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# Effectiveness and cost-effectiveness of unsupervised buprenorphine-naloxone for the treatment of heroin dependence in a randomized waitlist controlled trial

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ABSTRACT

*Background:* Access to opioid agonist treatment can be associated with extensive waiting periods with significant health and financial burdens. This study aimed to determine whether patients with heroin dependence dispensed buprenorphine-naloxone weekly have greater reductions in heroin use and related adverse health effects 12-weeks after commencing treatment, compared to waitlist controls and to examine the cost-effectiveness of this strategy.
*Methods:* An open-label waitlist RCT was conducted in an opioid treatment clinic in Newcastle, Australia. Fifty patients with DSM-IV-TR heroin dependence (and no other substance dependence) were recruited. The intervention group (n = 25) received take-home self-administered sublingual buprenorphine-naloxone weekly (mean dose, 22.7 ± 5.7 mg) and weekly clinical review. Waitlist controls (n = 25) received no clinical intervention. The primary outcome was heroin use (self-report, urine toxicology verified) at weeks four, eight and 12. The primary cost-effectiveness outcome was incremental cost per additional heroin-free-day.
*Results:* Outcome data were available for 80% of all randomized participants. Across the 12-weeks, treatment group heroin use was on average 19.02 days less/month (95% CI −22.98, −15.06, $p < 0.0001$). A total 12-week reduction in adjusted costs including crime of $A5,722 (95% CI 3299, 8154) in favor of treatment was observed. Excluding crime, incremental cost per heroin-free-day gained from treatment was $A18.24 (95% CI 4.50, 28.49).

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*Conclusion:* When compared to remaining on a waitlist, take-home self-administered buprenorphine-naloxone treatment is associated with significant reductions in heroin use for people with DSM-IV-TR heroin dependence. This cost-effective approach may be an efficient strategy to enhance treatment capacity.



## 1. Introduction

Methadone and buprenorphine maintenance attracts and retains individuals dependent on heroin or other opioids into treatment, and has substantial evidence of effectiveness in reducing drug related harms (Mattick et al., 2009, 2014). Methadone has typically been provided with direct observation of most doses, especially during induction, to minimize the risk of diversion to others. Access to take home or unsupervised doses of methadone is usually permitted over time for patients who demonstrate stability (see for example, Center for Substance Abuse Treatment, 2005, Treatment Improvement Protocol Series 43). However, daily supervision of opioid agonist treatment greatly increases treatment costs (Bell et al., 2007) and reduces access to treatment for people in more remote areas. The availability of opioid agonist treatment without dose supervision has the potential to expand access and reduce mortality and morbidity and has been adopted as the framework for buprenorphine treatment in the USA (Sullivan and Fiellin, 2008) and France (Fatseas and Auriacombe, 2007).

To date, the bulk of the evidence supporting buprenorphine effectiveness comes from trials based on supervised administration. The effectiveness for sublingual buprenorphine for opioid dependence has been established in five placebo-controlled clinical trials, each involving direct supervision of the medication (Fudala et al., 2003; Johnson et al., 1995; Kakko et al., 2003; Krook et al., 2002; Schottenfeld et al., 2008). Initial randomized trials establishing methadone treatment effectiveness also all involved direct supervision (Dole et al., 1969; Newman and Whitehill, 1979; Strain et al., 1993), as did subsequent trials comparing buprenorphine and methadone (Bickel et al., 1988; Fischer et al., 1999; Johnson et al., 2000, 1992; Kosten et al., 1993; Ling et al., 1996; Lintzeris et al., 2004; Magura et al., 2009; Mattick et al., 2003; Pani et al., 2000; Petitjean et al., 2001; Soyka et al., 2008; Strain et al., 1994a,b; Uehlinger et al., 1998).

While methadone is associated with moderately longer retention in treatment compared to buprenorphine in controlled studies (RR 0.83, 95% CI (0.73, 0.95), Mattick et al., 2014), data linkage studies show buprenorphine is associated with a reduced risk of overdose, particularly in the first four weeks of treatment (Kimber et al., 2015). Australian data also indicates that buprenorphine-naloxone (BNX) has less potential for extra-medical use by injection than the mono-buprenorphine tablet preparations (Larance et al., 2014). The safety and reduced risk of injecting BNX makes take-home self-administration possible, enabling greater treatment capacity without the requirements of costly supervised dosing.

An Australian randomized trial demonstrated that patients commenced on unsupervised dosing BNX treatment, attending for weekly collection of medication and brief clinical review, had identical clinical outcomes to those receiving daily-supervised dosing. That study also demonstrated that unsupervised BNX dosing is more cost-effective than supervised treatment, with a cost saving of approximately $A475 per patient (95% CI = $A405-545) over a 12-week period (Bell et al., 2007).

Reports of waiting lists for opioid agonist treatment in the USA range from 0 to 384 days, and in the UK 0 to 82 weeks (Ritter et al., 2013). Individuals waiting to access opioid agonist treatment may impose a substantial financial burden to the community (Adamson and Sellman, 1998; Moore, 2007). People who are dependent on heroin in rural Australia can face long waiting periods to access opioid agonist treatment, principally due to a lack of treatment positions in specialist (public clinic) or primary care settings (Ritter and Chalmers, 2009).

Access to interim methadone for people with heroin dependence on a waitlist has been trialed in the US. This research demonstrated that supervised methadone dosing with less frequent counseling and review conditions resulted in reduced heroin use and enhanced long-term retention in treatment compared to patients remaining on a waiting list (Schwartz et al., 2006; Yancovitz et al., 1991). A Norwegian placebo-controlled study of 16 mg mono-buprenorphine (daily supervised) delivered under interim conditions for patients on a waiting list for methadone treatment found that those randomized to buprenorphine had substantially reduced heroin use 12 weeks after commencing treatment (Krook et al., 2002). A feasibility study of interim buprenorphine using a computerized medication-dosing device in the USA has recently been published suggesting potential of this approach to minimize diversion (Sigmon et al., 2015).

