Take-home naloxone to prevent fatalities from opiate-overdose: Protocol for Scotland’s public health policy evaluation, and a new measure to assess impact

Sheila M. Bird1, Mahesh K. B. Parmar2, and John Strang3,4

1MRC Biostatistics Unit, Cambridge, UK, 2MRC Clinical Trials Unit, University College London, London, UK, 3King’s College London, London, UK, and 4National Addiction Centre, London, UK

Abstract

Aims: Scotland was the first country to adopt take-home naloxone (THN) as a funded public health policy. We summarise the background and rigorous set-up for before/after monitoring to assess the impact on high-risk opiate-fatalities. Methods: Evidence-synthesis of prospectively monitored small-scale THN schemes led to a performance indicator for distribution of THN-kits relative to opiate-related deaths. Next, we explain the primary outcome and statistical power for Scotland's before/after monitoring. Results: Fatality-rate at opiate overdoses witnessed by THN-trainees was 6% (9/153, 95% CI: 2–11%). National THN-schemes should aim to issue 20 times as many THN-kits as there are opiate-related deaths per annum; and at least nine times as many. Primary outcome for evaluating Scotland’s THN policy is reduction in the percentage of all opiate-related deaths with prison-release as a 4-week antecedent. Scotland’s baseline period is 2006–10, giving a denominator of 1970 opiate-related deaths. A priori plausible effectiveness was 20–30% reduction, relative to baseline, in the proportion of opiate-related deaths that had prison-release as a 4-week antecedent. A secondary outcome was also defined. Conclusion: If Scotland’s THN evaluation shifts the policy ground seismically, our new performance measure may prove useful on how many THN-kits nations should provide annually.

Keywords

Effectiveness, overdose deaths, performance measure, prevention, public policy, Scotland, take-home naloxone

Introduction

Opioid overdose is a major cause of premature death. Strategies that can reduce such deaths include enrolling opioid-dependent persons into opioid substitution therapy (OST) both in the community and during incarceration and educating users and peers about injection-related and other risk factors for overdose and how to respond. Key 4-week periods recognised as high-risk for opioid fatalities are: soon after prison-release, hospital-discharge, OST-initiation, and on leaving abstinence-oriented drug treatment.

Leading public health advocates in the addictions field have long argued that we should trial the distribution of naloxone to opioid users, including to prisoners-on-release, for peers and family to reverse overdoses that occur. Many countries have introduced small-scale programs to distribute naloxone to opioid users. It has been difficult, however, to evaluate the impact of these programs because fatal overdose is a relatively rare event and very large numbers of participants need to be studied to detect modest reductions in opioid fatalities on a national or regional basis. Gold-standard evidence would be from a randomised controlled trial, ideally in high-risk individuals such as released prisoners with a history of heroin injection, but the protocol for the N-ALIVE Trial reveals starkly that even such trials need to randomise tens of thousands of participants to determine the effect of naloxone on opioid-related deaths (Strang, Bird, & Parmar, 2013).

In 2011, Scotland became the first nation to adopt take-home naloxone (THN) as a funded public health policy and to put in place a science-led formal before/after evaluation. We summarise the background and rigorous set-up for Scotland’s before/after monitoring of its high-risk opioid fatalities.

Background

Naloxone’s UK licence

The injectable opiate antagonist naloxone is a prescription-only medicine in most countries. Since 2005, its UK-licence has permitted naloxone to be administered by anyone in an emergency to save the person’s life for whom naloxone was prescribed (Strang, Kelleher, Best, Mayet, & Manning, 2006). As of 2011, under new guidelines on immunity-for-prescriber-and-authorised-persons from Scotland’s Lord Advocate, naloxone can also be administered in Scotland by authorised persons, namely: those who come in contact with vulnerable

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Correspondence: Professor Sheila M. Bird, MRC Biostatistics Unit, Robinson Way, Cambridge CB2 0SR, UK. Tel: 44-1223-330368. Fax: 44-1223-330365. E-mail: sheila.bird@mrc-bsu.cam.ac.uk
Policy break-through: Neither of Scotland’s two previous THN pilot studies - based on Glasgow’s Drug Problem Centre during March 2007 to March 2008 (Shaw & Egan, 2008), and in Lanark (McAuley et al., 2010) – had included prescribing prior to prison-release. From August 2009, harm-reduction nurse-specialist Lisa Ross had overlapped community-based with prison-release prescribing of naloxone in Inverness, the constituency of Fergus Ewing, Scotland’s Minister for Safety and Communities (Gould, 2011).

Impressed by Inverness’s achievement in issuing 125 THN-kits in six months (and 19 “reported uses” including one fatality and one self-administration) when Highland region, as a whole, had an estimated 16 ORDs annually, Ewing (2010) decided to make THN available throughout Scotland to those at risk of opiate-overdose.

