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Executive Summary

A large number of studies have shown methadone maintenance treatment to be effective when delivered from specialist clinics to selected populations of opioid dependent clients. However, recent evidence from The Netherlands suggests that methadone programs that have relaxed criteria for entry and continuation in treatment may not be as effective as the traditional, specialist methadone clinics. A proposal to commence dispensing methadone to a population of young, "at risk" opiate injectors at a primary health care centre in Kings Cross, Sydney afforded the opportunity to evaluate a methadone program similar to those operating in The Netherlands. The key question posed by this evaluation was: Does methadone maintenance treatment, when integrated into an exisiting primary health care centre, help young, "at-risk" injecting opiate users to reduce their heroin use, crime, HIV risk behaviour and to improve their health? In order to answer this question, 70 applicants for treatment were randomised to receive methadone or not in addition to the usual care they had been receiving at the clinic and were assessed at intake and three months later. A series of analyses were performed in order to adjust for selective attrition between the two groups at three-month follow-up and to assess the influence of exposure to methadone treatment in the control group. These analyses indicated that exposure to methadone maintenance is associated with reductions in heroin use, crime and HIV risk behaviour, as well as improvements in health. Thus, it can be concluded that methadone maintenance is of benefit to young, "at risk" opiate injectors. This suggests that methadone maintenance services should be modified and expanded to attract a wider range of opioid dependent individuals into treatment, especially those more at risk and who find it difficult to comply with the protocols of the more traditional clinic regimen.

Introduction

The effectiveness of methadone maintenance in reducing illicit opioid use, crime and injection-related risk behaviour has been demonstrated in a number of studies and countries using a variety of study designs (Ward, Bell, Mattick & Hall, in press). However, virtually all of these studies have examined methadone maintenance as delivered in a traditional format to a traditional patient group. For much of the past 25 years in Australia and the United States, methadone has been delivered through a system of special purpose clinics, which have provided a variety of psychosocial support services and employed admission criteria and process rules to select a population of the opioid dependent who are likely to change their behaviour. The therapeutic demands of methadone clinics have probably influenced the perceived attractiveness of the treatment among opioid users, with the result that by the time individuals present for treatment they have usually been dependent for a number of years and suffered sufficient drug-related problems for long enough to be willing to submit to the clinic regimen.

Concern about the possibility of an increase in drug-related crime in the early 1980s led to proposals to expand the availability of methadone maintenance in New South Wales (Caplehorn & Batey, 1992; McArthur, 1995). These proposals were given impetus by the discovery of the relationship between injecting drug use and the spread of HIV. This has recently been reinforced by concern about the very high rates of exposure among injecting drug users to hepatitis B and C (Bell et al., 1990; Crofts et al., 1994). A similar expansion in methadone services has occurred in other countries, and has been accompanied by experiments with treatment philosophy and practice in an attempt to reach a broader population of opioid users and to more specifically target aspects of drug use associated with the spread of blood borne viruses (Gossop & Grant, 1991; Uchtenhagen, 1990).

As has been argued elsewhere (Ward, 1995), in Australia, the expansion of the methadone program has been accompanied by the following changes in the way in which treatment is delivered:

(a) the type and number of *ancillary services* have been reduced;
(b) the *sites* at which methadone is dispensed have become more varied and, as well as special purpose clinics, include primary health care settings and community pharmacies;
(c) the *types of people* for whom methadone is thought to be suitable has become more broadly defined; and,
(d) the *private sector* has been relied upon to expand treatment services.

The study described in this report addresses itself to the second and third of these changes in methadone treatment delivery, namely the site and the treatment population. This study arose, in part, from concerns that these variations in the delivery of methadone maintenance might lead to it being less effective than might otherwise be expected from research conducted in special purpose methadone clinics with groups of patients selected for their suitability for treatment.

The most well known and controversial variations to methadone maintenance treatment are the programs that have been developed in the Netherlands. Often termed "low threshold"

methadone programs, these programs offer methadone through a distribution network of buses and small clinics and do not require regular attendance or strict criteria for entry, hence the term low threshold (van Ameijden, 1994). The goals of these programs are to stabilise drug use and provide for regular contact with drug users, so that their social and medical needs might be better met. Although it was not a specific goal of these programs, it was hoped that the provision of methadone would also help in reducing and preventing the spread of HIV and other blood-borne infections through a reduction in injecting frequency and an increased exposure to AIDS educational materials. However, a series of studies of the Amsterdam methadone programs have found that these hopes have not been realised. This failure raises the question: How much can the traditional treatment protocols of methadone treatment be varied before it begins to substantially lose its effectiveness?

Hartgers, van den Hoek, Krijnen and Coutinho (1992) evaluated low threshold methadone programs in Amsterdam for the period 1985 to 1989 and found that they did not reduce the risk for, or the spread of, HIV infection. In a further series of studies which continued to follow the same cohort through to 1992, van Ameijden and colleagues found no evidence of a protective effect for daily methadone attendance on incidence of HIV infection (van Ameijden, van den Hoek, van Haastrecht & Coutinho, 1992), level of injection-related HIV risk behaviour (van Ameijden, van den Hoek & Coutinho, 1994), or the transition from non-injecting to injecting opioid use (van Ameijden, van den Hoek, Hartgers & Coutinho, 1994). Hartgers et al. (1992) and van Ameijden (1994) speculated that the use of less than optimal doses of methadone (< 40 mg per day) may be responsible for this apparent lack of effectiveness and that higher doses of methadone may be necessary to achieve better outcomes. However, the possibility must be raised that some individuals may be unresponsive to methadone maintenance regardless of the package within which it is delivered.