In contrast to the U.S and France, issues relating to the level of mandatory supervised dosing still confront clinicians and policy makers internationally. Regulations and guidelines in many countries (including the World Health Organization (WHO) guidelines) advise that patients initiating opioid maintenance treatment undergo daily supervised dosing for periods up to three months (Department of Health (England) and the devolved administrations, 2007; Gowing et al., 2014; WHO Department of Mental Health and Substance Abuse, 2009). It remains unclear in many jurisdictions whether programs with unsupervised or take-home self-administration of buprenorphine-naloxone would result in both individual patient and public health benefits compared to keeping patients on waiting lists for treatment, if this approach were introduced more broadly. To our knowledge, the effectiveness and cost-effectiveness of this approach to BNX maintenance treatment has not been evaluated in a randomized controlled trial compared to a no-treatment control group.

In the current study, we compared the effectiveness and cost effectiveness of take-home self-administration weekly dispensed buprenorphine-naloxone (with weekly clinical review) to a waitlist control condition for individuals with a heroin dependence awaiting opioid treatment.

## 2. Methods

### 2.1. Study design

Study design was an open label randomized controlled trial comparing the effectiveness and cost-effectiveness of take-home self-administered BNX treatment to remaining on a waiting list over a 12-week period. Fifty participants took part in the trial, conducted at a specialist community-based outpatient opioid agonist treatment clinic in Newcastle, NSW, Australia. At the end of the trial, waitlist randomized participants were given access to methadone or buprenorphine maintenance treatment on request. The study

protocol was approved by Hunter New England Human Research Ethics Committee, and registered on the Australian New Zealand Clinical Trials Registry (identifier: ACTRN12609000138280).

### 2.2. Participants

Participants were aged 18 years or older, met diagnostic criteria for a current heroin dependence disorder according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV-TR, American Psychiatric Association, 2000), had used heroin at least 20 of the 28 days and had stable accommodation in the local area. Female participants were required to use contraception during the study. Participants were ineligible if pregnant or breastfeeding, had children aged less than 16 years at home with current child protection services involvement, had a pending court case with a reasonable risk of a custodial sentence, had current DSM-IV-TR substance dependence to alcohol, benzodiazepines, amphetamines or cocaine, had any opioid agonist treatment in the previous four weeks, more than two weeks of consecutive opioid agonist treatment in the previous 12 weeks or had concurrent major medical or psychiatric conditions where immediate opioid agonist treatment and/or other treatments were clinically indicated.

Participants were recruited from the waiting list for treatment from the Newcastle and Cessnock public opioid agonist treatment clinics in regional NSW, Australia between Apr 28, 2009 and Oct 13, 2009. Participants completed screening with a research nurse. Study medical officers confirmed participants' eligibility, including urine drug testing. Female participants underwent a urine pregnancy (β-hCG) test. A research nurse or research assistant obtained voluntary written consent from all participants and completed study enrollment procedures.

### 2.3. Randomization

Independent researchers carried out random number allocation, block randomization (block size = 4) for the trial with a 1:1 allocation ratio. Study clinicians and researchers were unaware of the randomization technique or block size and unable to influence allocation. Randomized assignment of intervention occurred at the John Hunter Hospital Pharmacy Department, who were independent to the study, using a computer generated randomization sequence. The trial was open-label, as it is not feasible to attempt blinding with a waitlist control design.

### 2.4. Procedures

Participants randomized to treatment were inducted with an 8 mg dose of BNX on day one (4 mg supervised, 4 mg take-home), with 16 mg take-home medication provided for day two. The research nurse reviewed participants on day three to assess medication adherence, dose adequacy, drug use and cravings, and contacted the study medical officer if dose changes were required. Doses were clinically titrated with the goal of a target dose of 16–24 mg BNX (maximum dose of 32 mg), and provided doses for days three to seven.

A research nurse reviewed all treatment participants each week and assessed progress during a 15–20 min standardized medical management session. Medical management sessions included: participant confirmation of dose amount and time since last dose; questions relating to side effects and adverse event reporting if required; rating of any cravings; assessment of consciousness, speech and pupil dilation; participant self-report of BNX and illicit drug use in past seven days; changes in accommodation; recording of concomitant medication and supervised urine collection. Throughout the 12-weeks, BNX group participants attended the clinic weekly and one weeks' take-home medication was provided for self-administration. Dose titration could occur during each medical review session (at the end of weeks one, two, four, eight and 12) and was based on clinical assessment that comprised patient self-reported illicit opioid and other drug use, cravings, physical examination, urine drug screen results and assessment of patient progress in treatment. Standardised dose titration criteria were not used by the three study medical officers. Mean buprenorphine dose ± SD (range) for the intervention group were 21.0 ± 5.8 mg (16–32) at week 4, 22.3 ± 5.0 mg (16–32) at week 8 and 22.7 ± 5.7 mg (16–32) at week 12. Participants randomized to the waitlist did not have any scheduled clinical review appointments during the 12 week wait period.

Research assessments were conducted for both groups at baseline and at the end of week four, eight and 12. The following instruments were administered: Opiate Treatment Index (OTI, self-reported drug use and crime sections); the Short Form (SF-12); the Kessler 10 (K-10); and Question 1 from the World Health Organisation Quality of Life BREF (WHO QoL BREF) scale, "How would you rate your quality of life?" OTI results reported include: days of drug use in the last 28; Q score for heroin use (provides an estimate of recent quantity and frequency of use with decimal scores ranging from zero [abstinence] to two or greater [use greater than once a day]); and total crime (total score range: 0–16, Darke et al., 1991). SF-12 provides summary measures of mental and physical health (score range: 0–100, Jenkinson et al., 1997). K-10 is a measure of psychological distress in the preceding four weeks (score range: 10–50, Kessler et al., 2002). The WHO QoL BREF measures subjective aspects of quality of life (WHO QoL BREF, Question 1 has a five point rating scale: 1 = very poor to 5 = very good, Skevington et al., 2004; The WHO QoL Group, 1998). See Supplementary Material for further description of instruments. At each research interview urine was collected for gas chromatography-mass spectrometry (GCMS) testing of opioids (heroin/6-mam, buprenorphine, methadone, morphine, oxycodone, codeine); psychostimulants (cocaine, methamphetamine, dexamphetamine, amphetamine) and benzodiazepine. Treatment group urine drug screens were collected on a weekly basis.