The N-ALIVE team was alerted by the Scottish Prison Service (SPS) to a likely change in Scotland’s policy on THN. We wrote to Scottish ministers in March 2010 to urge that prisons be in the vanguard of any national THN policy; and to underline that, just as we could not have expected Scottish prisons to implement the N-ALIVE Trial’s randomised intervention without being resourced to do so, resourcing (to half the level envisaged for the pilot N-ALIVE Trial) would still be required for Scottish prisons properly to inform prisoners on how to administer naloxone and for its prescription to those with a history of heroin-injection, who are about one third of Scottish inmates (Taylor et al., 2013).

From 2011, Scotland’s prisons were resourced to prescribe naloxone-on-release for 5 000 eligible releases per annum. In addition, 6 000 prescriptions of THN by drug treatment agencies and doctors in the outside community were envisaged – in principle, sufficient to reach more than a third of all Scotland’s current injectors (King et al., 2013) and at least 20 times more prescriptions than Scotland’s annual number of ORDs which would have guaranteed a very high level of potential distribution.

individuals at risk of opiate overdose. As authorised persons, they may possess naloxone for the purpose of administering it in an emergency.

The UK’s Advisory Council on the Misuse of Drugs (ACMD) recommended in May 2012 that naloxone should be made more widely available in England; and that the government should ease restrictions on those who can be supplied with naloxone for its emergency-administration. The World Health Organization already lists naloxone as an essential medicine and is expected to issue guidance on take-home naloxone (THN) later in 2014.

Public policies in UK on take-home naloxone

In January 2011, Scotland became the first country to introduce THN as a funded public health policy. See McAuley, Best, Taylor, Hunter, and Robertson (2012) and Box 1 to know how Scotland’s THN policy came about. Wales announced a similar intention in May 2011 after a one-year demonstration project (Bennett & Holloway, 2011). On account of these policy changes, the pilot N-ALIVE Trial of naloxone-on-release can randomise in English prisons only (Strang et al., 2013).

Determinants of the effectiveness of take-home naloxone

Effectiveness in preventing fatalities at opiate overdose depends, of course, on the ratio of fatal to non-fatal opiate overdoses, which is generally low. For heroin overdoses in Australia, Darke, Mattick, and Degenhardt (2003) estimated that the ratio was one in 20 to one in 30. Secondly, for THN to be available at every opiate overdose, coverage needs to be broad amongst those at-risk and we should anticipate many more administrations than “lives saved” – precisely because the pre-existing fatality-rate is low per opiate overdose. Thirdly, effectiveness may be greater in a higher-risk milieu. Besides gender (male) and age-group (older than 34 years), known risk-factors for drugs-related death include: being recently-released from prison (Bird & Hutchinson, 2003; Merrall et al., 2010), recently-discharged from hospital (Merrall, Bird, & Hutchinson, 2013), recent heroin injector, declared misuse of alcohol and declared misuse of benzodiazepines (Pierce, Bird, Hickman, & Millar, 2014), whereas being in receipt of OST is protective (Degenhardt et al., 2009).

Aims and methods

Our aim is to describe the protocol-development for monitoring of Scotland’s THN-policy.

First, we present an evidence-synthesis on three key event-rates:

- fatality-rate per witnessed overdose;
- witnessed overdoses per client-year;
- experienced overdoses per client-year.

We do so using data from UK and USA studies of THN which had per-protocol follow-up of trainees for three to six months.

Next, using the evidence-synthesis, we suggest a performance measure for comparing between nations how many THN-kits are issued annually, and illustrate its application to Scotland.

Thirdly, the epidemiological and statistical considerations behind the chosen primary and secondary outcomes for Scotland’s evaluation of its THN policy are explained; and Scotland’s issue of THN-kits is judged by the above performance measure.

Specifically, we document Scotland’s before/after design-protocol ahead of the release of the three-year results from Scotland’s THN policy-evaluation, which are expected as official statistics in late October 2014.

Evidence-synthesis from THN studies with planned follow-up

Published before/after evaluations of naloxone training have consistently demonstrated that trainees’ knowledge, and their confidence, increased about the signs of overdose, and what to do in the event of overdose; and showed that the knowledge gained was retained adequately when trainees were re-tested at three or six months after training (Strang et al., 2008a,b; National Treatment Agency for Substance Misuse, 2011). We do not dwell further on this acquired knowledge.

