Parmar, M. K. B., Strang, J., Choo, L., Meade, A. M., & Bird, S. M. (2016). Randomized controlled pilot trial of naloxone-on-release to prevent post-prison opioid overdose deaths. *Addiction*. https://doi.org/10.1111/add.13668
Randomized controlled pilot trial of naloxone-on-release to prevent post-prison opioid overdose deaths

Mahesh K. B. Parmar1*, John Strang2*, Louise Choo1, Angela M. Meade1 and Sheila M. Bird3.

1MRC Clinical Trials Unit at University College London, LONDON WC2B 6NH

2National Addiction Centre at King’s College London, LONDON SE5 8AF

3MRC Biostatistics Unit, University of Cambridge Institute of Public Health, CAMBRIDGE CB2 0SR

* Joint first authors

Corresponding author: Sheila M. Bird

RUNNING HEAD: N-ALIVE to prevent opioid deaths post-release

CONFLICTS of INTEREST

MKB, LC, AMM: no conflicts of interest.

JS: JS is a researcher and clinician who has worked with a range of types of treatment and rehabilitation service-providers, including treatments within prison and on prison release. JS is supported by the National Institute for Health Research (NIHR) Biomedical Research Centre for Mental Health at South London and Maudsley NHS Foundation Trust and King’s College London. He has also worked with a range of governmental and non-governmental organisations, and with pharmaceutical companies to seek to identify new or improved treatments (including naloxone.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/add.13668

This article is protected by copyright. All rights reserved.
products) from whom he and his employer (King’s College London) have received honoraria, travel costs and/or consultancy payments. This includes work with, during past 3 years, Martindale, Reckitt-Benckiser/Indivior, MundiPharma, Braeburn/MedPace and trial medication supply from iGen. His employer (King’s College London) has registered intellectual property on a novel buccal naloxone formulation with which JS is involved. JS has also been named in a patent registration by a Pharma company as inventor of a concentrated nasal naloxone spray. For a fuller account, see JS’s web-page at http://www.kcl.ac.uk/ioppn/depts/addictions/people/hod.aspx.

**SMB:** SMB served on Scotland’s National Naloxone Advisory Group and co-authored the peer-review paper on before/after evaluation at 3-years of Scotland’s National Naloxone Policy. SMB holds GlaxoSmithKline shares.

**N-ALIVE pilot TRIAL’s CLINICAL TRIAL REGISTRATION:** ISRCTN34044390
Randomized controlled pilot trial of naloxone-on-release to prevent post-prison opioid overdose deaths

ABSTRACT

Background and aims: Naloxone is an opioid antagonist used for emergency resuscitation following opioid overdose. Prisoners with a history of heroin injection have a high risk of drug-related death soon after release from prison. The N-ALIVE pilot trial (ISRCTN34044390) tested feasibility measures for randomized provision of naloxone-on-release (NOR) to eligible prisoners in England.

Design: Parallel group randomized controlled pilot trial.

Setting: English prisons.

Participants: A total of 1685 adult heroin injectors, incarcerated for at least 7 days pre-randomization, release due within 3 months and more than 6 months since previous N-ALIVE release.

Intervention: Using 1:1 minimization, prisoners were randomized to receive on-release a pack containing either a single ‘rescue’ injection of naloxone or a control pack with no syringe.

Measurements: Key feasibility outcomes were tested against prior expectations: on participation (14 English prisons; 2800 prisoners), consent (75% for randomization), returned prisoner self-questionnaires (RPSQs: 207), NOR-carriage (75% in first 4-weeks) and overdose-presence (80%).
Findings: Prisons (16) and prisoners (1685) were willing to participate (consent-rate, 95% CI: 70% to 74%); 218 RPSQs were received; NOR-carriage (95% CI: 63% to 79%) and overdose-presence (95% CI: 75% to 84%) were as expected. We randomized 842 to NOR, 843 to control during 30 months but stopped early because only one third of NOR administrations was to the ex-prisoner. Nine deaths within 12 weeks of release were registered for 1557 randomized participants released before 9 December 2014.

Conclusions: Large randomized trials are feasible with prison populations. Provision of take-home emergency naloxone prior to prison release may be a life-saving interim measures to prevent heroin overdose deaths among ex-prisoners and the wider population.
Randomized controlled pilot trial of naloxone-on-release to prevent post-prison opioid overdose deaths

Mahesh K. B. Parmar1*, John Strang2*, Louise Choo1, Angela M. Meade1 and Sheila M. Bird3.

1MRC Clinical Trials Unit at University College London, LONDON WC2B 6NH

2National Addiction Centre at King’s College London, LONDON SE5 8AF

3MRC Biostatistics Unit, University of Cambridge Institute of Public Health, CAMBRIDGE CB2 0SR

* Joint first authors

Corresponding author: Sheila M. Bird

INTRODUCTION

Prisoners with a history of heroin injection have a high risk of drug-related death (DRD) soon after prison-release which was estimated at 5 DRDs per 1000 eligible releases on the basis of record-linkage studies in Scotland in 1996-991, and in England and Wales in 1999-2002.2 See also meta-analyses34.

Naloxone is an opioid antagonist that can be administered intramuscularly and is used by emergency services to reverse heroin/opioid overdose5. The feasibility of randomized provision of naloxone-on-release (NOR) to a high-DRD-risk population, such as inmates with a history of heroin injection use on their release from prison as proposed by Bird and Hutchinson1, had not been investigated. Prison-based randomized trials must address either a concern that applies specifically to prisoners (as here) - to counter the challenge that the same trial could equally well have been conducted in the outside community; or be able to point to parallel trials on the outside to answer the challenge of exploiting prisoners’ captivity.
One recent international review of non-randomized community initiatives on take-home naloxone, mainly in USA and UK, with follow-up for 3 to 6 months of their trainees, gave an estimated fatality rate at witnessed opioid overdose of 6% (upper 95% confidence limit: 11%), suggesting that a target for the annual distribution of naloxone-kits should be 9 to 20 times a nation’s annual number of opioid-related deaths. A recent comprehensive monograph has documented the historical development (from the 1990s) and spread of take-home naloxone programmes through North America, Europe and Australia; and considered their practical implementation, including the training of naloxone recipients in how to recognise and respond to an overdose. Although supported by the World Health Organization, barriers remain to accessing take-home naloxone: in most European jurisdictions, naloxone is a prescription-only medicine; in others (see below), its addition to the exempt list of prescription-only medicines did little to change clinical practice, take-home naloxone being deemed contentious by some, complex by others. When the notification of overdose events triggers a report to the police, this may discourage witnesses from contacting emergency medical services; and the need to inject naloxone can prove a psychological barrier for some responders as well as being a potential health risk for all who administer the injection.