An opportunity to examine the issues raised by the Dutch experience arose when a primary health centre located in central Sydney with a clientele similar to that described in the Amsterdam studies wished to develop a methadone program specifically to meet the needs of this population.

The Kirketon Road Centre (KRC) Pilot Oral Methadone Maintenance Program

The Kirketon Road Centre (KRC) is a primary health care centre located in Kings Cross, which is an inner city suburb of Sydney with an unusually high concentration of sex workers, drug users and at-risk youth. The KRC was set up in 1987 specifically to service this community as part of a nation-wide strategy to prevent the spread of HIV. Among the comprehensive range of services offered to the Kings Cross community, KRC provides both on-site and outreach medical, counselling, social welfare and needle and syringe exchange services.

In a further effort to meet the needs of the clients attending the KRC, it was decided in 1992 to apply for funding to commence a pilot, oral methadone maintenance program with the specific purpose of servicing "at-risk" opioid injectors who were unlikely to access, or remain in, traditional public methadone maintenance programs. Staff at the KRC believed that the existing rapport that had been established with these clients, in combination with a liberal attitude to drug use and attendance, would result in a program that would retain clients, and

lead to improvements in their health and to a reduction in their injection-related HIV risk behaviour. The integration of the prescription and dispensing of methadone into an existing primary health centre would be the first such program in Australia.

A proposal for the pilot methadone program was approved and as a condition of funding it was necessary that the program be evaluated. The National Drug and Alcohol Research Centre was approached to evaluate the service. Because of the similarity of the KRC methadone program to the Amsterdam program, and because of the evidence reviewed above questioning the effectiveness of low threshold programs in terms of one of the stated KRC goals (reducing HIV risk behaviour), it was decided that the study design which would afford the most unambiguous outcome would be the most appropriate. For this reason, a randomised design employing a control group that would continue to receive their usual care without methadone was considered and adopted.

The major objectives of the trial were to demonstrate the feasibility and effectiveness of methadone maintenance at the KRC. In accord with the stated goals of the program by KRC staff, the two major hypotheses for the trial would be that the addition of methadone to the usual care provided by the KRC would result in a reduction in the number of drug-related health problems experienced by clients and a reduction in drug-related HIV risk behaviour. Two additional hypotheses were adopted to explore the extent to which evidence of the effectiveness of traditional methadone maintenance treatment can be generalised to new settings and populations (recognising that these were not the stated goals of program staff). These hypotheses were that there would be reductions in opioid use and crime for patients enrolled in the KRC methadone program. The study also afforded the opportunity to examine the beliefs of the KRC staff, namely that their clientele was younger and more "at-risk" than the clientele of traditional methadone clinics, and that this high-risk group of young drug users would be retained in methadone treatment which would not be possible in a more traditional treatment setting.

Methods

Treatment Protocol

Methadone maintenance at the KRC aimed to follow what has come to be known in Australia as a "low intervention/ high supervision" model of treatment. It was low intervention in that no specific extra services over and above the prescribing and dispensing of methadone were to be offered. It involved high supervision, because take-home doses of methadone were not available and so the client had to present daily to the KRC. In practice, it was soon realised that the low intervention aspect of the program was something of a misnomer, because the regular presence of generalist medical practitioners, nurse practitioners, counsellors and social workers meant that more services were available than one would ordinarily find in a low intervention methadone maintenance regimen.

Other than for program evaluation purposes (see below), there was no urine testing, nor any policy of sanctions for illicit drug use. The overall harm reduction policy of the KRC was applied to the methadone program, and if clients participating in the program continued to use illicit drugs, then a message of safer drug use was emphasised. Methadone dosing took place in the same room that the needle and syringe exchange services were offered in, and

clients receiving methadone were able to avail themselves of these services in the same way as any other person. However, people who presented for methadone dosing in an intoxicated fashion were either told to return later in the day, or could make use of one of the waiting areas until they were in a fit state to be dosed. The only grounds for involuntary discontinuation from the program were physical violence against staff or property. Neither of these events occurred during the conduct of the study.

The doses of methadone employed were determined by the prescribing medical practitioner and the client, although there was a general intention to achieve doses in excess of 60 mg per day. Clients could adjust their dose within pre-specified constraints at the time of dosing in consultation with the person administering the methadone. Clients were thereby able to raise or lower their doses according to what they thought was best for them. Similarly, clients were not required to attend every day and could miss one or more days if they so wished. However, if the client had not attended for three or more days, then their methadone dose was reduced to a clinically safe level and adjusted upwards thereafter.