Instead, we focus on three event-rates ascertained during planned prospective follow-up of THN-trained clients (and/or controls, see Bennett & Holloway, 2011): fatality-rate at witnessed overdose; witnessed overdose rate per trainee-year; and experienced overdose rate per trainee-year. Because the fatality-rate at witnessed overdoses is generally low, we count as “survivors” those few for whom overdose-outcome was unknown.
Fatality-rate at witnessed overdose during planned follow-up

UK and USA naloxone studies which reported fatality-rates (namely, UK: Bennett & Holloway, 2011; Gaston, Best, Manning, & Day, 2009; McAuley, Lindsay, Woods, & Louttit, 2010; Strang et al., 2008a; USA: Galea et al., 2006; Seal et al., 2005; Tobin, Sherman, Beilenson, Welsh, & Latkin, 2009; Wagner et al., 2010) were broadly consistent in their reported fatality-rate at witnessed overdoses during three to six months of planned follow-up as being:

UK studies: $1/16 + 1/16 + 1/3 + 1/24 = 4/59$ (7%)  
USA studies: $4/35 + 2/22 + 2/20 + 1/17 = 5/94$ (5%)  
(see Appendix for details).

Thus, the combined prospective follow-up from eight THN studies suggests that trainees may encounter a fatality-rate of around 6% at witnessed overdoses (9/153; 1 fatality in 17 witnessed overdoses; 95% confidence interval: 2–11%).

Witnessed overdose rate per trainee-year

The UK studies with planned follow-up (the above-mentioned studies and Shaw & Egan, 2008) reported a witnessed overdose rate of 61 witnessed overdoses during a minimum of 1167 person-months; or 0.63 witnessed overdoses per client-year (95% Poisson confidence interval: 0.4–0.8) (Appendix). Clients recruited into THN studies in the USA seem to have been in a higher-risk milieu insofar as their witnessed overdose rate was 129 witnessed overdoses during 861 person-months; or 1.80 per client-year (95% Poisson confidence interval: 1.5–2.1).

Experienced overdose rate per trainee-year

By contrast, the experienced overdose-rate in UK studies was four-fold lower at 14 overdoses experienced during a minimum of 1065 person-months; or 0.16 experienced overdoses per client-year (95% Poisson confidence interval: 0.1–0.3).

Interpretation

Our evidence-synthesis for UK clients (0.63 witnessed versus 0.16 experienced overdoses per client-year) is broadly consistent with the self-reported account that trainees in the Drug Overdose Prevention and Education (DOPE) Project were the victim in only 30% (85/287) of notified administrations of THN (Enteen et al., 2010). Trainees seem to witness 2–4 times as many overdoses as they themselves experience, a ratio that can be broadly interpreted as the average number of witnesses present per witnessed opiate overdose.

For THN to be present at an opiate overdose, naloxone needs to have been prescribed either to the victim or to at least one of those who are co-present. In principle, naloxone should be administered to those for whom it was prescribed, but the practice is often different.

If the average number of witnesses at a witnessed opiate overdose were three (as above) and, independently, the three witnesses and victim each had a one third chance of having been prescribed THN, and three-quarters chance of carrying it still, then the probability would be under a third that none of them carried THN (namely: 0.75**4).

New performance measure for how many THN-kits to issue annually

Our evidence-synthesis has shown that THN-trainees may encounter a fatality-rate of 6% (95% CI: 2–11%) at attended overdoses, somewhat higher and less certain than reported by Darke et al. (2003).

For THN to be available at every witnessed opiate-overdose, a national THN-policy should aim to issue to at-risk clients around 20 times as many THN-kits as there are opiate-related deaths (ORDs) per annum; and at least nine times as many (ORDs/0.11).

Scotland has around 400 ORDs per annum and so might aim to prescribe 8000 THN-kits annually; and at least 3600 (where 3600 = 400/0.11). Corresponding minimum targets for Wales, England and USA are: at least 770, 9600 and 328,000 THN-kits annually (Appendix).

Notice that if an initial 8000 THN kits were issued mainly to Scotland’s 20,000 persons who inject drugs (PWIDs), then very soon a third of them would be in possession of THN (King, Bird, Overstall, Hay, & Hutchinson, 2013; Overstall, King, Bird, Hay, & Hutchinson, 2014).

We recommend that a nation’s annual provision of THN-kits should be 9–20 times its recent-past mean annual number of ORDs; and that nations ensure minimum annual THN-provision of at least nine times their recent-past mean annual number of ORDs.

Monitoring plan for Scotland’s take-home naloxone policy

Primary outcome for monitoring

The N-ALIVE team wrote to Scottish ministers in May 2010 with suggestions on how to optimise monitoring of the impact of Scotland’s THN policy (Ewing, 2010) while taking into account Scotland’s rising trajectory of ORDs (Table 1).

Mainly as a consequence of Scotland’s heroin-injector epidemic in the early 1980s, and also on account of higher drugs-related-death rate in older opiate users (Pierce et al., 1998), we reasoned that Scotland’s THN policy was being introduced against a potentially still-rising trajectory of age-related ORDs. As added complication, Scotland – together with Wales and England (Appendix) – experienced a heroin drought in 2010/11.