Data collected for the cost-effectiveness analysis included: study-related treatment costs, other health system costs and crime data. Study-related treatment costs included staffing (nursing, medical, pharmacy) and medication costs (using clinic electronic health records) and health service utilities (proportional allocation of clinic expenses). Other health care costs included visits to general practitioners and other medical specialists, medications costs, emergency department and hospital outpatient presentations over the study period. A record of all clinic contacts was maintained during the study. The cost of each clinic visit was calculated from the use of medical, nursing, other staff and urine toxicology, valued at unit costs provided by the New South Wales state Department of Health. Hospital resource use (including inpatient and emergency department visits) was taken from Hunter New England Health administrative records. Health resource use delivered in the community (non-hospital doctor visits and non-study pharmaceuticals) was provided from linked Federal government records. Study buprenorphine-naloxone and non-study medical, investigation and pharmaceutical costs were calculated using national re-imbursement rates (Australian Government Department of Health and Ageing, 2009a,b). Hospital inpatient and outpatient costs were calculated using diagnostic related group and national hospital cost data (Commonwealth of Australia, 2010). Crime costs utilized self-reported crime (OTI crime score), with costs calculated using Australian Institute of Criminology data (property crime: $A544.41/incident, fraud: $A323.58/incident, violent crime:

$A1907.74/incident, Rollings, 2008). Mortality was assessed by confirmation with the National Coroners Information System.

### 2.5. Outcomes

The primary outcome was self-reported heroin use confirmed by urine toxicology, with secondary outcomes of other substance use, physical and mental health, WHO QoL BREF Question 1, 'How would you rate your quality of life', and crime. The primary outcome of the cost-effectiveness analysis was the incremental cost per additional heroin-free-day, calculated as the difference in the mean health and crime-related costs between the intervention group and the waitlist group divided by the difference in the sample mean of heroin free days over the 12-week period.

An independent Clinical Monitoring Committee, comprising addiction medicine specialists at an independent health service, assessed progress of participants and had the authority to remove participants from either trial condition if their health status deteriorated significantly during the trial. Data on adverse events were collected throughout the study.

### 2.6. Statistical analyses

For the effectiveness analysis continuous data have been summarized using descriptive statistics including the number of observations used in the calculation (n), mean, and standard deviation (SD). Categorical data have been summarized as counts and percentages of each category.

Analyses were performed on those who were randomized to the BNX program (Intention to treat, ITT) and those who completed the BNX program. Data are presented for the ITT population, unless stated otherwise. Where data were missing, the baseline observation was carried forward. For continuous and count outcomes, between-group differences at each time-point were assessed using linear regression with adjustment for the baseline value of the outcome, the effect averaged over time was also estimated using mixed effects regression models that included fixed effects for the baseline value of the outcome variable, treatment group and time (as categorical), and a random intercept to account for the serial correlation induced from longitudinal measurements, results are presented as least-square means with 95% confidence intervals. Binary outcomes were compared at each time-point using Fishers exact test, and the average effect over time was estimated using log-binomial regression with a generalized estimating equation (GEE) framework, results are presented as relative risks with 95% confidence intervals. Robust (Huber-White) variance estimators were used for all models. As a sensitivity analysis, we estimated treatment group differences for count outcomes using negative binomial regression models, the conclusions remained the same and so these models are not reported. A sample size of n = 50 (25 per group), calculated a priori, was required to detect a 40% difference in heroin use at day 84, with 80% power and standard levels of significance ($p < 0.05$). This degree of difference in heroin use has been seen in similar studies (Schwartz et al., 2006; Yancovitz et al., 1991). Interim analysis was not undertaken. Cohen's kappa was used to test for agreement between self-report and urine toxicology. All analyses were programmed in SAS v9.1 (SAS Institute, Carry, NY) or later and Stata V14 (Statacorp, College Station, TX).

For the cost-effectiveness analysis, *t*-tests were used for differences in means and where variables were non-normally distributed, bias corrected bootstrapped standard errors were calculated. Cost data were skewed and in a supplementary analysis recycled predictions of mean costs in each group were estimated from a generalized linear regression adjusting for baseline costs after a series of tests for the best family (modified Park test) and link function, modified Hosmer-Lemeshow and Copas tests (Glick et al., 2014, p. 115). The analysis was repeated after removing severe outliers based on Cook's $D > 4/n$ (Belsley et al., 1980). The data were initially analyzed using intention to treat and then in a sensitivity analysis, missing data were replaced with baseline.

## 3. Results

Participant recruitment occurred between Apr 28, 2009 and Oct 13, 2009. Seventy-five patients were screened for entry to the study (see Fig. 1). Twenty-four were not eligible – most commonly for not completing the assessment process. Fifty-one patients were eligible and signed the consent form, and 50 were randomly allocated. One participant in the active treatment group was withdrawn from the study during the induction phase (probable precipitated withdrawal) and replaced according to the study protocol. At the week four data collection time point, 24 (96%) BNX participants and 20 (80%) waitlist controls completed assessments; at week eight, data was collected for 23 (92%) and 18 (72%) participants in the BNX and waitlist groups respectively. Twenty-two participants (88%) in the active treatment group and 18 (72%) in the waitlist group completed the 12-week trial according to the study protocol and were followed up at week 12 (80% total follow-up). Intention to treat analysis was performed on 25 participants in each group.

Participants were predominantly male, in their fourth decade of life and had completed approximately 10 years of education (Table 1). Participants reported poor levels of physical and mental health, quality of life and high unemployment rates at baseline. All participants had a DSM-IV-TR heroin dependence (and no other substance dependence). Participants had used heroin for around 14 years, twice daily (OTI Q score), most days of the month and spent approximately $A190 on heroin/day (Table 2). Tobacco (96%) and cannabis (80%) were frequently used, while other drug use including amphetamines and alcohol were less frequent. Almost 90% had attempted some treatment previously, most commonly methadone maintenance (60%) and withdrawal treatment (68%). Participants who were randomized to BNX were similar to the waitlist group in demographic and other baseline characteristics (see Tables 1 and 2).

Table 3 and Fig. 2 demonstrate self-reported heroin use between the two groups over the 12-week study period, with marked differences between groups at each time point for the ITT population. The BNX treatment group displayed a significant reduction in all self-reported heroin use measures, at all three time points, and as an effect over time (12 weeks) compared to the waitlist controls. Self-reported use of other opioids (e.g., illicit methadone, buprenorphine, buprenorphine-naloxone, morphine, oxycodone) was also significantly lower in the treatment group (see Table 3).