In 2005, naloxone was added to UK’s exempt list of prescription-only medicines that can be administered by anyone to save life in an emergency. Bird, Parmar and Strang then applied to the UK Medical Research Council (MRC) for funding to conduct a randomized effectiveness study of NOR for prisoners with a history of heroin use by injection. The definitive NALoxone INvestigation (N-ALIVE) trial was to investigate if NOR could reduce DRDs in the first 4 weeks after release by 30% and in weeks 5-12 by 20%. In 2008, MRC funded the N-ALIVE pilot trial to randomize the first tenth of 56,000 prisoners needed for the main trial: half in Scotland, the other half in 15 prisons in England and Wales. The rationale for the N-ALIVE trial has been previously described.
In January 2011, Scotland became the first nation to make both community-based take-home naloxone and NOR for eligible prisoners a funded public health policy.\textsuperscript{6,13-15} Wales followed suit later in 2011.\textsuperscript{16} Accordingly, N-ALIVE was conducted in English prisons only, and its target accrual reduced to 2,800 participants.

Our \textit{a priori} estimation of the likely effectiveness of naloxone\textsuperscript{1} accounted for some-one else being present four-fifths of opiate overdoses\textsuperscript{12}; and that, most often, the others present (peers or family-members) were willing to intervene but lacked effective means\textsuperscript{17}.

We report the key feasibility outcomes of the N-ALIVE pilot trial compared with prior expectations in the trial protocol (ISRCTN34044390)\textsuperscript{18}, as follows:

i) Participation by prisons and prisoners;

ii) Consents for randomization, Returned Prisoner Self-Questionnaire (RPSQ), phone-contact sub-study;

iii) Receipt of RPSQs;

iv) NOR-carriage and overdose-presence;

v) Whether the N-ALIVE main trial could go ahead as planned, including assessment of to whom NOR was administered.
METHODS

Design: plausible effectiveness and main trial size, plus key assumptions to be checked by pilot trial

N-ALIVE was a randomized controlled trial of parallel groups (see Figure 1). Research-trained prison-based N-ALIVE workers recruited and consented eligible prisoners.

The N-ALIVE main trial was to investigate if NOR could reduce DRDs in the first 4 weeks after release by 30%, from 140 to 98 per 28,000 eligible releases; and in weeks 5-12 by 20%, from 35 to 28 per 28,000 eligible releases, for which randomization of 56,000 eligible releases would be needed for 80% power at 5% significance level. In 2008, MRC funded the N-ALIVE pilot trial to randomize the first tenth of 56,000 prisoners needed for the main trial: half in Scotland, the other half in prisons in England and Wales.

Our a priori estimation of NOR’s likely effectiveness in the main trial took into account that: a) someone else is present at 80% of opiate overdoses\(^{12}\); b) 75% of ex-prisoners randomized to NOR would carry NOR in the first 4-weeks, reducing to 50% in weeks 5-12, but negligible thereafter\(^{18}\); c) most often, the others present (peers or family-members) are willing to intervene\(^{17}\) but, conservatively, we assumed a 50:50 chance that present others would have the presence of mind to locate, assemble and administer NOR to the ex-prisoner\(^{18}\). Hence, NOR’s plausible effectiveness at reducing DRDs was 80%*75%*50%, or 30%, in the 1st 4-weeks, but reduced to 20% in weeks 5-12.

In Scotland and in England and Wales, the N-ALIVE pilot trial was to test our key assumptions on i) participation, ii) consents, iii) receipt of RPSQs, iv) NOR-carriage and overdose presence, and hence v) whether the N-ALIVE main trial could go ahead as planned, including by assessment of to whom NOR was administered.
Because the N-ALIVE pilot trial could randomize in English prisons only, its target accrual reduced to 2,800 participants, sufficient for assessing i) to v) for England. Key outcome measures and prior expectations for the pilot trial\(^{18}\) are detailed in Table 1. The N-ALIVE pilot trial was approved by Essex 2 Research Ethics Committee.

**Data Collection**

Study forms were sent by our prison-based N-ALIVE workers to MRC Clinical Trials Unit by post or fax. Reporting of release-date was particularly important as marking the start of a participant’s at-risk period. Screening logs for eligibility were introduced in September 2012.

The randomization form checked a potential participant’s eligibility and consents and provided the information needed for minimization (see below). Other forms recorded the participant’s release-date or date of prison-transfer. Information on date and cause of death within 4, 12 weeks and six months of a participant’s N-ALIVE release-date was obtained from the Office for National Statistics by checking periodically against registered deaths, most recently on 21 April 2016. The RPSQ was designed to answer objectives iv) and v).

**Eligibility, Randomization and Consent**

Eligibility criteria were age greater than 18 years (upper limit of 44 removed 16 months into the trial because 10% of otherwise eligible prisoners were being excluded, see Table 2), history of heroin use by injection, incarcerated for at least 7 days, expected release date within 3 months of randomization-date, not previously randomized in N-ALIVE trial and then consent withdrawn prior to release, and written informed consent. Exclusion criteria were known history of anaphylactic reaction to naloxone, confirmed/declared pregnancy or pregnancy intended within six months, normally resident outside of UK, and randomization-date within six months of most recent N-ALIVE release-date (or, if missing, within one year of previous randomization-date).
Participants were randomized (1:1) by MRC Clinical Trials Unit to receive on release a pack containing either a single ‘rescue’ injection of naloxone or a control pack which did not contain naloxone – there was no placebo. Minimization (with 80:20 randomization) was applied across: gender, age-group (18-24, 25-34, 35+ years), re-randomization, management of opioid dependency at randomization (substitution, detoxification, other), and likely interval from randomization to index release (within 28 days, 4-12 weeks).

Consent for mortality follow-up was mandatory at the time of consent for randomization, but could be withdrawn while participants were still in prison: in such a case, the participant would be withdrawn from the trial and no attempt would be made to provide a pack on release. Additionally, prisoners were asked for their consent for i) record-linkage to establish if participants had had any admissions to accident and emergency departments for non-fatal overdose in the 12 weeks following their N-ALIVE release-date; and ii) randomization in a once-only phone-contact sub-study\(^{18}\), see Figure 1 and Supplementary.

The trial was double-blind prior to release so that, while the participant was still in custody and pre-release, neither the participant nor prison-based N-ALIVE staff nor prison staff knew the allocation. Participants learned their allocation when they opened the pack at the time of their release.
**N-ALIVE packs**

Each prison had a supply of pre-numbered sealed N-ALIVE packs\(^19\). Control and naloxone packs were identical in appearance, sounded alike when shaken, and were similar weights. All packs contained the N-ALIVE DVD, a wallet and had tamper-evident stickers attached.

The wallet in the control pack did not contain a syringe. The wallet in the naloxone pack included all the same material as the control wallet but also contained a pre-filled syringe, the unscrewed plunger rod for the syringe and a safety-covered, sterile-packed hypodermic needle, see **Supplementary**. The plunger had been removed from the syringe barrel so that both fitted into the N-ALIVE wallet; both had to be fitted to the syringe before use. The syringe contained 2mg of naloxone hydrochloride in 2ml of solution, for once-only intramuscular injection in the event of overdose. During information and consent sessions, participants were advised on how to administer the N-ALIVE-recommended 0.8mg intramuscular dose of naloxone. For trial purposes, the naloxone needed to be a single product\(^19\). As none of the available products fitted our needs well, the correct dose in single product form was most crucial. Accordingly, we selected the 2mg pre-loaded syringe as an acceptable formulation for the pilot trial period\(^19\); which necessitated additional instructions for administration to be limited to a 0.8mg dose.