Because of the substantially higher ORD-risk for opiate-users recently-released from prison (Merrall et al., 2010; Seaman, Bettle, & Gore, 1998), we reasoned that Scotland’s THN-policy should impact particularly on ex-prisoners’ ORDs. We proposed that, whatever the number of Scotland’s ORDs, monitoring should focus specifically on the proportion of all ORDs that have prison-release as a 4-week antecedent. Focussing on this proportion, rather than on the absolute numbers of ORDs, means that the inevitable
annual variation in ORDs does not invalidate the before/after comparison.

Historically about one in eight of Scotland’s drugs-related deaths had occurred in the 4-weeks after prison-release (Bird & Hutchinson, 2003) and, since Table 1 shows that three-quarters of Scotland drugs-related deaths are ORDs, the proportion of Scotland’s ORDs that occurred in the 4 weeks following prison-release was thought likely to be about one in six (~17%).

However, when the proportion was finally abstracted (which was not until January 2012), only 130 (10.5%) of Scotland’s 1240 ORDs in 2007 + 2008 + 2009 had been released from prison in the 4 weeks prior to death (Information Services Division Scotland, 2012).

**Statistical power for effectiveness-target**

Scotland’s effectiveness-target was a plausible THN-related 20–30% reduction in the pre-THN percentage of ORDs with prison-release as a 4-week antecedent, which spans the range of effectiveness assumptions made by Coffin and Sullivan (2013) and the N-ALIVE Trial (Strang et al., 2013).

Table 2 sets out the implications for Scotland’s statistical power to detect a 20% to 30% THN-related reduction during 2011–2013, given that the pre-THN percentage was actually nearer to 10% than 17%. Power reduced from around 80–90% with the lower pre-THN percentage.

Had 17% indeed been the appropriate pre-THN percentage, then Scotland would have had reasonable power to detect even a one-fifth (20%) reduction in the percentage of ORDs with prison-release as a 4-week antecedent provided that the number of ORDs in 2011 + 2012 + 2013 was 1200 or more; and good power to detect 25% effectiveness even if Scotland’s three-year total of ORDs were to fall from 1200 to 900 either due to THN or for unconnected reasons.

However, the substantially lower pre-THN percentage of ORDs with prison-release as a 4-week antecedent meant, in effect, that an extended THN-monitoring period (up to five years for the before/after periods, each with 2000 ORDs) would be needed to restore 80% power for Scotland to detect a quarter (25%) reduction in its primary outcome: such as from 10% of ORDs pre-THN to 7.5% after-THN. But a 30% reduction to 7% could still be identifiable within three years (2011 + 2012 + 2013).

**Secondary outcome with prison-release or hospital-discharge as 4-week antecedent**

Two other 4-week antecedents merit consideration when monitoring national THN-policies – hospital-discharge (Merrall et al., 2013) or initiation onto opiate-substitution therapy (OST) in the 4 weeks prior to ORD (Cornish, Macleod, Strang, Vickerman, & Hickman, 2010; Degenhardt et al., 2009). Both feature in a longer list of naloxone priority groups and risk-factors for opioid-induced respiratory depression (Albert et al., 2011). However, only hospital-discharge could be adopted in Scotland where OST-prescriptions are seriously lacking in individual identifiers prior to 2008 (Ferguson, 2012).

Substantially ahead of publication (Merrall et al., 2013) Bird, Merrall and Hutchinson had informed Scotland’s Chief Medical Officer (Professor Harry Burns) in December 2010 about their finding that the initial 4-weeks after hospital-discharge were a period of high drugs-related death risk for Scotland’s drug-treatment clients, and Professor Burns alerted doctors accordingly.

The task of establishing the percentage of Scotland’s ORDs in 2006–2010 who were either released from prison or discharged from a hospital-episode in the 4 weeks prior to ORD fell to Scotland’s Information Services Division. The 5-year baseline for this secondary outcome will be formally published on 28 October 2014, when the after-THN percentage for 2011–2013 will also be reported for both primary and secondary outcomes. Preliminary work has, however, demonstrated that the pre-THN baseline percentage for Scotland’s secondary outcome is around 20% so that the power calculations in Table 2 remain applicable.

**Progress so far**

The Information Services Division Scotland (2014) reported the percentage of Scotland’s ORDs in 2011 + 2012 who were released from prison in the 4-weeks prior to death as 7%, being {36 + 22}/(430 + 399). Whilst encouraging, more definitive conclusions must await the 3-year results (expected in late October 2014).