Study Design

The design employed to evaluate the KRC pilot methadone maintenance program was an open, two-group, pre-post randomised controlled trial. Subjects eligible for treatment were randomised to received a daily oral dose of methadone in addition to the usual care they received at KRC (hereafter referred to as the methadone treatment group), or they were assigned to a control condition in which they continued to receive usual care only (hereafter referred to as the control group). Study participants were to be assessed at baseline, and then again at three- and six-months. The study was open in the sense that keeping clinicians and clients blind to study conditions was not possible. Similarly, because one of the authors (JW) was involved in the design of the study and carried out all of the randomisations and research interviews, it was not possible to have the evaluation assessments conducted in a blinded fashion. The only blinding possible was that the laboratory that carried out the urinalysis tests was unaware of the nature of the study and the conditions to which each of the subjects had been assigned.

Randomisation was achieved by way of a lottery in which subjects selected an envelope from a bundle, each of which contained a slip of paper with the word "Methadone" or the words "Usual Care" typed on it. Randomisation took place after the completion of the assessment process for entry to the study and the first study interview, which included the taking of a urine sample. It was decided *a priori* that couples would be randomised together so that they would both either be in or out of treatment, because having one member of a couple in methadone maintenance while the other is not adversely affects their response to treatment (Waldby, 1988).

In an attempt to reduce "resentful demoralisation" (Cook & Campbell, 1979), subjects in the control condition were told that if the pilot program was deemed successful, they would be offered the first places that became available at the completion of the study. At the same time, it was considered unethical to totally refuse access to a treatment that has been shown to reduce the risk of injection-related infections. Therefore, as part of the usual care offered to clients in the control condition, referral to nearby public and private methadone clinics was made available. It was thought when planning the study that the number of referrals in the

control condition, and the amount of time control subjects spent in traditional methadone treatment, would give some indication of the extent to which the clients attending the KRC were unable to access or remain in methadone treatment elsewhere.

Design Modification

The study design was modified at the completion of the three-month follow-up interviews, when it was decided to halt the study and offer subjects in the control condition who were not receiving methadone the opportunity to enter methadone treatment at the KRC. There were three reasons for this change:

a) clinician concerns about the negative effects of randomisation (see section below on ethical issues) and, in particular, about the health and safety of some subjects in the control condition made continuing the trial difficult to justify in the light of the other two reasons set out below;

b) as a result of offering immediate referral to non-KRC methadone programs after assessment for the study, a significant proportion of the subjects in the control condition were receiving, or had received, methadone treatment elsewhere; and,

c) three-month follow-up rates differed significantly between the treatment and control conditions.

The latter two reasons when combined suggested that definitive conclusions about the effectiveness of methadone at the KRC, when compared to the absence of methadone, would be difficult to draw and, in the light of clinician concerns, it no longer seemed warranted to expose control subjects to further risks.

Ethical Issues

A study protocol was submitted to, and approved by, the research ethics committee responsible for overseeing medical research conducted in the area of Sydney where the trial took place (the Eastern Sydney Area Health Service Research Ethics Committee). There were three main areas of ethical concern connected with the conduct of this study: informed consent, confidentiality and the use of a randomised design with a no-treatment control group. Informed consent and confidentiality were dealt with by the use of a consent form in the case of the former, and in the case of the latter that all completed research interview forms and computer files containing interview data were kept in locked cabinets or password-protected files. Issues raised by the use of a randomised design are discussed separately in the next section.

Randomised Controlled Trials

The use of randomisation in the evaluation of medical treatments, or the provision of social services, raises an ethical dilemma when the treatment or service concerned is compared to what would happen in the absence of the intervention. This dilemma arises out of the fact that a treatment or service that may assist the target group concerned has to be refused for the

duration of the study in order for the evaluation to take place. The rationale for refusing treatment is that the long-term good of the majority is more important, and is served by rigorously evaluating interventions, when compared with the short-term harm of refusing treatment to a control group for the purposes of the evaluation or the prospect of continuing to promote ineffective alternatives (Feinstein, 1985; Lebacqz, 1983; Oakley, 1990). An important aspect of the use of randomised designs is uncertainty about the treatment in question. According to Oakley (1990):

> "It is important to note that the prerequisite for any RCT [randomised controlled trial] is *uncertainty* about the effects of a particular treatment. If something is known to work (and to be acceptable and without harmful effects) then there is no reason to put it to the test in the form of a trial" (p. 27, italics original).

In the case of the current study, as noted in the introduction, it was believed at the time of designing the evaluation that there was sufficient uncertainty about the effectiveness of the low threshold methadone program in Amsterdam to warrant the use of a randomised design.

Randomisation was further justified by the fact that there were a limited number of places available and that it would not be possible to meet the demand for treatment among KRC clients. In this sense randomisation seemed an ethical solution, assuming equal need for treatment, to the question of who to treat and who not to treat. It was also thought that it might have the added benefit of reducing resentment among those who did not receive treatment, because all applicants would understand that they had a 50:50 chance of entering treatment (Cook & Campbell, 1979). As it turned out, resentment was a major problem, and may explain the unwillingness on the part of some control subjects to participate in follow-up interviews.

A number of other ethical principles were followed in order to lessen the impact of randomisation on control subjects. The principle outlined by Lebacqz (1983) that 'those who bear the burden should reap the benefits' was followed in that control subjects were promised that if the KRC program continued to exist (which it has), then they would be offered the first places that became available after the study finished.