**Returned Prisoner Self-Questionnaire**

We asked participants if they were willing to complete an anonymous follow-up questionnaire, if they returned to prison within six months of their most recent N-ALIVE release date. The RPSQ identified the participant’s randomized assignment and the time-interval between the preceding N-ALIVE release-date and completion-date but, to encourage frankness, the identity of the respondent was not recorded. Forms were neither checked nor overseen by the N-ALIVE worker unless the respondent so chose.
Statistical Analysis

All validly randomized participants who were released from custody before 9 December 2014 are included in the analyses.

Simple summary statistics for percentages or counts (together with 95% confidence intervals, CIs) are used to assess consistency with prior expectations: on consents, RPSQs, NOR-carriage in the 1st 4-weeks, overdose presence and the use made of NOR to save the life of others than those for whom it was prescribed. Comparison of rates between NOR versus control group, based on RPSQs, is by chi-squared or Fisher’s exact test, as appropriate.

Formal comparison of risk-behaviours versus perception between NOR versus control is based on a composite score for risk-behaviours, derived post-hoc from RPSQs. Early cessation of randomization in the N-ALIVE pilot trial made it unlikely that subsequent NOR-evaluations would be individually randomized. We therefore needed to make best use of the N-ALIVE pilot trial’s data to explore whether those randomized to NOR had increased the riskiness of their heroin use soon after release, as distinct from how participants perceived that their behaviour had been changed by taking part in N-ALIVE.

Risk Score

To analyse how provision of NOR impacted on participants’ heroin use and related risk behaviours soon after release, a risk score based on RPSQ responses was devised by SMB and AMM; and agreed by JS and MKBP (see Supplementary for how individual questions were scored) before being implemented by LC and tested for interaction (NOR versus control) against perceived behaviour-change.
RESULTS

Recruitment: prisons and participants

The trial was conducted in 16 prisons in England. Based on screening logs, the consent-rate for randomization among eligible prisoners was 72% (1283/1777, 95% CI: 70% to 74%), just short of our prior assumption of 75% (Table 1).

Between May 28th 2012 and December 8th 2014, we randomized 1685 participants (842 to NOR; 843 to control). Nine participants are considered ‘not-randomized’ because they were withdrawn prior to release: four withdrew consent for mortality follow-up prior to their release, while five were found to be ineligible, see Figure 2 [CONSORT].

Consent to complete the RPSQ was given by 85% of participants (1417/1676), better than our prior expectation of 75%. Consent to take part in the phone-contact study was provided by 56% (946/1676, 95% CI: 54% to 59%) of participants, better than our prior assumption of 50%.

Re-Randomizations

Of the 129 participants randomized more than once, 61 had received naloxone on the first occasion while 68 received control, consistent with expectation (64.5 each) if prior allocation did not influence the decision to be re-randomized.

Early cessation of randomization: decisions by Trial Steering-Data Monitoring Committee (TS-DMC)

We closed the trial to accrual on 8th December 2014, ahead of our planned closure date. An unscheduled interim analysis of the feasibility outcomes of the N-ALIVE pilot trial was prompted by the release on 28th October 2014 of the 3rd year of results from Scotland’s National Naloxone Programme, see Figure 3.
When randomization to N-ALIVE stopped, all participants who remained in custody were to be offered naloxone on their release, including those due to receive a control pack. The Principal Investigators at our prisons so agreed. Participants were otherwise followed up per-protocol.

**Baseline Characteristics**

The baseline characteristics and treatment allocation of the 1557 randomized participants who were released by 8\textsuperscript{th} December 2014 (93\% of the 1676 who were eligible to receive a pack on release) are shown in Table 2.

**Provision of Packs on Release**

Of those participants released before 8\textsuperscript{th} December 2014, 81\% received their N-ALIVE pack on release (1266/1557; 95\% CI: 79\% to 83\%).

**RPSQs: Return-rate and Findings**

We received 218/1557 (14\%) RPSQs by December 8\textsuperscript{th}, 2014; 205 with information on treatment assignment (112 naloxone; 93 controls), consistent with our prior expectation of 207 (95\% CI: 179 to 235), see Table 1. Median and mean time (sd) from release-date to RPSQ-completion were 64 and 80 (62) days.

(a) naloxone carriage and administration: Of RPSQ-respondents assigned to NOR, 76\% (85/112; 95\% CI: 68\% to 84\%) told a family member or friend about their naloxone (Table 3) and 71\% (80/112; 95\% CI: 63\% to 79\%) reported carriage of naloxone in the first 2-weeks post-release, consistent with prior expectation (Table 1). Naloxone acquisition from other sources occurred at a non-differential, low rate (12/205, 95\% CI; 2.6\% to 9.1\%). More often, RPSQ-respondents reported that their NOR had been administered to ‘save’ someone else (14\%; 16/112) than themselves (5\%; 5/112), see also Figure 3.
Twenty-one percent (23/112) reported administration of naloxone to themselves or another before the arrival of a doctor or ambulance versus 9% (8/93) for controls (chi-square on 1df = 5.64; p=0.02). Cumulative accounting for overdose victims being taken to hospital was 26% (29/112) for NOR versus 28% (26/93) for controls; chi-square on 1df = 0.11 (p=0.74).

(b) personal drug use, injecting and overdose events: Two-thirds of RPSQ-respondents had used heroin in the first fortnight post-release (67%, 137/205).

Half (105/205) of the RPSQ-respondents had injected in the first fortnight – 58% (65/112) for NOR and 43% (40/93) of controls; 26% (53/205; 95% CI: 20% to 32%) had injected when alone in the first 2-weeks post-release, on a mean of six days out of 14 (95% CI: 4.9 to 7.1 days), broadly consistent with our prior expectation of someone else present at 80% of opiate overdoses (Table 3; Table 1).

Five percent of RPSQ-respondents (10/205) had personally experienced an overdose within the first fortnight – 7% (8/112) for NOR and 2% (2/93) of controls (Fisher’s exact test, p=0.12). Thereafter until re-imprisonment, the proportion personally overdosing was 5% (11/205) for NOR and controls alike.

(c) witnessed overdoses and actions taken: Fifteen percent of RPSQ-respondents (31/205) had personally witnessed an overdose in the first fortnight post-release – 17% (19/112) for NOR and 13% (12/93) of controls. Thereafter until re-imprisonment, the witness-proportion was 15% (30/205) for NOR and controls alike.