**Number of THN-kits issued in Scotland**

In the financial year 2011/2012, 3458 THN-kits were issued in Scotland, 715 of them by Scottish prisons: nearly nine...
times Scotland’s recent-past annual number of ORDs (Information Services Division Scotland, 2012). In the financial year 2012/13, 3833 THN-kits were issued in Scotland, 746 of them by Scottish prisons (Information Services Division Scotland, 2013).

**Targets**

Scotland’s National Naloxone Advisory Group (NNAG) proposed regional performance targets, in accordance with which the community-issue of THN-kits should have increased substantially in 2013/14. Despite some stellar performances by individual Scottish prisons (Information Services Division, 2014), even the best-performing achieved only half the notional THN prescription-rate for prisons which was, in effect, to make THN available for all opiate-dependent liberations. And so, in 2014/15, NNAG set as the minimum target for prisons’ issue of THN-kits: one quarter of their estimated number opioid-dependent liberations (that is: around 1700 THN-kits across all Scottish prisons). Each prison’s opioid-dependent percentage was based on its own surveillance data (in November and February of 2010/11 to 2012/13) for opioid positivity among those it received into custody.

**Re-supply**

In 2011/12 + 2012/13, 909 reasons for community re-supply to persons-at-risk were given as: 342 administrations (with 47 (14%) to the prescribee), 401 losses, 108 expired or confiscated and 58 not known. Reasons for re-supply of 115 prisoners were: 23 administrations (with eight (35%) to the prescribee), 38 losses, seven expired or confiscated and 47 not known. These preliminary data are consistent with ex-prisoners’ higher likelihood of administration to the prescribee (z-score = 2.08, p < 0.05).

**Carriage**

In 2011/12 (and repeated in 2013/14), Scotland’s Needle-Exchange Surveillance Initiative (NESI, see Allen et al., 2010) included new questions for PWIDs about their access to, and carriage of, THN. The NESI respondents were asked if they carried their THN-kit with them; and from whom they had received their naloxone (prison or community-prescriber). The NESI surveillance suggested that THN-kits were prescribed preferentially for those with a history of recent heroin injection. In particular, an impressive 11% of 586 NESI interviewees in July or August 2011 had already been prescribed THN-kits (95% confidence interval: 8% to 13%). However, only 19 of NESI’s 119 prescribees (16%) carried their THN-kit with them at the time of interview.

**Summary**

Scotland issued nearly 7300 THN-kits in the first two financial years of its THN policy but its THN-prescribing in 2013/14 and 2014/15 needed to increase substantially to reach the performance target of 8000 THN-kits per annum. Scotland’s THN-provision across three financial years will be reported later in 2014 together with the percentage of its ORDs in the calendar years 2011 + 2012 + 2013 that had
either prison-release or hospital-discharge as a 4-week antecedent.

Discussion

Ministerial approvals for national THN programmes followed local initiatives in Inverness in Scotland (Gould, 2011) and by a Welsh demonstration project (Bennett & Holloway, 2011), both of which extended naloxone training to prisons. Additional impetus for Scotland was a high toll of ORDs: more in 2006–2010 (1970) than deaths from HIV/AIDS in the thirty years from 1983–2012 (1864).

What Scotland lacked by not adopting formal experimentation (Strang et al., 2013) is made good by an insightful evaluation which, from the outset, was designed to be sufficiently powerful to detect a 20% to 30% THN-related reduction in the proportion of Scotland’s ORDs which had occurred in the 4-weeks after prison-release (primary outcome); and/or hospital-discharge (as secondary outcome).

Before/after evaluations can readily be complicated by confounding or the unexpected – respectively, Scotland’s rising trajectory of ORDs and lower-than-expected baseline proportion of ORDs in 2006–2010 with prison-release as a 4-week antecedent, which turned out to be 10% not 17% as extrapolated from 1996–1999 (Bird & Hutchinson, 2003). With the added complication of heroin drought, rigour is required in the evaluation. Scotland’s secondary outcome was specified to restore 80% statistical power for modest effectiveness in the initial three years (2011–2013) of Scotland’s THN policy provided that adequate coverage of THN-kits during those initial three years was achieved and that Scotland’s ORDs averaged around 400 per annum.

Based on evidence from THN-studies with structured follow-up, we have suggested that nations gauge the sufficiency of their per-annum THN provision against a target of 20 times their recent-past mean annual number of ORDs, with minimum provision being at least nine times. Scotland achieved minimum provision in the initial two years of its THN policy and, aided by target-setting, has accelerated provision thereafter. For Wales, England and USA, minimum annual provision of THN-kits would be: 770, 9600 and 328,000 respectively.

Scottish prisoner-releases apart, the vast majority of reported THN-administrations were by the person for whom naloxone had been prescribed, not the prescribee (only 47/342: 14%) and so lower than the 30% reported by San Francisco’s DOPE Project (Enteen et al., 2010).