A further safeguard was put in place at the request of KRC staff in the form of an agreement that the study would be abandoned if subjects in the control group were seen to be at serious ongoing risk to their welfare. Put more generally, the study would be abandoned, or the design changed, if the harm appeared to be outweighing whatever benefits were thought to accrue from the study (Lebacqz, 1983). As described above, this safeguard was taken up after the completion of the three-month interviews and is discussed more fully above in the section describing how and why the study design was modified.

Eligibility Criteria

To be eligible for the study applicants had to satisfy the following inclusion criteria:

- opioid dependence;

- registered KRC client for at least three months; and,
- 16 years of age or over.

However, applicants who satisfied the inclusion criteria were ineligible if any of the following exclusion criteria were met:

- enrolled in MMT in the past month;
- required to enter MMT as condition of bail or parole;
- serious criminal charges pending;
- serious mental disorder present (e.g. schizophrenia, major affective disorder);
- suffering from chronic pain;
- permanent resident outside KRC catchment area; and,
- seeking short-term methadone withdrawal program (i.e. less than six months maintenance).

Opioid dependence was clinically assessed by a medical practitioner who based this assessment on applicants' self-reported history of drug use, attempts to discontinue drug use and psychosocial dysfunction, as well as physical signs of injecting drug use (e.g. recent injection marks), medical history and physical signs of intoxication or withdrawal. To keep the study population limited to the intended target group, all study participants had to be registered KRC clients and to reside in the KRC catchment area (i.e. within the Eastern and Central Sydney Area Health Services districts). This criterion was important because of the difficulty in accessing free, public methadone treatment at the time of the study, and because of the expectation of the local health authorities that the KRC would service clients from its specified catchment area.

A number of exclusion criteria were established to prevent, as much as possible, disruption to the conduct of the trial (Armitage, 1983). In order to ensure availability for the full study period of six months, people who were facing serious criminal charges which might result in imprisonment, or those on weekend detention, were not eligible to join the study. Similarly, applicants who were seeking long-term methadone-assisted detoxification were also excluded. Individuals addicted to opioids because of chronic pain conditions were also excluded, because they were thought to differ from the typical injecting drug user. Finally, in order to ensure that the interview schedule could be completed by all subjects, and again that they be available for the full six months, individuals with a recent history of or current serious mental disorder (schizophrenia, major affective disorder or organic brain syndrome) were not eligible to join the study.

Subjects

Sample Size

The sample size employed in the study was determined by four factors:

- the sample sizes employed in previous randomised controlled trials of methadone

maintenance treatment in which a no-treatment control group had been used for comparisons;

- the relevant New South Wales regulations which specify how many individuals can be dosed with methadone in a given environment;
- the number of individuals that KRC staff felt could be maintained on methadone without disrupting the other functions of the clinic; and,
- funding constraints which limited the number of subjects who could be paid on three occasions for their time and travel to participate in the study interviews (see below for details of payment of subjects).

As a result of the above considerations, power calculations were originally carried out to determine the likelihood of detecting an effect should one exist on comparisons between two groups each consisting of 25 individuals. Using the Design-Power software (Bavry, 1987) package, and using independent groups t-tests as the basis for between-group comparisons, it was found that with 25 patients per group, and the alpha level set at 0.05, a difference between the two groups of 0.80 of a standard deviation would be detected with a power of 0.79. These calculations indicated that even with a relatively small sample size, the large effect sizes seen in previous randomised studies of methadone maintenance (Dole et al., 1969; Gunne & Grönbladh, 1981) would be detected with a high level of power in this study.

Subject Recruitment

Clients making use of KRC services were alerted to the existence of the study by way of notices placed in the KRC waiting room, outreach buses and local welfare centres. KRC staff also mentioned the study to appropriate candidates during consultations and outreach work. Potential subjects for the study volunteered themselves to participate by coming to the KRC and making an appointment to be assessed for suitability. Recruitment took place between September and November 1993.

Excluded Subjects

Five individuals completed valid baseline interviews but were excluded from the study for failing to meet one of the eligibility criteria. Two of these individuals were found to be registered methadone patients at a nearby clinic and therefore were ineligible for treatment. One person was assessed but disappeared and failed to return for randomisation, and another was discovered to be amphetamine dependent and to have never used opioids. Finally, one individual was discovered to be on weekend detention from before the commencement of the study, and therefore was not available for methadone dosing on a daily basis for the full study period. In none of the cases described in this paragraph was assignment to treatment condition, or capacity to respond to treatment, a consideration in the decision to exclude, or not exclude, any individual from the study (Armitage, 1983).

Study Sample

Seventy-five individuals were accepted into the study and completed valid baseline interviews. As noted in the previous section, five of these individuals were excluded from the study for various reasons. This left 70 study subjects, with 35 each being assigned to the

treatment and control groups. As a group these subjects had an average age of 25 years, 30% were female, 66% were male and 4% were transgender. The sample should not be regarded as representative of injecting opioid users in the Kings Cross area or even of those who attend the KRC. This sample was a group of injecting opioid users attending the KRC who wanted to enter methadone treatment and were willing to participate in a study to do so.