Effect over time analysis, across the 12 week period, revealed that self-reported heroin use was 19.02 days less per 28 days (95% CI −22.98, −15.07; $p < 0.0001$) in the BNX group (Mean days used ± SD; 4.07 ± 7.72) compared to those remaining on the waitlist (23.37 ± 8.10). Heroin OTI Q score was 1.67 points lower (95% CI −2.06, −1.28; $p < 0.0001$) in participants receiving treatment (Mean score ± SD; 0.33 ± 0.80) relative to controls (1.93 ± 1.04), indicating self-report heroin use was approximately five times lower in the BNX group. Compared to the waitlist group, a significant reduction of $79.04 (95% CI, −129.02, −29.06, $p = 0.0025$), over the 12 weeks, in the cost of heroin per day used in the treatment group was also observed (Mean $ ± SD, BNX = 54.53 ± 115.75; waitlist = 124.37 ± 101.72). While other opioid use was less frequent, those randomized to receive BNX showed a decrease of 6.77 days (95% CI, −9.83, −3.71, $p < 0.0001$) in self-reported use of other opioids over the study period compared to controls (Mean days ± SD: BNX = 0.2 ± 0.59; waitlist = 6.08 ± 8.56). Further detail on individual time point data is provided in Table 3. Results over the 12 weeks are adjusted for baseline measurement of the outcome and time.

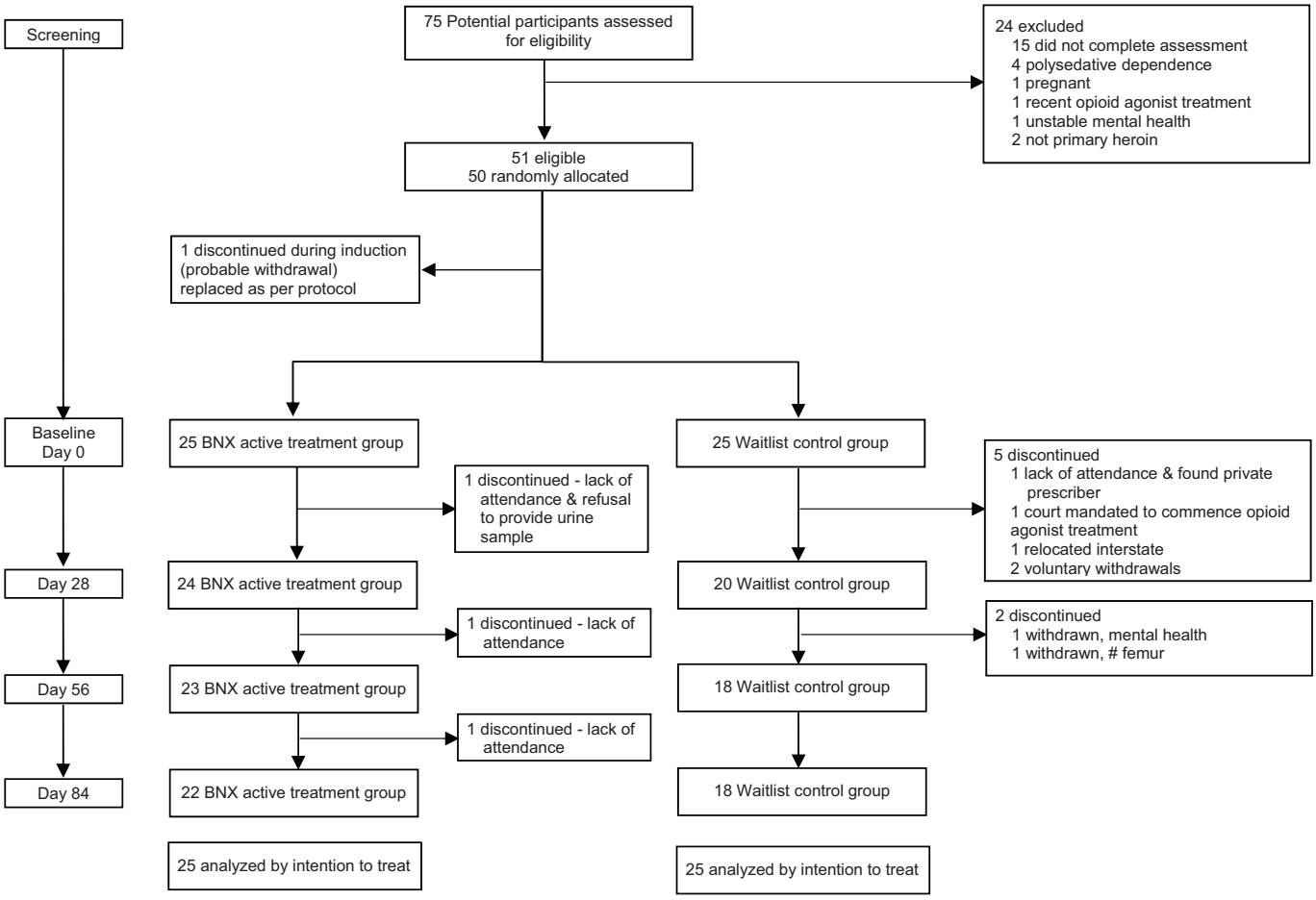


**Fig. 1.** Trial profile, recruitment and progress of study participants. Following screening exclusions, 50 trial participants were randomized (one to one allocation ratio) to either the buprenorphine-naloxone active treatment group or the waiting list control group. Trial subjects were assessed at baseline (day zero), and at the end of week four (day 28), week eight (day 56), and week 12 (day 84) for heroin use, other substance use, health, quality of life, crime and cost-effectiveness. Participant numbers at each phase of the protocol, drop-out rate, and reasons for withdrawal/exclusions are provided. # indicates fractured; BNX buprenorphine-naloxone.

**Table 1**
Baseline characteristics.

| | BNX group (n = 25) | Waitlist (n = 25) | Total (n = 50) |
|---|---|---|---|
| Age, years, mean (SD) | 36.1 (7.3) | 37.7 (9.0) | 36.9 (8.1) |
| Gender, male, n (%) | 15 (60%) | 13 (52%) | 28 (56%) |
| 12+ year education, n (%) | 0 (0%) | 1 (4%) | 1 (2%) |
| Employed, n (%) | 0 (0%) | 5 (20%) | 5 (10%) |
| OTI crime total score, mean (SD) | 2.4 (2.6) | 2.9 (2.6) | 2.7 (2.6) |
| WHO QoL BREF Question 1, mean (SD) | 2.5 (0.8) | 2.8 (0.9) | 2.6 (0.9) |
| *How would you rate your quality of life?* | | | |
| Mental health (K-10) score, mean (SD) | 29.2 (8.7) | 27.2 (9.0) | 28.2 (8.9) |
| Physical health (SF-12) score, mean (SD) | 40.8 (10.7) | 45.9 (9.2) | 43.3 (10.2) |
| Mental health (SF-12) score, mean (SD) | 29.5 (11.6) | 32.0 (13.6) | 30.7 (12.5) |

Instrument score range: OTI crime total (0–16); SF-12 (0–100); K-10 (10–50).WHO QoL BREF Question 1 (1 = very poor to 5 = very good).