England’s prison-based N-ALIVE Trial will not test the effectiveness of THN at reducing deaths from opiate-overdose among those for whom naloxone was not prescribed. This is either a focal-strength (Strang et al., 2013); or a potential weakness from the wider-community perspective (Walley et al., 2013). Before/after policy evaluations explicitly take the wider-community perspective by not heeding whether the averted overdose fatalities are those for whom THN was specifically prescribed or their peers.

As modelled by Coffin and Sullivan (2013), the impact of distributing naloxone to 20% of heroin users in the USA was a very modest, albeit cost-effective, 6% reduction in the number of ORDs. (According to NESI, Scotland achieved naloxone distribution to 11% of its current injectors by mid-2011). However, systematic time-trends in ORDs (their rising trajectory in Scotland, for example) or idiosyncratic variations (in heroin supply) or mere random variation readily conspire to disguise so modest a signal in before/after comparison of the number of ORDs. Even if there were only random variation to contend with, the comparison would need to be based on several thousand ORDs, not several hundred as in Wales, for a mere 6% reduction in ORDs to be discerned by the yardstick of statistical significance.

Policy equipoise internationally gave England a special opportunity to commit to a randomised controlled trial of naloxone-on-release as a potentially effective approach to reducing the high risk of fatalities from opiate-overdose soon after prison-release. The N-ALIVE Trial’s expectation is for one fatality to be prevented per 600 prisoners randomised to naloxone-on-release. By contrast, the baseline ‘number needed to treat’ as modelled by Coffin and Sullivan (2013) was around 230 due in part to their more optimistic assumption that the proportion in possession of naloxone at an overdose who would attempt overdose-reversal would be 80%.

We have set out in detail the epidemiological rationale and statistical power for Scotland’s science-led before/after evaluation of its THN policy and, importantly, we have done so in advance of the release of Scotland’s primary and secondary outcome data for 2011–2013 and provision of THN-kits in 2013/14 (expected in late October 2014).

If Scotland’s 3-year results entrench, rather than pull back from, the first two years’ reduction in the proportion of ORDs with a 4-week prison antecedent (down from 10% of 1970 ORDs in 2006–2010 to 7% of 829 ORDs in 2011 + 2012), Scotland’s before/after THN evaluation could shift the policy ground so seismicly that it would call into question the continued absence of funded THN schemes in other countries.

If so, our new performance measure may prove useful: a country’s annual provision of THN-kits should be at least nine times its recent-past mean annual number of ORDs.

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In August of each year, National Records Scotland notifies Scotland’s Information Services Division about all opiate-related deaths in Scotland in the preceding calendar year. Look-back to the 4-week antecedents (prison-release or hospital-discharge) of the notified opiate-related deaths is conducted by staff of the Information Services Division and the outcomes are reported as Official Statistics.

As requested by SMB, Professor Avril Taylor kindly incorporated additional questions about THN into her 2011/12 and 2013/14 Needle Exchange Surveillance
Initiatives (NESI). Full details will be published by the NESI team.

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Declaration of interest

The three authors are principal investigators for the pilot N-ALIVE Trial. All authors declare as a competing interest that the three-year results from Scotland’s before/after evaluation may have implications for whether and how randomisation continues in the N-ALIVE Trial.

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### Appendix

**Evidence-synthesis from THN studies**

We adduce evidence on three key event-rates from UK and USA studies on THN, namely: witnessed overdoses per client-year, experienced-overdoses per client-year, and fatality-rate per witnessed overdose.

The Welsh evaluation by Bennett and Holloway (2011) had included a rapid evidence assessment, which identified 10 heterogeneous pre-post evaluations of naloxone distribution programmes (USA: 6, England: 2, Scotland: 2) (see their Tables A1 and A2). We focus attention solely on event-rates that were ascertained during planned prospective 3-month or follow-up, namely:

- Witnessed overdoses per client-year
- Experienced-overdoses per client-year
- Fatality-rate per witnessed overdose

Secondly, because the fatality-rate at witnessed overdoses was generally low, we have counted as ‘survivors’ those for whom overdose-outcome was unknown.

With the above two rules in force, the UK/USA THN-studies seem broadly consistent in the outcome of witnessed overdoses during planned follow-up, namely:

- UK studies: 1/16 + 1/16 + 1/3 + 1/24 deaths = 4/59 (7%)
- USA studies: 4/35 + 0/22 + 0/20 + 1/17 deaths = 5/94 (5%).

The combined literature thus suggests that trainees may encounter a fatality-rate as high as 6% at witnessed overdoses (9/153; 1 fatality in 17 expected, the experienced overdose-rate of 1.3 per 100 person-months).