Study Procedures

Intake Procedure

The assessment process for the study consisted of three stages, which are set out below.

a) KRC clients interested in joining the methadone study were initially assessed by a nurse practitioner, or a counsellor, to determine their suitability. This included the taking of a clinical history and establishing that the person was an opioid user.

b) If deemed suitable for the study, the client then proceeded to an appointment with a medical practitioner authorised to prescribe methadone, who established that they were opioid dependent and eligible to be prescribed methadone.

c) The third step was the study interview, at which time the author interviewed the subject, took a urine sample, paid the subject (A$20) and completed the randomisation process.

Clients randomised to the treatment condition were then registered in accordance with the New South Wales Health Department guidelines, and once approval was received (usually the same day), the first dose of methadone was given. It was usual for the whole assessment process to be completed on the same day.

Follow-up Interviews

At the time of the baseline research interview, subjects provided contact information for themselves and for one significant other, usually a relative with a stable address and telephone number. Subjects were told that they would be contacted by the author after three and six months for a second and third research interview. Payment was to be A$30 at the three-month interview and A$40 at the six-month interview.

Two weeks before the date for their follow-up interviews, an attempt was made to contact each subject. In the case of the treatment subjects who remained in treatment, this was simply a matter of leaving a note for them in their clinical file. With the control subjects, this proved a much more difficult task and involved sending out letters and making telephone calls to subjects and the contact person they had listed. When this failed, outreach workers looked out for subjects on the street and asked around discreetly to determine their whereabouts.

Three-month follow-up interviews took place between December 1993 and February 1994.

Subjects were interviewed as close as possible to three months after the date of their baseline research interview. A cut-off date for three-month interviews was set at the end of February. The mean follow-up time for the group as a whole was 13.9 weeks (range 11 to 23). As at the end of February 1994, 54 (77%) of the original 70 study subjects had been traced and interviewed. This varied across the study conditions, with 89% (n=31) of the treatment group and 66% (23) of the control group completing valid follow-up interviews (χ^2= 7.48, df = 1, *p*= 0.006). Two members of the control group interviewed at three months had spent virtually the whole of the follow-up period in prison and were interviewed within days of their release. These two subjects were excluded *a priori* from the analysis, because it was thought that their behaviour in the month prior to interview in prison would not be typical of their behaviour in the community. This left 52 valid subjects for statistical analyses, 31 in the treatment condition and 21 in the control group.

Attempts to determine the fate of individuals who did not return for their second interview revealed that of the four drop-outs from the methadone treatment group, one individual had not returned since the baseline interview, one was in prison (New South Wales Department of Corrective Services, personal communication, 30 March 1994) and the fate of two remained unknown. For the 12 subjects in the control group lost to follow-up, one had died, three were in prison (New South Wales Department of Corrective Services, personal communication, 30 March 1994) and the fate of the remaining eight remained unknown.

Outcome Measures

There were four major outcomes for evaluating the success or otherwise of the KRC pilot methadone program:

- heroin use;
- crime;
- HIV risk behaviour; and
- number of drug-related health problems.

All four of these outcomes were measured by self-report using the Opiate Treatment Index (OTI), which is described in the next section. Heroin use was also assessed by the taking of a urine sample at the time of interview which was tested for the presence of morphine and its metabolites. Morphine is detectable in urine for one to two days after the use of heroin (Lewis & Chesher, 1990). There was "fair" agreement between self-report and the results of the urine tests for detecting heroin use as defined by Feinstein (1985). At both baseline (97% versus 87%; n = 63) and follow-up (72% versus 59%; n=52; kappa = .307) self-report revealed more heroin use than urine test when the self-reports and urine test results of individuals who reported using heroin in the past two days were compared with those who reported using more than two days ago or not at all in the past month. This suggests that self-report may be a more valid measure of recent heroin use than urinalysis. It is certainly less conservative.

As well as the four outcomes listed above, there were a number of ancillary outcomes also of interest. As well as changes in behaviour as a result of treatment, as noted in the introduction, staff at the KRC held a number of beliefs about their clientele which they believed justified the existence and nature of the pilot methadone program. They believed that their clients would be younger and more "at-risk" than clients attending traditional public methadone clinics. They also believed that they would provide access to methadone for clients who would not attend a traditional methadone clinic and that this would be reflected in better retention rates than might otherwise be expected with their client group.

Interview Schedule

The interview schedule was based on the one developed for a study evaluating public methadone clinics in the Sydney area, which is described in detail in Ward (1995). Where possible the same questions were employed to enable comparability between the two study samples.

Baseline Interview Schedule

Demographics and Recent Treatment History

This section collected demographic information, details of drug use, criminal background and drug treatment history, as well as exposure to and satisfaction with treatment received at the KRC in the recent past.

Opiate Treatment Index (OTI)

As well as measures on the major outcomes of heroin use, HIV risk behaviour, crime and drug-related health status, the OTI provides quantitative measures of non-opioid drug use, social functioning and psychological health. All these outcome domains are assessed for the month prior to interview, except for the OTI Social Scale which refers to the six-month period prior to interview. On all scales, higher scores indicate higher levels of dysfunction. Measures other than the four major outcomes were collected for use in assessing bias in treatment assignment and for possible use as covariates in the data analysis.