(d) opinions about NOR and the N-ALIVE trial: Taking part in N-ALIVE was positively associated with safer heroin use by 60/112 (54%) RPSQ-respondents randomized to NOR and 30/93 (32%) of controls (chi-square on 1df = 9.37, p<0.002). Suggestions made by 113 RPSQ-respondents were most...
commonly: ‘everyone should get naloxone’ (22), ‘everyone should get naloxone not just 50:50’ (10); ‘availability and access’ (11); ‘safer perception’ (8), ‘education and awareness’ (8); and ‘research trial a good idea’ (6), see Supplementary. Fifty difficulties were cited, the top three being: ‘didn’t get naloxone’ (12), ‘no pack on release’ (7) and ‘police not aware’ (6).

Four difficulties were potential adverse events: (1) because police were unaware of the N-ALIVE pilot trial, one ex-prisoner would have been arrested but for intercession by a drug-intervention-programme worker; (2) ex-prisoner’s partner was worried about children finding his naloxone; (3) acquaintance of another ex-prisoner took the naloxone “to see if he got a buzz from it”; and (4) ex-prisoner was unsure how much of naloxone to administer to a person who had overdosed.

**Risk Score**

Table 4 shows that RPSQ-respondents’ mean risk score was not significantly different between NOR (3.9) and controls (3.5). We observed an interaction (p=0.049) between randomized assignment, self-reported safer behaviour and mean risk score: for controls, but not for NOR, RPSQ-respondents’ mean risk score was significantly lower for those who self-reported safer behaviour (2.4) versus not (4.0).

**Drug-Related Deaths**

Only half of the DRDs registered in England and Wales in a specific calendar year actually occur in that calendar year\textsuperscript{22,23} and so it was necessary to wait at least a year to report on DRDs.

Nine deaths had occurred in the 12 weeks post-release among 1557 randomized participants and were registered with the Office for National Statistics before 21 April 2016 (Table 1 and Supplementary). Five were DRDs, consistent with our null-expectation of 9.7 DRDs in 12-weeks after release; but only two DRDs occurred in the 1\textsuperscript{st} 4-weeks, well below our null-expectation of 7.9 (Table 1).
Of the four opioid-related DRDs, three were randomized to NOR of whom one was released without his pack. The participant whose DRD was not opioid-related was also randomized to NOR and had been released without his pack.

**DISCUSSION**

The N-ALIVE pilot trial has randomized more prisoners than any other prison-based, individually randomized controlled trial in Europe. We have shown that large-scale trials of public health interventions are feasible within prisons. Prisoners themselves showed enthusiasm for the N-ALIVE trial - their consent rate was excellent (72%).

The N-ALIVE pilot trial stopped early because its own data together with those from Scotland’s National Naloxone Programme were persuasive that approximately two-thirds of NOR administrations were *not* to the ex-prisoner for whom NOR was assigned. We had no means of knowing the identities of these other persons: confounding of N-ALIVE’s control group could have occurred. The N-ALIVE pilot trial ceased because individualized randomization to NOR cannot offer a clear-cut answer: other trial designs are required.

We were concerned that a 50% consent-rate combined with 50% contact-rate for the half randomized to actual phone-contact would mean that only 195 phone-interviews would be likely to be achieved from 1557 randomized participants. In practice, the achievement was lower still with 81 successful phone interviews. By contrast, RPSQs which were specifically designed to protect the respondent’s confidentiality achieved their anticipated response-rate.

Other prior assumptions were vindicated by the feasibility trial. Few actual or potential adverse events were reported: one reply-card informed us that naloxone had been administered to an
overdose victim who had survived but had experienced withdrawal symptoms; one ex-prisoner had faced arrest because the police were not sufficiently aware of the N-ALIVE trial; and two respondents cited their or a partner’s concern for safer packaging lest children might access the naloxone.

Notwithstanding RPSQ-respondents’ eight reports of overdose in the first fortnight for NOR versus two for controls, and comparable injection rates in the first fortnight post-release (Table 3), RPSQ-respondents randomized to NOR self-reported safer heroin use compared with controls. However, our risk score comparisons (Table 4) showed a significant interaction whereby only for controls did the mean risk score align with self-reported safer behaviour. Returned prisoners randomized to NOR perceived greater safety than their RPSQ answers demonstrated, which suggests some risk compensation about which Strang et al.24 forewarned, see also other prevention policies from seat-belt legislation to safety helmets25-27, where a degree of risk compensation detracted in a small way from the policy’s overall benefit. N-ALIVE participants’ main suggestion was that naloxone should be made more widely available to all those at-risk.

To our knowledge, no previous contemporaneous before/after policy-evaluation and randomized trial of effectiveness has had the same primary outcome: here, DRDs or opioid-related DRDs with a 4-week antecedent of prison-release6 9 14. The N-ALIVE team convened its TS-DMC ahead of the release of the third year results from Scotland’s National Naloxone Programme.6 21 Consistency between RPSQ-responses on the administration of NOR (another vs self, 15:5) and Scotland’s data on the utilization of NOR by those who applied for re-supply (21:12) convinced the TS-DMC that an individually-randomized main trial was infeasible because only one-third of NOR administrations was to the ex-prisoner, two-thirds to another person whose identity was unknown to the N-ALIVE trial.

No reliable inference about NOR’s effectiveness for reducing DRDs in the 12 weeks post-release can be drawn from the early-cessation N-ALIVE pilot Trial: five registered DRDs (four randomized to NOR,
of whom two were released without their pack) were fewer than our a priori null-expectation (9.7), perhaps because the expectation was too high rather than as a reflection of NOR’s effectiveness. However, the 15% fatality-rate (95% CI: 6% to 24%) at overdoses which our RPSQ-respondents witnessed, typically within 12 weeks of their N-ALIVE release-date, suggests that our ex-prisoners were present at higher-fatality-risk overdoses than suggested by an evidence-synthesis which gave a 6% fatality-rate (95% CI: 2% to 11%) at witnessed opioid overdoses. Explanations for the higher fatality-rate reported by our recidivists range from chance through assortative mixing of ex-prisoners – who then share the same high DRD-rate post-release - to ex-prisoners’ high DRD-risk being due to a higher fatality-rate per overdose (rather than to higher overdose-rate with common fatality-rate per overdose).

The Scottish results, data on cost-effectiveness of naloxone, World Health Organization recommendations on naloxone, UK’s legal change on provision of naloxone, England’s increase in opioid-related DRDs, and prisoners’ support for initiatives like the N-ALIVE pilot trial make it timely for England and others to introduce a funded national naloxone policy; but also to evaluate, as Scotland did. In summer 2016, the National Institute for Health Research issued an evaluation-call for naloxone studies in England. This call could address alternative, licensed non-injectable formulations of naloxone or divert attention from England’s failure to fund a naloxone policy: NOR with, or without, take-home naloxone.

Our findings add trial-based evidence to the growing consensus that pre-provision of take-home emergency naloxone can enable life-saving interim measures to prevent overdose deaths, and that the period after prison-release is not only a time of great concentration of such deaths but also of opportunity to prevent this major contribution to the global burden of disease. [3882 words]
Research in context

Evidence before this study

The N-ALIVE pilot trial was the first randomized controlled trial to investigate provision of naloxone-on-release (NOR) to prisoners who have previously injected heroin. The MRC funded the N-ALIVE pilot trial to investigate the feasibility of a fully-powered randomized trial.