In UK studies with planned follow-up, the witnessed overdose rate was 5.2 per 100 person-months (61 witnessed overdoses during a minimum follow-up of 1167 person-months); or 0.63 per client-year (95% Poisson confidence interval: 0.4–0.8). By contrast, and to be expected, the experienced overdose-rate of 1.3 per 100 person-months (14 overdoses experienced during a minimum follow-up of 1065 person-months) was lower, namely: 0.16 per client-year (95% Poisson confidence interval: 0.09–0.26).

Clients recruited to studies of THN in the USA seem to have been in a higher-risk milieu insofar as the witnessed overdose rate was 15.0 per 100 person-months (129 witnessed overdoses during 861 person-months); or 1.80 per client-year (95% Poisson confidence interval: 1.5–2.1).

### New performance measure for provision of take-home naloxone kits: application to UK and USA

We recommend that nations’ annual provision of THN-kits should be nine to 20 times their recent-past mean annual number of ORDs; and that nations ensure minimum annual THN-provision of at least nine times their recent-past mean annual number of ORDs.

Scotland (with population: 5 millions) has around 400 ORDs per annum, see Table A2, and so might aim to prescribe 8000 THN-kits annually; and ensure provision at least 3600. The corresponding targets in Wales and England would be 1700 and 21,300 THN-kits to be prescribed annually; and at least 770 and 9600.

In 2008, there were 36,450 drug overdose deaths in the USA (population: 314 millions). The Centers for Disease Control and Prevention (2012) reported that, in 2010, 48 out of 50 community-based opioid overdose prevention programs providing naloxone in the United States of America had distributed 38,860 vials in a 12-month period. Thus, USA’s distribution of THN-kits in 2010 was about 1/20th only of that which a national programme in USA might have to aim for.

The mean number of ORDs per annum per-million-of-population varies between nations because the prevalence of opioid dependency varies considerably. For this reason, we suggest that targets for THN-provision be not set on a naive per-million-of-population basis.

Provision of 8000 THN-kits per annum in Scotland translates to around 1600 per-million-of-population; but 21,300 per annum in England translates to only 400 per-million-of-population. With target-provision in the USA of roughly 583,000 THN-kits, USA’s required provision on a per-million-of-population basis would be around 1700, more akin to Scotland than to England.
### Table A1. Summary of key event-rates: THN studies in UK and USA.

| Study                        | Trainees’ take-home naloxone rate | Trainees’ follow-up rate at 3 or 6 months (m) | Witnessed overdose rate per 100 person-months (pms) | Experienced overdose rate per 100 person-months (pms) | Reported outcome of witnessed overdose-events |
|------------------------------|----------------------------------|-----------------------------------------------|---------------------------------------------------|---------------------------------------------------|---------------------------------------------|
| Strang et al., 2008a         | 160/176                          | 186/239                                       | 3.4 [16 in 186*2.5 m = 465 pms]                    | 0.43 [2 in 186*2.5 m = 465 pms]                    | 1/16 died. [Two uses by staff]              |
| Gaston et al., 2009          | 49/70 but 46/70 were analysed who had 0, 3, 6 m follow-ups | 5.8 [16 in 46* 6 m = 276 pms]                 | 0.36 [1 in 46 * 6 m = 276 pms]                     |                                                   | 1/16 died or 1/7. [already dead; but outcome not known for nine. No trainee used Naloxone at witnessed overdose.] |
| National Treatment Agency, 2011 | 417 Naloxone kits supplied to trained carers in 16 pilots costing £98,280 during July 2009 to Feb. 2010 (per kit supplied: £236). |                                                   |                                                   |                                                   | 0/20 died. 18 Naloxone-uses before August 2011, one to prescriber, all survived as did two non-N resuscitations. |
| HMP Eastwood Park            | 447 trainees in 1st 6 m, of whom 96 released with Naloxone. |                                                   |                                                   |                                                   | 3 "reported" uses of Naloxone.              |
| McAuley et al., 2010         | 19/23 clients were issued with Naloxone (18 "buddies" also trained) | 2.9 [3 in 17*6 m = 102 pms]                     |                                                   |                                                   | 1/3 died; two "saves" via Naloxone administrations |
| Glasgow Naloxone Programme, March 2007 to March 2008 as reported by Shaw and Egan, 2008. | (120+5)/(120+40) = 125/160 (Community + prison) | 1.6 [2 Naloxone-used overdoses witnessed in ≥120 pms: 40*≥3 m; p32] | 0.83 [1 in at least 40* 3 m ≥ 120 pms] | 1/11 overdose victims died. [naloxxone used for 10, two by staff; re-supply obtained by 28 users who had administered naloxone]; 1/11 recent prison-release: p37–39. |
| Welsh evaluation: cases, Bennett and Holloway, 2011 | 40/176 user-trainees re-interviewed at 3 months (at least . . .) and 15/31 family-members: p26 |                                                   |                                                   |                                                   | 1/22 died when N-used, or 1/28 replenishments (6 = status NK) |
| Welsh evaluation: controls, see Bennett & Holloway, 2011 | Over 600 trained during 1-year pilot | 644 kits given out by Feb 2011; 48 used. |                                                   |                                                   |                                                   |
| UK summary                   | 34 users in control areas, of whom 4 reported no events | 11.8 [24 overdose events in 34* 6 m = 204 pms] | 4.9 [10 overdose events in 34* 6 m = 204 pms] | 5.2 [61 in at least 1167 ms] | 1/34 died, see Pages 117–120. Or 1/24 witnessed events |
|                             |                                  | 4.9 [10 overdose events in 34* 6 m = 204 pms] |                                                   |                                                   |                                                   |
|                             |                                  | 7/137 = 5.1% died [1 in 20]; or 4/59 = 6.8% died [1 in 15] |                                                   |                                                   |                                                   |