Three-month Follow-up Interview Schedule

The interview at three-months repeated the measures taken at baseline for comparative purposes. Questions about aspects of methadone treatment known to play a role in response to treatment (methadone dose and duration of treatment) were also collected for use as potential covariates in the data analysis.

Data Analysis

The information collected was entered onto a personal computer and analysed using SPSS for Windows (Version 6.0). At intake, seven individuals did not provide a urine sample, resulting in missing observations for urinalysis results for these subjects.

A series of analyses were conducted to test major and minor hypotheses, to examine the influence of major sources of bias, and to explore relationships between possible predictors and major outcomes. These analyses and the results obtained are described below.

a) *Intention-to-treat analysis*. An intention-to-treat analysis was performed to examine whether there were differences in the four major outcomes (health status, HIV risk behaviour, heroin use and crime) between the two study groups at follow-up. A further analysis examined changes over time within the two groups on these outcomes.

b) *Adjusting for bias.* Two sources of possible bias were identified as perhaps influencing the results of the analysis described in a) immediately above, namely, selective attrition bias and contamination bias. An examination of possible differences in the reduced study groups at follow-up revealed that three variables of 22 measured at baseline (cocaine use, OTI Health Scale score and previous exposure to psychiatric treatment) were found to differ between the two groups.[1] As well as differences on these three measures, a significant proportion of the control group were exposed to methadone treatment and/or were still in treatment at the time of interview, a form of bias that Sackett (1979) refers to as contamination bias (the control group is contaminated by the experimental manoeuvre). The analysis described in a) was repeated using multivariate regression procedures that allowed for the use of the variables identified as possible sources of bias as covariates.

c) *Self-selected methadone analysis.* To examine the more general question concerning the effectiveness of methadone treatment in this population, and to complement the assessment of contamination bias outlined above, the study participants were regrouped into those who were receiving methadone treatment (KRC or non-KRC) at the time of the follow-up interview and those who were not. The between- and within-group comparisons described in a) above were repeated on the re-formed study groups. Systematic differences between the two re-formed study groups were examined on all possible predictor variables (22 in all), and the two groups were found to differ on one variable, namely age first charged with a criminal offence, a finding that given the number of comparisons performed may have been due to chance. Although the latter might have been the case, the analysis was repeated using regression procedures that adjusted for the difference in age first charged.

d) *KRC versus public methadone clinics analysis.* The relative effectiveness of the KRC methadone program was examined by comparing, on the four major outcomes, those in treatment at three months at the KRC with those in treatment for a similar length of time at three public methadone clinics as reported in Ward (1995).

e) *Methadone dose-response analysis.* To further elucidate the role of methadone itself in improved outcome, the relationship between daily dose of methadone and heroin use was examined.

f) *Analysis of "at-risk" status of KRC clients.* Beliefs about the youthfulness and "at-risk" status of KRC clients participating in the pilot methadone program were examined by a series of comparisons with the public methadone clinic study participants.

g) *Retention rates of KRC clients at KRC and non-KRC methadone clinics.* The

[1]It is recognised that one of these differences may be due to chance.

belief that the KRC would be able to retain clients at a higher rate than traditional methadone clinics was explored by comparing the retention rate, and the average treatment duration, of clients in the methadone group with that of clients assigned to the control group who accessed methadone elsewhere.

h) *Analysis of bias due to non-independence of observations among couples.* The randomising of couples as pairs to study groups was likely to have resulted in a series of correlated observations that would have violated the assumption of the non-independence of observations of all of the statistical procedures employed. This was confirmed by work done by Mr A. Saei, a doctoral candidate in mathematical statistics at the National Centre for Epidemiology and Population Health, Australian National University who worked on this data set as part of his research. He identified a "household effect" which indicated that the observations of the couples were highly correlated and may result in some bias being present in the results of the statistical analyses (A. Saei, personal communication, 24 February, 1995). In order to determine if this was the case, all of the between- and within-group comparisons were repeated after one member of each couple had been randomly selected and then removed from the analysis.

Multiple Testing

For the reasons set out below, no adjustment has been made to the *p* value as a result of the conduct of multiple statistical tests during the analysis of the data reported on in this report. Firstly, for the intention-to-treat analysis treated separately, the reasons for this are two-fold: there was a reduction in the sample size due to losses to follow-up resulting in a reduction of the effective sample size for the purposes of estimating statistical power from 25 to 21 subjects, and there was a likely dilution of the effect of treatment due to exposure to the treatment in the control group (i.e. there was a likely reduction in effect size due to contamination bias). The reduction in both the number of subjects and the effective size that was likely to be observed reduces the statistical power available to detect differences should they exist (Freeman, 1993; Royall, 1986). Even assuming the large effect size (0.8) seen in previous studies, a re-estimation of the statistical power if a simple Bonferroni adjustment was applied (the *p* value divided by 4 for 4 comparisons) indicated that with 21 subjects per group, and the alpha level set at .0125 (= .05/4), the power would be reduced to .50 which is much less than the level usually deemed to be acceptable (Cohen, 1992). Secondly, the presence of selective attrition and contamination bias necessitated the adoption of a strategy that involved a series of analyses, and therefore many statistical tests. Any stringent application of adjustments to the alpha criterion value as a result of multiple testing would render the detection of any effect, large or small, in these analyses almost impossible due to the small sample size.