Added value of this study

The N-ALIVE pilot trial has shown that it is feasible to conduct a large prison-based randomized controlled trial, with good participation from both prisons and prisoners. The finding that two-thirds of administrations of NOR were to someone unknown to the N-ALIVE pilot trial means that alternative research designs should be considered for preventative interventions against fatal overdose.

Implications of all the available evidence

The N-ALIVE pilot trial has demonstrated the feasibility of recruiting many prisons, and consenting large numbers of prisoners, to take part in randomized evaluations that matter to prisoners. The practicality of NOR has now been demonstrated in two prison systems (by Scotland’s National Naloxone Policy and by the N-ALIVE pilot trial) and so prisons, internationally, can deliver NOR.

Scotland’s non-randomized before/after policy evaluation demonstrated the effectiveness of NOR and community-based take-home naloxone (jointly) for reducing opioid-related deaths in the 4-weeks after prison-release. Two-thirds of administrations of NOR (Scotland; N-ALIVE) were to someone other than the ex-prisoner for whom NOR was prescribed. The N-ALIVE pilot trial reacted promptly to external data from Scotland and from the trial itself to close the N-ALIVE trial to recruitment.
Between 6,000 and 8,000 drug-induced deaths are reported in Europe every year, with opioids their major cause. The European Monitoring Centre for Drugs and Drug Addiction exhorts member-states that many of these deaths could be prevented by adequate peer intervention using naloxone. Age-related rising numbers of opioid-related DRDs complicate before-after evaluations, as in Scotland.

ACKNOWLEDGEMENTS

Co-Principal Investigators: Mahesh KB Parmar, Sheila M Bird, John Strang

N-ALIVE Pilot Trial team: Angela Meade (Project Lead), Louise Choo (Trial Statistician), Monica Mascarenhas (Trial Manager)

Former N-ALIVE Pilot Trial team members: Gemma Wood, Emma Beaumont, Laura Nichols, Tracey Pepple, Demelza Nock, Nicola Muirhead, Julie Bakobaki, Susan Hennings, Lizzie Armstrong

Our prison-based PIs were given the opportunity to comment on the paper and we are grateful for all comments received. The PIs were: HMP Bristol, Karen Alloway; HMP Nottingham, Andrew Bickle; HMP Exeter, HMP Dartmoor and HMP Channings Wood, Christine Brown; HMP Winchester, Anand Nadaradjou; HMP Liverpool, Mohammed Faizal; HMP Leeds, Nat Wright; HMP Lincoln Neil Wright and Andrew Bickle; HMP Dovegate, Tina Dunsdon; HMP Holloway, Farukh Alam; HMP Oakwood, Ashley Logan; HMP Elmley and HMP Rochester, Beatrice Tagliavni; HMP Doncaster, Andrew Bickle and Ramneesh Puri; HMP Gloucester: Sarah Welsh (invited to join TS-DMC after HMP Gloucester closed to accrual).

Trial Steering and Data Monitoring Committee – Independent Members: Professor Deborah Ashby (chair), Dr Roy Robertson, Dr Sarah Welch, Mr John Podmore and Mr Jason Gough (until October 2014).
The N-ALIVE pilot trial was approved by the Mental Health Research Network for inclusion into their portfolio of studies. MHRN staff took on the role of N-ALIVE worker at many of our prisons. Our N-ALIVE workers were:

HMP Bristol: Karen Alloway, Jane Makin, Michelle Phillips, Sheila Shatford;
HMP Nottingham: Julie Mernick, Natalie Marking, Amy Shuttlewood, Elizabeth Butcher (nee Andrew)
HMP Exeter, HMP Dartmoor and HMP Channings Wood: Sian Lison, Sue Bartram, Rebecca Bishop, Robert Bright;
HMP Winchester: Winner Chimbwanda, Nicky Holdaway, Sazini Malata;
HMP Liverpool: Kelly Palethorpe, Heather Morrison, Lorraine Bickerstaffe;
HMP Leeds: Philippa Hearty, Christine Butt;
HMP Lincoln: Amy Shuttlewood, Elizabeth Butcher (nee Andrews), Anne Chafer, Diane Brennan;
HMP Dovegate: Kim Thompson, Tim Lewington;
HMP Holloway: Saloni Dosani;
HMP Oakwood: Angela Hoadley, Gurdees Watson (nee Takhar);
HMP Elmley and HMP Rochester: Jack Thornton, Laiza Rangarira;
HMP Doncaster: Amy Shuttlewood, Elizabeth Butcher (nee Andrew);
HMP Gloucester: Genevieve Riley, Emma Page, Simon Ball

Finally, and most importantly, we acknowledge and thank our prisoner participants.
FUNDING and ROLE of FUNDING SOURCE:

The pilot N-ALIVE Trial was grant-funded by the Medical Research Council (MC_G0800012) and co-ordinated by the MRC Clinical Trials Unit at University College London, which core-funds MKBP, LC and AMM.

SMB was funded by Medical Research Council programme number MC_U105260794.

JS is core-funded by his university, King’s College London.

The MRC’s funding board had no role in data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.
REFERENCES

1. Bird SM and Hutchinson SJ. Male drugs-related deaths in the fortnight after release from prison: Scotland, 1996–99. *Addiction* 2003; 98: 185–190.

2. Farrell M and Marsden J. Acute risk of drug-related death among newly released prisoners in England and Wales. *Addiction* 2008; 103: 251–255.

3. Merrall ELC, Kariminia A, Binswanger IA, Hobbs M, Farrell M, Marsden J, Hutchinson SJ, Bird SM. Meta-analysis of drug-related deaths soon after release from prison. *Addiction* 2010; 105: 1545 – 1554.

4. Kinner SA, Forsythe S, Williams G. Systematic review of record linkage studies of mortality in ex-prisoners: why (good) methods matter. *Addiction* 2013; 108: 38-49.

5. Clarke S, Dargan P, Jones AL. Naloxone in opioid poisoning: walking the tightrope. *Emergency Medicine Journal* 2006; 22: 612-616. See doi:10.1136/emj.2003.009613.

6. Bird SM, Parmar MKB and Strang J. Take-home naloxone to prevent fatalities from opiate-overdose: Protocol for Scotland’s public health policy evaluation, and a new measure to assess impact. *Drugs Education Prevention Policy* 2014; 22: 66–76.

7. Strang J, McDonald R (Editors). *Preventing opioid overdose deaths with take-home naloxone*. European Monitoring Centre for Drugs and Drug Addiction, Lisbon: January 2016.
8. World Health Organization. *World Health Organization recommendations on community management of opioid overdose*. Geneva, November 2014. Accessed 05012016: http://apps.who.int/iris/bitstream/10665/137462/1/9789241548816_eng.pdf?ua=1&ua=1

9. Strang J, Bird SM and Parmar MKB. Take-home emergency naloxone to prevent heroin overdose deaths after prison release: Rationale and practicalities for the N-ALIVE randomized trial. *Journal of Urban Health* 2013; 90: 983–996.

10. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council Guidance. *British Medical Journal* 2008; 337:a1655.

11. Strang J, Kelleher M, Best D, Mayet S, Manning V. Preventing heroin overdose deaths with emergency naloxone – new legislation broadens scope of potential providers and contexts. *British Medical Journal* 2006; 333: 614-615.

12. Strang J, Powis B, Best D et al. Preventing opiate overdose fatalities with take-home naloxone: pre-launch study of possible impact and acceptability. *Addiction* 1999; 94: 199 – 204.

13. McAuley A, Best D, Taylor A, Hunter C and Robertson R. From evidence to policy: The Scottish National Naloxone Programme. *Drugs: Education, Prevention & Policy* 2012; 19: 309-319.
14. Bird SM, McAuley A, Perry S, Hunter C. Effectiveness of Scotland’s National Naloxone Programme for reducing opiate-related deaths: a before (2006-10) versus after (2011-2013) comparison. *Addiction* 2015; doi: 10.1111/add.13265.

15. McAuley A, Munro A, Bird SM, Hutchinson SJ, Goldberg DJ, Taylor A. Engagement in a National Naloxone Programme among people who inject drugs. *Drug and Alcohol Dependence* 2016; 162: 236 – 240. DOI: [http://dx.doi.org/10.1016/j.drugalcdep.2016.02.031](http://dx.doi.org/10.1016/j.drugalcdep.2016.02.031)

16. Bennett T, Holloway K. Evaluation of the take home naloxone demonstration project. Welsh Assembly Government Social Research. 2011; Retrieved from: [http://wales.gov.uk/about/aboutresearch/social/latestresearch/naloxoneproject/](http://wales.gov.uk/about/aboutresearch/social/latestresearch/naloxoneproject/)

17. Strang J. Death matters: understanding heroin/opiate overdose risk and testing potential to prevent deaths. *Addiction* 2015; 110 Supplement 2: 27 – 35. See doi: 10.1111/add.12904.

18. N-ALIVE protocol, accessed 04012016: [http://www.ctu.mrc.ac.uk/13391/13399/18277/n-alive_trial_protocol](http://www.ctu.mrc.ac.uk/13391/13399/18277/n-alive_trial_protocol).

19. Meade AM, Bird SM, Strang J, Pepple T, Nichols LL, Mascarenhas M, Choo L, Parmar MKB. Methods for delivering Europe’s largest prison-based trial: the Naloxone-on-release pilot randomized trial (N-ALIVE). *Trials* 2016; under review.

20. Bird SM, Strang J, Ashby D, Podmore J, Robertson JR, Welch S, Meade AM, Parmar MKB. External data required timely response by the Trial Steering-Daat Monitoring Committee for the NALoxone InVEstigation (N-ALIVE) pilot trial. *Communications in Contemporary Clinical Trials* 2016: under review.
21. Information Services Division Scotland. *National Naloxone Programme Scotland – naloxone kits issued in 2013/14 and trends in opioid-related deaths.* 28 October 2014. Accessed 05012016: http://www.isdscotland.org/Health-Topics/Drugs-and-Alcohol-Misuse/Publications/2014-10-28/2014-10-28-Naloxone-Report.pdf.

22. Bird SM. Counting the dead properly and promptly (Editorial). *Journal of the Royal Statistical Society Series A (Statistics in Society)* 2013; 176: 815-817.

23. Public Health England. *Trends in drug misuse deaths in England, 1999 to 2014.* See http://www.nta.nhs.uk/uploads/trendsdrugmisusedeaths1999to2014.pdf. Accessed 05042016.

24. Strang J, Powis B, Best D, Vingoe L, Griffiths P, Taylor C, Welch S, Gossop M. Preventing opiate overdose fatalities with take-home naloxone: pre-launch study of possible impact and acceptability. *Addiction* 1999; 94: 199-204.

25. Chirinko RS, Harper EP. Buckle up or slow down? New estimates of offsetting behavior and their implications for automobile safety regulation. *Journal of Policy Analysis and Management* 1993; 12: 270–296.

26. Shelton JD. Ten myths and one truth about generalized HIV epidemics. *Lancet* 2007; 370: 1809-1811. doi:10.1016/S0140-6736(07)61755-3.

27. Thompson CJ, Carlson SR. Increased patterns of risky behaviours among helmet wearers in skiing and snowboarding. *Accident Analysis Prevention* 2015; 75: 179 – 183. See doi: 10.1016/j.aap.2014.11.024.

This article is protected by copyright. All rights reserved.
28. Coffin, PO and Sullivan, SD. Cost-Effectiveness of Distributing Naloxone to Heroin Users for Lay Overdose Reversal. *Annals of Internal Medicine* 2013; **158**:1-9

29. *Changes to UK legislation regarding naloxone prescribing*. Accessed 050116:

   http://www.legislation.gov.uk/uksi/2015/1503/made.

30. Deaths related to drug poisoning in England and Wales, 2016 registrations. *ONS Statistical Bulletin*. September 2016. Accessed 09092016:

   https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/deathsrelatedtodrugpoisoninginenglandandwales/2015registrations.

31. Degenhardt L, Hall W. Extent of illicit drug use and dependence, and their contribution to the global burden of disease. *Lancet* 2012; 379: 55 – 70. doi: 10.1016/S0140-6736(11)61138-0. PMID: 22225671.
Table 1: Feasibility outcomes: summary of prior assumptions and actual findings

| Outcome                      | Prior Assumption                                                                 | Actual                                                                                           | Comment                                      |
|------------------------------|----------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|----------------------------------------------|
| Number of Participating Prisons | 11 prisons in Scotland  
14 prisons in England                                                                    | 16 prisons in England (15 open, 1 closed to recruitment)                                         | Consistent with expectation                  |
| Target Participant Accrual   | 5600 participants  
Original sample size requirement was up to 10% of 56,000 participants           | Target revised down to 2,800 for England due to non-participation of prisons in Scotland and Wales.  
Feb 2014: Interim target revised to 1500 by Aug 31, 2014  
Actual accrual at 31/8/14 was 1392 participants.  
1500 participants achieved on 8/10/14.  
Final accrual at Dec 8th, 2014: 1685 participants | Early cessation, see Figure 3                                                        |
| Consent for randomization by eligible prisoners | 75%                                                                             | Based on screening logs, the consent-rate for randomization among eligible prisoners was 72% (1283/1777); 95% CI: 70% to 95% | Upper 95% confidence limit is just short of our prior |
| **Consent to Returned Prisoner Self Questionnaire (RPSQ)** | prior expectation of 75% | Consent to complete the RPSQ was given by 85% of participants (1417/1676); 95% CI: 83% to 86%. | Above expectation |
| **Consent to secondary randomization in the phone-contact ancillary study** | prior assumption of 50% | Consent to take part in the phone-contact study was provided by 56% (946/1676); 95% CI: 54% to 59%. | Above expectation |
| **Number of Returned Prisoner Self-Questionnaires (RPSQs)** | 333 recidivist self-questionnaires expected from 2500 randomized & released participants and so we expected 333/2500x1557=207 RPSQs | 218 received from 1557 randomized and released participants | Consistent with expectation |
| **Carriage rate in 1st 4 weeks after release** | 75% | RPSQ 71% (80/112), 95% CI: 63% to 79% | Consistent with expectation |
| **Someone else present at overdose** | 80% | Based on RPSQs: 53/205 (26%; 95% CI: 20% to 32%) of recidivists reported having injected when alone, and had done so on a mean of 6/14 days. Hence, 95% CI for | Consistent with expectation |
someone else present is: 68% to 80%.