(continued)
| Study            | Trainees' take-home naloxone rate | Trainees' follow-up rate at 3 or 6 months (m) | Witnessed overdose rate per 100 person-months (pms) | Experienced overdose rate per 100 person-months (pms) | Reported outcome of witnessed overdose-events |
|------------------|---------------------------------|-----------------------------------------------|-----------------------------------------------------|------------------------------------------------------|---------------------------------------------|
| Enten et al., 2010 | Between September 2003 and December 2009, 1,942 unduplicated users trained, all prescribed naloxone | 399 overdose-events were reported-back by 215 trainees (11%) who had sought refills. Overdose-events were reason for 399/1020 (40%) refill requests. >0.6 {399+ overdose events in approx. 1,942 * 3 yrs * 12 = 69,912 pms}. | 6/693 naloxone-treated overdose victims died; outcome not known for 36 naloxone-administered overdose victims. |
| Wagner et al., 2010 | 93 IDU-trainees; 69 agreed to 3 m follow-up, but 3 not trained. | 47/66 IDU-trainees followed-up at 3 months. | 24.8 {35 overdoses responded to by 22/47 responder-trainees in 3*47 = 141 pms}. Also note 74.7 {148 overdoses witnessed by 32/66 trainees in 3 m prior to training = 198 pms} | 12.1{24 overdoses reported by 10/66 trainees in 3 m prior to training, i.e. in 3 * 66 = 198 pms} | 4/30 died {but outcome unknown for 5 overdoses; naloxone administered at 28/35 witnessed overdoses}. |
| Tobin et al., 2009 | [85/250 participants assessed at 6 m] | >9.4 {48/85 witnessed at least 1 overdose in 85 * 6m = 510 pms} | Not stated | 0/22 naloxone-used overdose victims died. |
| Seal et al., 2005 | 24/24 IDU-trainees had monthly re-interviews for 6ms | 13.9 {20 witnessed in 24 * 6m = 144 pms} | 0/20 died. Naloxone was administered at 15/20. |
| Galea et al., 2006 | 22/25 trainees followed-up at 3 m | 39.4 {11/22 witnessed 26 overdoses in 22 * 3 m = 66 pms} | 1/17 died in specified/most recent overdoses with known outcome, naloxone was used for 10/17. |
| USA summary | | | 15.0 {129 in 861 pms} | No data prospectively | 5/94 = 5.3% died {1 in 19} |
Table A2. Opiate-related drug deaths (here defined by mention of heroin/morphine or methadone or buprenorphine) by year of death: for Scotland, Wales and England.

| Year of Death | Scotland: population of 5.3 millions* | Wales: population of 3.1 millions* | England: population of 53.5 millions* | Great Britain |
|---------------|---------------------------------------|-----------------------------------|--------------------------------------|--------------|
| 2006          | 328                                   | 62                                | 978                                  | 1368         |
| 2007          | 370                                   | 76                                | 1126                                 | 1572         |
| 2008          | 445                                   | 92                                | 1041                                 | 1578         |
| 2009          | 432                                   | 109                               | 1115                                 | 1656         |
| **4-year MEAN** | **394**                                      | **85**                            | **1065**                              | **1544**     |

*See http://www.ons.gov.uk/ons/rel/pop-estimate/population-estimates-for-uk–england-and-wales–scotland-and-northern-ireland/mid-2011-and-mid-2012/stb—mid-2011—mid-2012-uk-population-estimates.html

**Due to late registration of coroner-referred deaths in England and Wales, ORDs in 2012 in England and Wales (and hence in Great Britain) are, as yet, under-counts by about 5%.

**See https://www.rss.org.uk/site/cms/newsarticle.asp?chapter=15&nid=79