Only one person at day 28 and day 56, and three people at day 84 had a negative self-report of heroin use contradicted by a positive urine test; Cohen's kappa ranged from 0.36 to 0.47 for agreement between self-report and urine toxicology at the time points. Fig. 3 shows urine opioid toxicology for morphine and/or 6-mono-acetylmorphine (6-MAM) at baseline and days 28, 56 and 84. There were significantly fewer positive urine results for the combined outcome of morphine and/or 6-MAM in the treatment group compared to the waitlist control at 28 days (BNX = 9 (36%), waitlist = 21 (84%); p = 0.0012) and at 56 days (BNX = 11 (44%), waitlist = 21 (84%); p = 0.0072) in the ITT population. The differences were not statistically different at 84 days (BNX = 12 (48%), waitlist = 19 (76%); p = 0.0792). Overall post treatment measures, the treatment group were 48% less likely to have a positive urine test for either morphine or 6-MAM than the waitlist group [RR (95% CI) = 0.52 (0.35, 0.77); p = 0.0013)]. Opioid urine toxicology for the treatment group during the study is shown in Fig. 4. Positive opioid results dropped from 88% at day one and remained at 52% or less during the rest of the study period. There was no evidence of between group differences for use of other substances, including tobacco, alcohol, cannabis and amphetamines (Table 4).

Compared to controls, significant and sustained improvements were seen in the treatment group at all time points and as an effect over time for crime, quality of life and mental health (Table 4).

**Table 2**
Baseline substance use.

| | BNX group (n = 25) | Waitlist (n = 25) | Total (n = 50) |
|---|---|---|---|
| Days of heroin use in previous 28 days (OTI heroin days), mean (SD) | 25.0 (4.6) | 25.4 (3.6) | 25.2 (4.1) |
| OTI Q score, heroin use, mean (SD) | 2.19 (1.5) | 1.82 (0.9) | 2.0 (1.2) |
| Proportion reporting heroin use in past month, *n*(%) | 25 (100%) | 25 (100%) | 50 (100%) |
| Cost of heroin/day used ($A), mean (SD) | 219.8 (204.5) | 153.0 (104.7) | 186.4 (164.3) |
| Years heroin use, mean (SD) | 12.8 (8.4) | 14.2 (10.9) | 13.5 (9.6) |
| Previous opioid treatment, *n*(%) | 20 (80%) | 19 (76%) | 39 (78%) |
| Other Opiate use, OTI days in last 28, mean (SD) | 6.5 (6.9) | 4.0 (6.3) | 5.2 (6.6) |
| Tobacco use, OTI days in last 28, mean (SD) | 26.9 (5.6) | 26.9 (5.6) | 26.9 (5.5) |
| Cannabis use, OTI days in last 28, mean (SD) | 19.0 (11.7) | 16.4 (12.6) | 17.7 (12.1) |
| Alcohol use, OTI days in last 28, mean (SD) | 4.6 (8.8) | 2.3 (3.9) | 3.5 (6.8) |
| Amphetamine use, OTI days in last 28, mean (SD) | 2.0 (3.6) | 0.5 (0.7) | 1.3 (2.7) |

Instrument score range: OTI Q score provides an estimate of recent quantity and frequency of use, scores range from zero indicating abstinence to a score of two or greater indicating more than once a day (See Supplementary Material for further interpretation of Q scores).

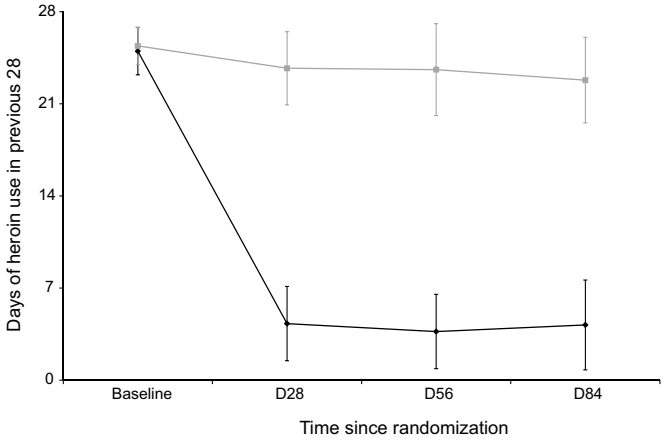


**Fig. 2.** Number of days of heroin use in past 28. Heroin use, measured as number of days used in the past 28, was assessed at day zero (baseline), 28, 56, and 84 by self-report. Participants randomized to receive buprenorphine-naloxone treatment (black, n = 25) displayed a significant reduction in heroin use at all three time points ($p<0.0001$) over the 12 week period relative to waitlist controls (grey, n = 25). Data are presented as mean ± 95% CI.

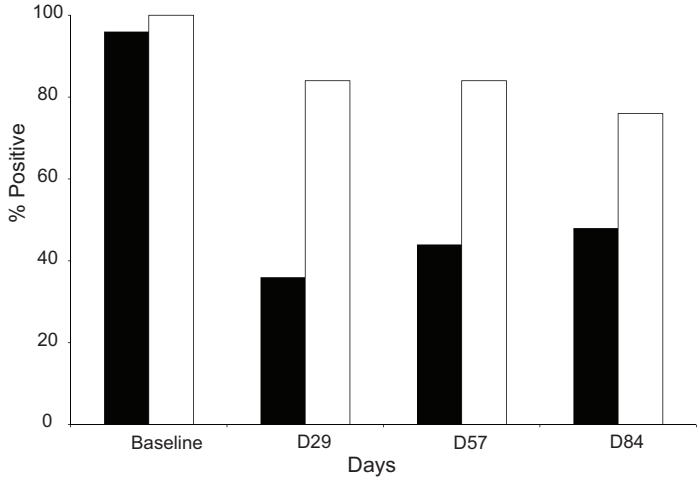


**Fig. 3.** Urine toxicology results at baseline, day 29, 56 and 84. Compared to waitlist (white, n = 25) controls the buprenorphine-naloxone (black, n = 25) treatment group provided significantly fewer positive urine drug screen results for the combined outcome of morphine and/or 6-mono-acetylmorphine (6-MAM) at 28 ($p = 0.0012$) and 56 ($p = 0.0072$) days in the intention to treat population (ITT) population. No differences were observed at 84 days ($p = 0.0792$).