Telephone questionnaire:
Heroin use in the past three days was reported by 31/81 (38%) of telephone contacts, 10 of whom had injected when alone (12%; 95% CI: 5% to 20%). If the past 3-day rate is taken as representative of the rate throughout the first 4-weeks, then 95% CI for someone else being present at injector’s overdose is 80% to 95%.

Both consistent with our prior expectation that someone else is present at 80% of opiate overdoses.

Pooled estimate (based on weights 61% and 39%) is 79%; 95% CI: 75% to 84%.

| Telephone Questionnaire Phone contacts | Based on the (Probability of consent) x (Probability of being randomized to Phone Contact) 81 out of 1557 randomized and released participants. | Well below expectation |
|----------------------------------------|-------------------------------------------------------------------------------------------------|------------------------|

This article is protected by copyright. All rights reserved.
| Drug-related Deaths in 1st 4 weeks and next 8 weeks after release | We expect $1/200 \times 1557 = 7.9$ or 8 DRDs in 1st 4-weeks after release if NOR is not effective; and a further $1/800 \times 1557 = 1.9$ or 2 DRDs in the next 8 weeks. | 2 DRDs in 1st 4-weeks post-release; a further 3 DRDs in the next 8 weeks were registered with Office for National Statistics by 21 April 2016. |
| Non-fatal overdose-related admissions within 12 weeks of index release | We assume participants’ non-fatal overdose admissions to Accident & Emergency within 12 weeks of index release to be between two and eight times as many as DRDs with 2-3 times as many DRDs being our best estimate, thus we expect 20-30 (but up to 80) non-fatal overdose-related Accident & Emergency admissions. | Awaiting Hospital Episode Statistics data from Health and Social Care Information Centre. |
Table 2: Baseline Characteristics for 1557 Participants Randomized and Released by 8th December, 2014

| Characteristic                                      | NOR                  | Control               | All                   |
|-----------------------------------------------------|-----------------------|-----------------------|-----------------------|
|                                                     | Mean 35 years         | Mean 35 years         | Mean 35 years         |
|                                                     | s.d. 7 years          | s.d. 6 years          | s.d. 7 years          |
| Age (Mean & s.d.) years                            |                       |                       |                       |
| N                                                   | %                     | N                     | %                     | N                     | %                     |
| Age categories (N, %) years                         |                       |                       |                       |
| 18-24                                               | 40 5                  | 40 5                  | 80 5                  |
| 25-34                                               | 381 50                | 385 50                | 766 50                |
| 35-44                                               | 290 38                | 302 39                | 592 39                |
| 45+                                                 | 47 6                  | 46 6                  | 93 6                  |
| Gender (N, %)                                       |                       |                       |                       |
| Males                                               | 762 98                | 771 98                | 1533 98               |
| Females                                            | 12 2                  | 12 2                  | 24 2                  |
| Treatment for Addiction (at Randomization) (N, %)    |                       |                       |                       |
| Opiate substitution                                 | 496 64                | 503 64                | 999 64                |
| Opiate detoxification                               | 163 21                | 163 21                | 326 21                |
| Other (eg Naltrexone, no current treatment)         | 114 15                | 116 15                | 230 15                |
| Not recorded                                        | 1 <1                  | 1 <1                  | 2 <1                  |
| Likely Incarceration Interval (N, %)                |                       |                       |                       |
| (Date of randomization-Expected Release Date at randomization) |                       |                       |                       |
| Within 28 days                                      | 532 69                | 540 69                | 1072 69               |
| 4-12 weeks                                         | 171 22                | 175 22                | 346 22                |
| >12 weeks                                          | 17 2                  | 13 2                  | 30 2                  |
| Unknown release date                                | 54 7                  | 55 7                  | 109 7                 |

This article is protected by copyright. All rights reserved.
Table 3: Responses to Returned Prisoner Self Questionnaire

| Self-Questionnaire                  | NOR                        | Control                   | Total          |
|-------------------------------------|----------------------------|---------------------------|----------------|
| Number of Forms Completed           | 112 (51%)                  | 93 (43%)                  | 205            |
| Time from previous release          | Mean 79, Sd. 59            | Mean 85, Sd. 66           | Mean 82, sd. 63|
| to completion of questionnaire (days)| Median 64                  | Median 64                 | Median 64      |
|                                    | IQR 37-108                 | IQR 39-119                | IQR 38-108     |
| Told family member/friend about Naloxone | 76% (85/112)              | NA                        | NA             |
| Told someone about Naloxone         | 79% (89/112)               | NA                        | NA             |
| Carriage rate of Naloxone           | 71% (80/112)               | NA                        | NA             |
| How Often did you carry it?         |                            |                           |                |
| All                                 | 76% (61/80)                | NA                        | NA             |
| Most                                | 16% (13/80)                | NA                        | NA             |
| Some                                | 6% (5/80)                  |                           |                |
| No response                         | 1% (1/80)                  |                           |                |
| What did you do with the Naloxone?  |                            |                           |                |
| Saved other                         | 14% (16/112)               |                           |                |
| Saved self                          | 5% (5/112)                 |                           |                |
| Lost it                             | 13% (14/112)               |                           |                |
| Had it taken away/stolen            | 10% (11/112)               |                           |                |
| Given it away                       | 7% (8/112)                 |                           |                |
| Thrown it away                      | 2% (2/112)                 |                           |                |
| Broke the syringe                   | 2% (2/112)                 |                           |                |
| No answer given | 48% (54/112) |
|-----------------|-------------|

| Heroin use in the **first 2** weeks after leaving prison | |
| (Yes or No) | 69% (77/112) | 65% (60/93) | 67% (137/205) |
| (Smoke/inject) | 66% (74/112) | 65% (60/93) | 65% (134/205) |
| N=74, Mean 9/14 days, sd 5 days | N=60, Mean 8/14 days, sd 5 days | N=134, Mean 9/14 days, sd 5 days |
| (Inject) | 58% (65/112) | 43% (40/93) | 51% (105/205) |
| N=65, Mean 9/14 days, sd 5 days | N=40, Mean 10/14 days, sd 5 days | N=105, Mean 9/14 days, sd 5 days |
| (Inject, alone) | 23% (26/112) | 29% (27/93) | 26% (53/205) |
| N=25, Mean 6/14 days, sd 5 days | N=26, Mean 6/14 days, sd 4 days | N=51, Mean 6/14 days, sd 4 days |