The usual cautions for drawing inferences from exploratory analyses were employed to reduce the probability that undue confidence would be placed in any of the findings that arose from the data analysis. The requirements that findings be replicated elsewhere, be plausible and make theoretical sense were adopted as safeguards against incautious inference. That is, confidence is greater for findings that have been replicated in other studies and other settings, and novel findings are scrutinised for the extent to which they make sense in terms of what is known about methadone maintenance and opioid dependence. The further

safeguards of reporting on all tests performed, and on whether they were decided upon before or during the data analysis, makes clear the number of total tests performed and whether they were derived from prior testing, so that an estimate of the validity of the findings can be made (Hochberg & Tamhane, 1987; Rothman, 1986).

Comparisons Between Groups

Comparisons between groups on the OTI scores for self-reported heroin use, HIV risk behaviour, crime and health were conducted using the Mann-Whitney test, which is appropriate for comparisons between independent samples on variables measured at an ordinal level or above. Exploratory comparisons (e.g. to examine possible sources of bias) were conducted using the Mann-Whitney test or Student's *t*-test for independent samples where distributions approximated normality. Comparisons between the two groups on the results of urine tests for the presence of morphine, and the proportion in each group reporting needle sharing, were conducted using the Pearson chi-square test and the odds ratio, or relative risk where appropriate, is reported to indicate the size of the effect. The alpha level was set for all tests at $p = .05$. Because of the small sample size, in cases where the expected direction of the outcome favoured treatment over controls, one-tailed tests were used. Where the direction of the outcome was unknown, as in exploratory analyses, a two-tailed alpha criterion was employed.

Pre-Post Comparisons Within Groups

To further elucidate the relationship between group membership and the major outcomes of heroin use, HIV risk behaviour, crime and health, comparisons between measures taken at baseline and at three months were conducted within groups. For variables measured on a continuous scale (self-reported heroin use, crime, HIV risk behaviour, physical health) the Wilcoxon matched-pairs signed-ranks test was used. For the urine test results, McNemar's χ^2 test, or its binomial equivalent for small samples, was used which is appropriate for comparisons between related samples for binary measures.

Results

Sample Characteristics

Demographic characteristics and baseline functioning for the two study groups and the sample as a whole at baseline are summarised in Table 1.

Table 1 *Demographic characteristics and baseline functioning*

Variable	**Treatment** (n=35)	**Control** (n=35)	**Total** (n=70)
Continuous	*Mean*	*Mean*	*Mean*
Age (years)	27	24	25
Education (years)	9	9	9
Age first drug use (years)	15	14	14
Age first injected (years)	17	16	17
Age first addicted to heroin (years)	18	18	18
Categorical	**%**	**%**	**%**
Sex work in past month	34	43	39
Shared needle in past month	34	51	43
Gender			
Female	31	29	30
Male	69	63	66
Transgender	0	9	4
Urinalysis (n=63)[a]			
Morphine	84	90	87
Cocaine	42	19	30[b]
Benzodiazepines	29	37	33

[a] Reduced sample size due to 7 missing observations. [b] χ^2 =4.02, *p*, two tailed = .045

As can be seen from this table, 43% of the sample reported having shared a needle in the month prior to interview, 61% reported involvement in crime, and approximately one-third in each case returned a urine sample positive for benzodiazepines and/or cocaine. The level of reported sharing is similar to that reported recently by Baker and colleagues (Baker, Kochan, Dixon, Wodak & Heather, 1994) for a sample of Sydney injecting drug users not currently in treatment, but much higher than those reported by Darke and colleagues (Darke, Hall & Carless, 1990 = 20%; Darke, Baker, Dixon, Wodak & Heather, 1992 = 21%; Darke, Swift, Hall & Ross, 1994 = 15%).

The randomisation was successful in creating two equivalent groups, except for cocaine use where the treatment group (42%) included twice as many cocaine users as the control group (19%). The disproportionate number of cocaine users in the treatment group suggested cocaine as a possible covariate in outcomes where it may be influential. There were no statistically significant differences between the two groups on baseline measures of the major outcome variables (heroin use, crime, HIV risk behaviour and drug-related health problems).

Between Groups: Treatment vs Control Comparisons

The results of Mann-Whitney tests of the four major hypotheses for continuous variables are tabled below. As Table 2 indicates, statistically significant differences between the two study groups were found for the OTI Crime and OTI Health scores, with the differences favouring the treatment group. There were no statistically significant differences in the heroin and HIV risk behaviour measures.