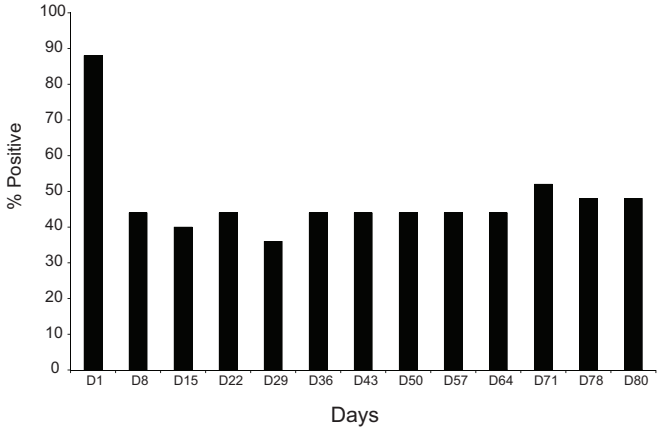


**Fig. 4.** Weekly urine toxicology for buprenorphine-naloxone (BNX) treatment group. Weekly urine drug screens were performed on participants randomized to receive BNX for the combined outcome of morphine and/or 6-mono-acetylmorphine (6-MAM). On day one of the study 88% (n = 22) participants returned a positive screen. This percentage dropped to between 36 and 52% for the reminder of the study. Data presented on ITT population, n = 25.

Across the 12 weeks: the average OTI crime total score was 2.12 points lower (95% CI −2.88,−1.36; $p < 0.0001$) in BNX participants (Mean score ± SD; 0.48 ± 1.03) compared to controls (2.9 ± 2.80); on average the score for the WHO QoL Question 1 'How would you rate your quality of life?' was increased by 0.95 points (95% CI 0.62, 1.28, $p < 0.0001$) in those receiving treatment (3.6 ± 0.73) compared to waitlist (2.8 ± 0.89); the Kessler 10 total score was reduced in the BNX group (18.57 ± 5.86) by 8.86 points (95% CI −11.71, −6.01, $p < 0.0001$) relative to controls (26.37 ± 9.22); and the SF-12 Mental Component score increased by 11.57 points (95% CI, 6.69, 16.45, $p < 0.0001$) in the treatment group (43.17 ± 12.27) compared to waitlist (33.13 ± 12.35). See Table 4 for further detail on individual time point data. Results over the 12 weeks are adjusted for baseline measurement of the outcome and time. There were no between group differences seen in the SF-12 physical health subscale. No deaths in either group were reported during the study period or 12 months after study completion.

Three serious adverse events were recorded: two participants from the waitlist group (one fractured neck of femur and one mental health deterioration) and one from the treatment group (bruised ribs from a motor vehicle accident). Seven patients randomized to the waitlist control condition discontinued participation: two withdrawn by the Clinical Monitoring Committee (one fractured neck of femur, one mental health deterioration); one court mandated to commence opioid agonist treatment; one moved interstate; four either discontinued voluntarily, found a private prescriber or did

**Table 3**
Self-report heroin and other opiate use during study.

| Outcome Measure | Day 28 | | | Day 56 | | | Day 84 | | | Effect Over Time (12 weeks) BNX compared to Wait list | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | BNX | Waitlist | P value | BNX | Waitlist | P value | BNX | Waitlist | P value | Mean monthly difference between groups (95% CI) | P value |
| Days of heroin use in previous 28 days (OTI heroin days), mean (SD) Missing data imputed (ITT) | 4.3 (7.2) | 23.7 (7.1) | <0.0001 | 3.7 (7.2) | 23.6 (8.9) | <0.0001 | 4.2 (8.7) | 22.8 (8.3) | <0.0001 | −19.02 (−22.98, −15.07) | <0.0001 |
| Days of heroin use in previous 28 days (OTI heroin days), mean (SD) Completers only. | 2.4 (2.8) (n = 24) | 23.1 (7.8) (n = 20) | <0.0001 | 1.7 (2.3) (n = 23) | 22.8 (10.3) (n = 18) | <0.0001 | 1.1 (1.7) (n = 22) | 21.6 (9.5) (n = 18) | <0.0001 | −20.23 (−23.71, −16.75) | <0.0001 |
| OTI Q score, heroin use mean (SD), ITT | 0.3 (0.6) | 2.1 (1.2) | <0.0001 | 0.3 (0.6) | 1.9 (1.0) | <0.0001 | 0.5 (1.1) | 1.8 (1.0) | <0.0001 | −1.67 (−2.06, −1.28) | <0.0001 |
| Proportion reporting no heroin use in past month, n (%) | 9 (36%) | 0 (0%) | 0.004 | 9 (36%) | 1 (4%) | 0.011 | 12 (48%) | 1 (4%) | 0.001 | OR = 13.19 (1.81, 95.72) | 0.011 |
| Cost of heroin/day used ($A) mean (SD), ITT | 52 (108.2) | 126.3 (105.8) | 0.0040 | 48.8 (108.8) | 109.7 (70.8) | 0.0070 | 62.8 (130.3) | 137.1 (128.6) | 0.0200 | −79.04 (−129.02, −29.06) | 0.0025 |
| Other opioid use, OTI days in last 28, mean (SD), ITT | 0.4 (0.9) | 6.2 (8.0) | <0.0001 | 0 (0.2) | 6.1 (8.9) | <0.0001 | 0.2 (0.5) | 6.0 (9.0) | 0.0003 | −6.77 (−9.83,−3.71) | <0.0001 |

NB: The test of significant differences between groups at each time point is through an ANCOVA model adjusting for baseline measurement of the outcome or Fishers exact test for binary outcomes.
Instrument score range: OTI Q score provides an estimate of recent quantity and frequency of use, decimal scores range from zero indicating abstinence to a score of two or greater indicating more than once a day (See Supplementary Material for further interpretation of Q scores)