| Self-overdose <=2 weeks of release | |
| Overdose* | 7% (8/112) | 2% (2/93) | 5% (10/205) |
| Someone present | 8/8 | 1/2 | 9/10 |
| Naloxone given | 3/8 | 2/2 | 5/10 |
| Taken to hospital | 4/8 | 2/2 | 6/10 |

| Self-overdose >2 weeks of release | |

This article is protected by copyright. All rights reserved.
|                          | 4% (5/112) | 6% (6/93) | 5% (11/205) |
|--------------------------|------------|-----------|-------------|
| Overdose                 | 3/5        | 6/6       | 9/11        |
| Someone present          | 3/5        | 3/6       | 6/11        |
| Naloxone given           | 4/5        | 4/6       | 8/11        |
| Taken to hospital        |            |           |             |
| Presence at overdose of  |            |           |             |
| others <=2 weeks of release |          |           |             |
| Present                  | 17% (19/112) | 13% (12/93) | 15% (31/205) |
| Naloxone given           | 10/19      | 1/12      | 11/31       |
| Taken to hospital        | 12/19      | 8/12      | 20/31       |
| Survived                 | 17/19      | 11/12     | 28/31       |
| Presence at overdose of  |            |           |             |
| others >2 weeks of release|            |           |             |
| Present                  | 15% (17/112) | 15% (13/93) | 15% (30/205) |
| Naloxone given           | 7/17       | 2/13      | 9/30        |
| Taken to hospital        | 9/17       | 12/13     | 21/30       |
| Survived                 | 13/17      | 11/13     | 24/30       |
| Naloxone acquisition-rate| 4% (5/112) | 9% (8/93) | 6% (13/205) |
| chi-square on 1df = 1.46 |            |           |             |
| p=0.226                  |            |           |             |

Do you think taking part in N-ALIVE changed your own use of heroin in the first 2 weeks after release?

|                          | 38% (43/112) | 65% (60/93) | 50% (103/205) |
|--------------------------|--------------|-------------|---------------|
| No                       | 54% (60/112) | 32% (30/93) | 44% (90/205)  |
| Safer Heroin Use         | 2% (2/112)   | 3% (3/93)   | 2% (5/205)    |
| Riskier Heroin Use       |              |             |               |

* Fisher’s exact test: p=0.116.
### Table 4: Risk Score Comparison, based on answers to RPSQ

| Risk Score Comparison (lower score, less risky) | N   | Median | Mean  | sd  | Se(Diff) | Observed Difference (95% CI for Difference) |
|------------------------------------------------|-----|--------|-------|-----|----------|---------------------------------------------|
| Random Assignment                                |     |        |       |     |          |                                             |
| NOR                                             | 112 | 4.00   | 3.86  | 3.34| 0.48     | 0.34 (0.34)                                |
| Control                                         | 93  | 2.00   | 3.52  | 3.43|           | (-0.59 to 1.27)                           |
| Safer behaviour as N-ALIVE participant?         |     |        |       |     |          |                                             |
| No change/Unsafe                                | 115 | 3.00   | 3.87  | 3.54| 0.47     | 0.38 (0.38)                                |
| Safer                                           | 90  | 4.00   | 3.49  | 3.18|           | (-0.54 to 1.30)                           |
| Safer behaviour as N-ALIVE participant? (answers by those assigned to control group) |     |        |       |     |          |                                             |
| No change/Unsafe                                | 63  | 3.00   | 4.03  | 3.50| 0.71     | 1.60* (1.60)                               |
| Safer                                           | 30  | 2.00   | 2.43  | 3.07|           | (0.20 to 3.00)                             |
| Safer behaviour as N-ALIVE participant? (answers by those assigned to NOR group) |     |        |       |     |          |                                             |
| No change/Unsafe                                | 52  | 3.50   | 3.67  | 3.61| 0.64     | -0.35* (-0.35)                             |
| Safer                                           | 60  | 4.00   | 4.02  | 3.12|           | (-1.61 to 0.91)                            |

**Test for Interaction:** Difference in differences* (Control-NOR)=1.94,  
Se for Difference in differences* (Control-NOR) = 0.98  
Hence, 95% CI for Difference in differences* is from 0.008 to 3.876 (p=0.049)
Figure 1: N-ALIVE pilot trial design and outcome measures

A full list of the trial’s outcome measures is described in the N-ALIVE protocol, which is available on the N-ALIVE webpage: [http://www.ctu.mrc.ac.uk/13391/13399/18277/n-alive_trial_protocol](http://www.ctu.mrc.ac.uk/13391/13399/18277/n-alive_trial_protocol)
**Figure 2: CONSORT Diagram for N-ALIVE pilot Trial**

NB. Screening records have been kept only since September 2012 to provide a snapshot of the proportions deemed eligible and subsequently randomized.

* Excluded from Intention-to-Treat (ITT) analysis participants released after recruitment closure (n=48, 40)

** Included in Per-Protocol (PP) analysis participants released with pack only.
Figure 3: Explanation of the decision by N-ALIVE’s Trial Steering – Data Monitoring Committee (TSDMC) to cease randomization in the N-ALIVE pilot trial

An unscheduled interim analysis of the feasibility outcomes of the N-ALIVE pilot trial was prompted by imminent release on 28th October 2014 of the 3rd year results from Scotland’s National Naloxone Programme.

This interim analysis showed that the N-ALIVE participants who received naloxone were more likely to use it to save another person’s life rather than use on self in a ratio of approximately 3:1 (Another: Self (A:S), 15:5 then; 16:5 now); which was corroborated in broad terms by the Scottish data for NOR (A:S, 21:12). This dual finding had major implications for the main N-ALIVE trial, which was designed around individual randomization.

First, mortality for the majority of those to whom naloxone was administered would not be captured as we were following up only the N-ALIVE participants.

Second, individuals in the control group of the trial could potentially receive the naloxone, thereby diluting the size of any effect of naloxone in the trial context.

Even if, at best, half the administrations of NOR were on self (17/53, 99% CI: 15% to 49%), the size of the trial (with individual randomization) needed reliably to detect the required effect-size of 20% to 30% reduction in DRDs would be infeasibly large.
As the main trial could not go ahead as planned, it was not appropriate to continue randomizing participants to the N-ALIVE pilot trial. This decision was unanimously agreed by the TS-DMC. This decision was also approved by our appointed Essex 2 Research Ethics Committee.

The finding that Scotland’s percentage of opioid-related deaths with a 4-week antecedent of prison-release had decreased from 193/1970 (9.8%) in 2006-2010 to 76/1212 (6.3%) in 2011-2013 (p<0.001) led the TS-DMC to advise that, when randomization to N-ALIVE stopped, all participants who remained in custody be offered naloxone on their release, including those who had been due to receive a control pack.