled and Trauma care (TRUST), Institute of Life Science, College of Medicine, Swansea University, Singleton Park, Swansea, UK

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Contributors RO had the original idea for the study and developed a first draft of a business case for funding from Welsh Government. RO also assisted with development of training materials and provided comments on drafts of REC applications and the study protocol. CM amended business case, drew study group together, drafted study protocol, support materials and REC applications. HS helped develop study protocol and design and assisted with drafts of REC applications and study protocol. IR provided advice on study design, supported REC submission and presentation, randomisation methodology and commented on study protocol. GL drafted study training materials, assisted with gaining paramedic expressions of interest, provided valued expertise on operationalisation of the study and contributed to drafts of the protocol.

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Competing interests None.

Ethics approval South East Wales Research Ethics Committee, Panel C.

Provenance and peer review Not commissioned; peer reviewed for ethical and funding approval prior to submission.

Data sharing statement Further details of the study protocol can be requested from the corresponding author.

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