**Table 4**
Other substance use, crime, quality of life and mental health.

| Outcome Measure | Day 28 | | | Day 56 | | | Day 84 | | | Effect Over Time (12 weeks) BNX compared to Wait list | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | BNX | Waitlist | P value | BNX | Waitlist | P value | BNX | Waitlist | P value | Mean monthly difference between groups (95% CI) | P value |
| Tobacco, OTI days in last 28, mean (SD), ITT | 26.8 (5.8) | 26.4 (6.3) | 0.327 | 26 (6.7) | 26.4 (6.8) | 0.327 | 25.1 (8.3) | 25.1 (7.6) | 0.772 | −0.29 (−1.56, 0.97) | 0.650 |
| Alcohol, OTI days in last 28, mean (SD), ITT | 5.1 (8.3) | 2.4 (3.6) | 0.322 | 3.8 (6.6) | 4.1 (8.0) | 0.168 | 5.5 (9.2) | 2.2 (4.8) | 0.352 | 0.04 (−1.88, 1.96) | 0.969 |
| Cannabis, OTI days in last 28, mean (SD), ITT | 19.2 (12.5) | 14.9 (12.4) | 0.231 | 19.4 (11.8) | 16.7 (12.0) | 0.804 | 17.8 (12.0) | 14.8 (12.4) | 0.631 | 0.96 (−1.26, 3.19) | 0.396 |
| Amphetamines, OTI days in last 28, mean (SD), ITT | 1.7 (4.2) | 0.8 (1.1) | 0.775 | 2.5 (5.1) | 0.8 (2.3) | 0.619 | 3.2 (7.2) | 0.6 (0.9) | 0.333 | 0.47 (−0.85, 1.77) | 0.487 |
| OTI crime total score mean (SD), ITT | 0.6 (1.2) | 3.2 (2.6) | <0.0001 | 0.5 (1.1) | 2.7 (3.0) | 0.0001 | 0.3 (0.9) | 2.8 (2.9) | <0.0001 | −2.12 (−2.88, −1.36) | <0.0001 |
| WHO QOL Question 1, mean (SD), ITT *How would you rate your quality of life?* | 3.6 (0.6) | 3.1 (0.9) | 0.0007 | 3.7 (0.7) | 3.1 (0.9) | 0.0011 | 3.9 (0.7) | 3.1 (0.6) | <0.0001 | 0.95 (0.62, 1.28) | <0.0001 |
| K-10 Total Score mean (SD), ITT | 19.8 (5.6) | 27 (9.0) | <0.0001 | 18 (5.7) | 26.1 (9.4) | <0.0001 | 17.9 (6.3) | 26 (9.3) | <0.0001 | −8.86 (−11.71, −6.01) | <0.0001 |
| SF-12 Mental Component Score mean (SD), ITT | 40.6 (12.9) | 31.3 (12.4) | 0.0001 | 44.5 (12.2) | 34.5 (12.6) | <0.0001 | 44.4 (11.8) | 33.6 (12.1) | <0.0001 | 11.57 (6.69, 16.45) | <0.0001 |

NB: Differences between groups are adjusted for baseline measurement of the outcome and time.
Instrument score range: OTI crime total score (0–16); WHO QoL Question 1: (1 = very poor to 5 = very good); K-10 (10–50); SF-12 (0–100).

**Table 5**
Difference in cost and outcomes by group over 12 weeks.

| | BNX Mean (SD) | Waitlist Mean (SD) | Difference (95% CI) |
|---|---|---|---|
| Heroin free days | 68.0 (25.8) | 13.9 (23.1) | 54.6 (40.0–67.0) |
| Health Costs ($A) | 1822 (584) | 828 (1442) | 995 (250–1520) |
| Total Cost [2] ($A) | 2187 (847) | 10460 (16675) | −8273 (−16507 to −1401) |
| Adjusted cost[3] | 2873 (4097) | 8595 (12257) | −5722 (−8145 to −3299) |

($A) 1. No imputed missing data to baseline, n = 40; 2. Including crime n = 40; 3. Including crime with imputed missing data to baseline and excluding 4 outliers n = 46.

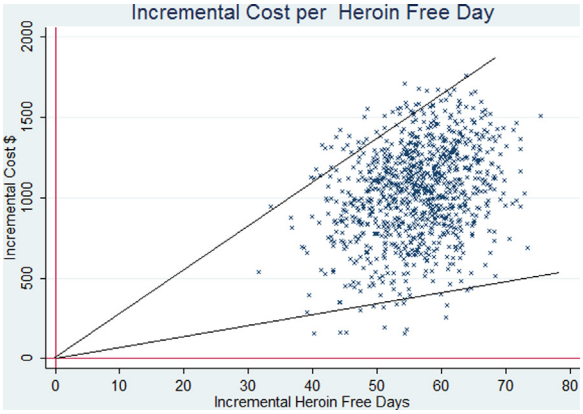


**Fig. 5.** Incremental cost-effectiveness. Distribution of the difference in incremental mean costs per additional heroin free day, as estimated by the bias-corrected non-parametric bootstrapping method. Data are presented as bootstrapped means with diagonal lines indicating 95% CI. n = 50.

not attend. An additional two waitlist participants (one pregnancy withdrawn by the Clinical Monitoring Committee and one voluntary withdrawal) discontinued in the last week of the trial however, final time point data was collected and utilized for analysis. Three patients were discontinued from the treatment arm for lack of attendance/non-compliance (Fig. 1).

Table 5 summarizes the cost-effectiveness results. The total health-sector cost during the 12 weeks of the trial was significantly higher for those randomized to buprenorphine-naloxone compared to the waiting list. When crime costs are included, there was a significant financial saving of $A8,273.38 (95% CI 1401.09, 16,506.77) from the intervention ($A5,722.42; 95% CI 3299.42, 8154.64, adjusted for baseline differences and skewness in the cost-effectiveness data). When crime costs are excluded, the incremental cost per heroin-free day gained from buprenorphine-naloxone compared to waiting is $A18.24 (95% CI 4.50, 28.49). Imputing baseline values for missing data did not alter this result substantially (see Fig. 5 for distribution of incremental cost per heroin free day).

## 4. Discussion

This study demonstrated that when compared to remaining on a waiting list, participants with a DSM-IV-TR heroin dependence treated with sublingual buprenorphine-naloxone achieved a significant reduction in heroin use and crime, and improvement of mental health and quality of life parameters over a 12-week period.

As seen in Fig. 3, the decrease in self-reported heroin use in the BNX group was supported by a significant reduction in return of positive drug screens for morphine and/or 6-MAM, compared to controls, at 28 and 56 days. Additionally, as highlighted above, those participants randomized to receive BNX were half as likely to have a positive urine test as the waitlist group across all time points. The BNX group demonstrated an immediate response in reduced 6-MAM/morphine positive urine screens at week one that continued throughout the study (Fig. 4). The treatment effect may have been over-estimated in the BNX group as sampling occurred on a weekly basis, however, the significant positive effect over time with regards illicit heroin or other opioid use during the treatment period is notable and consistent with the effects of opioid agonist treatment.

The positive treatment effect of buprenorphine maintenance has previously been seen in placebo-controlled studies (Fudala et al., 2003; Johnson et al., 1995; Kakko et al., 2003; Krook et al., 2002; Schottenfeld et al., 2008). The magnitude of effect size in terms of reduction of heroin use is similar to that seen in two waiting list randomized studies of methadone (Schwartz et al., 2006; Yancovitz et al., 1991). While this single-site trial is limited by the use of a small sample with no placebo group; it should be noted that a recent US trial with a similar design has reported similar effects of buprenorphine maintenance reducing heroin use (Sigmon et al., 2016). The baseline characteristics of participants in the current study are comparable to those seen in the Australian Treatment Outcome Study of patients with heroin use problems (Ross et al., 2005). The enrolment criteria for the current study excluded participants with substance dependence to alcohol, benzodiazepines, amphetamines and cocaine. This may impact on the generalizability of the findings seen in the current study as clinical populations do consist of people with multiple concurrent substance dependence. Importantly, a higher retention rate was observed in the current study than in most buprenorphine maintenance studies of similar duration (Mattick et al., 2014). Moreover, the conditions of this study are similar to buprenorphine-naloxone maintenance treatment, as carried out in office-based settings in the USA, and therefore provide support for this model of treatment.

The current study also demonstrated a significant positive impact of buprenorphine treatment on mental health symptoms, psychosocial functioning, quality of life outcomes and reduction in drug-related crime consistent with other studies of buprenorphine treatment. Reduction in crime (measured using Addiction Severity Index scores, Kakko et al., 2003) and improvements in quality of life (measured using the WHO QoL BREF, Bell et al., 2007) and in well-being and life satisfaction (measured using a visual analogue scale and the temporal satisfaction with life scale, Krook et al., 2002) have been reported. Differences in the instruments used do not permit a direct comparison of effect size of the secondary outcomes measured. Furthermore, interim methadone wait-list studies (Schwartz et al., 2006; Yancovitz et al., 1991) do not include crime, quality of life or psychological symptoms as outcomes.

Take-home self-administration of buprenorphine warrants consideration in Australia and other countries that mandate supervised buprenorphine dosing. Regular supervision of all dispensed doses is an approach developed for methadone maintenance treatment, due to concern regarding the diversion, the risk of hazardous use by injection and particularly the risk of overdose if used by non-tolerant individuals. In health environments where resources remain scarce, unsupervised dosing of buprenorphine-naloxone is more cost-effective than supervised administration of the medication (Bell et al., 2007).

The health care costs of maintaining participants on BNX and remaining heroin-free were very moderate ($A18.42 per heroin free day, 95% CI 4.50, 28.49). This result is consistent with other Australian data on the costs per heroin-free-day of opioid agonist treatment (Bell et al., 2007). There were savings from BNX treatment compared to remaining on a waitlist of $A5,722.42 (95% CI 3299.42, 8154.64) per patient for the 12-week period. The most significant driver of the cost differential between groups was the reduction in crime. The estimates of adjusted cost difference used in this study are conservative.

### 4.1. Conclusions

The current study is the first cost-effectiveness study of treatment for heroin dependence where a no treatment/wait list control group has been used. This study provides an important platform for future research in larger multi-site clinical trials to implement and potentially enhance the generalizability of this treatment approach. It will be imperative for future research to also investigate the effectiveness of further reducing clinical contact time in this paradigm.

## Conflicts of interest

AD reports grants from NSW Ministry of Health – Untied Research Grant, during the conduct of the study; and in 2007 AD received travel support and an honorarium to speak at a conference in France, from Schering Plough, who, at that time held an international distribution licence for buprenorphine (excluding USA and Australia). AB, CS, JH, KR, and MJ report grants from NSW Ministry of Health – Untied Research Grant, during the conduct of the study. AG reports grants from NSW Ministry of Health – Untied Research Grant, during the conduct of the study and others from Indivior, outside the submitted work. AH, as Director of the Centre for Health Economics, has had contracts with the Australian Government to evaluate pharmaceutical submissions for listing on the Pharmaceutical Benefits Scheme. JB reports personal fees from Indivior, personal fees from Martindale, grants from Reckittbenckiser, outside the submitted work CO, DB, JA, and PG have nothing to disclose. NL has received educational grant for investigator led research (from Indivior for evaluating methadone to buprenorphine transfers), and honoraria from Pharmacom Media for participation in educational forums regarding opioid dependence.

## Contributors

AD – Literature search, study concept, design, clinical assessments, analysis and interpretation, writing, critical review of manuscript.

AB – Literature search, analysis and interpretation, writing, figures, critical review of manuscript.

CO – Statistical data analysis and interpretation, writing, critical review of manuscript.

AH – Cost-effectiveness analysis and associated figures, critical review of manuscript.

AG – Study concept and design, clinical assessments, critical review of manuscript.

CS – Study concept and design, clinical assessments, critical review of manuscript.

KR – Study co-ordination, participant recruitment, data collection, critical review of manuscript.

JA – Study design, analysis and interpretation, critical review of manuscript.

DB – Statistical data analysis, critical review of manuscript.

PG – Cost-effectiveness analysis, critical review of manuscript.

JH – Data collection, critical review of manuscript.

MJ – Analysis, interpretation, writing and critical review of manuscript.

JB – Study concept and design, critical review of manuscript.

NL – Study concept, design, data interpretation, critical review of manuscript.

All authors have approved the final article version.

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NSW Ministry of Health provided financial support in the form of an untied research grant to conduct the study. The funding source had no involvement in study design; in the collection, analysis and interpretation of the data; in the writing of the report or the decision to submit for publication.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.drugalcdep.2017.01.016.

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