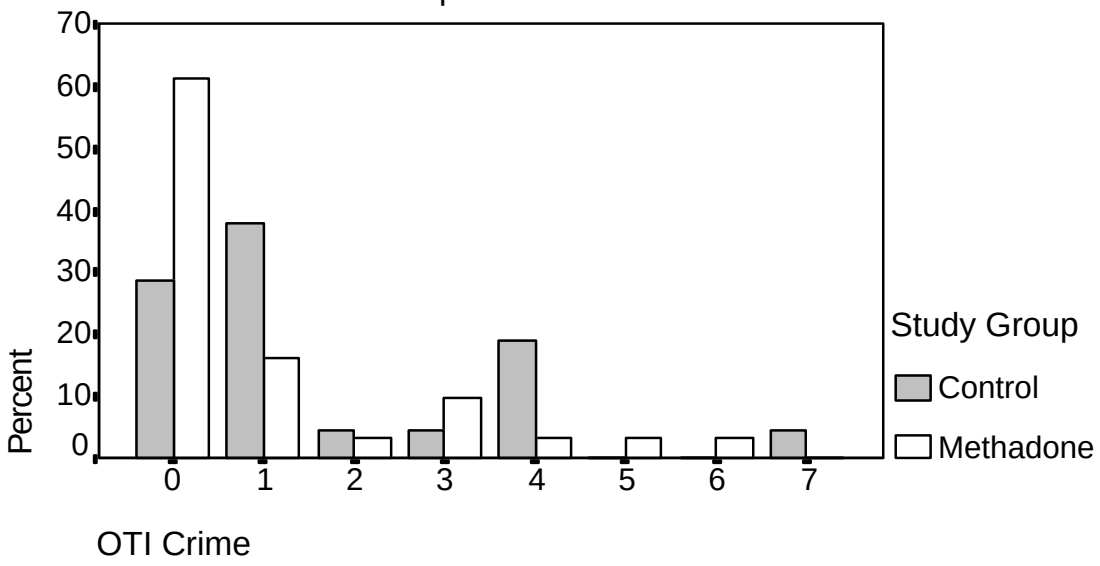
Table 2 *Results of Mann-Whitney tests for treatment-versus-controls comparisons on continuous variables*

Outcome	**Treatment** (n=31) (median)	**Control** (n=21) (median)	***z*** **statistic**	***p***[a]
OTI Heroin	0.1	0.8	-0.84	.199
OTI Crime	0	1	-1.99	.023
OTI Health	10	17	-2.77	.002
OTI HRBS	8	9	-0.55	.290

[a]One-tailed

The median scores for the two groups on crime signify no crime in the treatment group (median = 0) and less than weekly crime among the controls (median = 1), suggesting a small, but meaningful, advantage due to treatment. The nature of the relationship between study group and crime is depicted in detail in Figure 1 below, where it can be seen that 61% of the methadone treatment group reported no crime in the month prior to their follow-up interview compared with 29% of the control group.

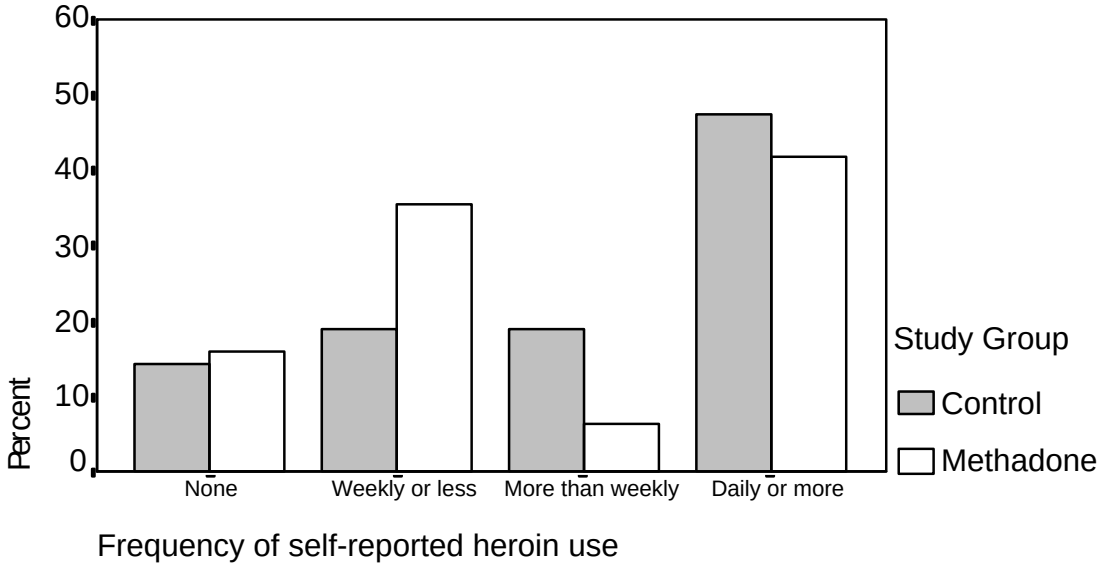
Figure 1 OTI Crime scores by study group at three-month follow-up



The difference between the medians of the two groups on the OTI Health scores of seven points was reflected in the mean difference between the two groups (6.99, 95% CI 2.67-11.31). This can be interpreted as suggesting that, on average, individuals in the control group reported seven more drug-related health problems than members of the treatment group.

The median scores for the two groups on the OTI heroin scale suggest a typical score of less than weekly use for the treatment group and almost daily use for the control group. Because of the small sample size, it is necessary to investigate the nature of the differences between the two groups further in order to establish whether the lack of any apparent difference between the two groups is due to a lack of statistical power. Figure 2 depicts the relationship between study group and self-reported heroin use. This figure shows that while there is little difference in the proportions of subjects reporting abstinence and daily use across the two groups, there are differences in those reporting weekly or less and more than weekly levels of use.

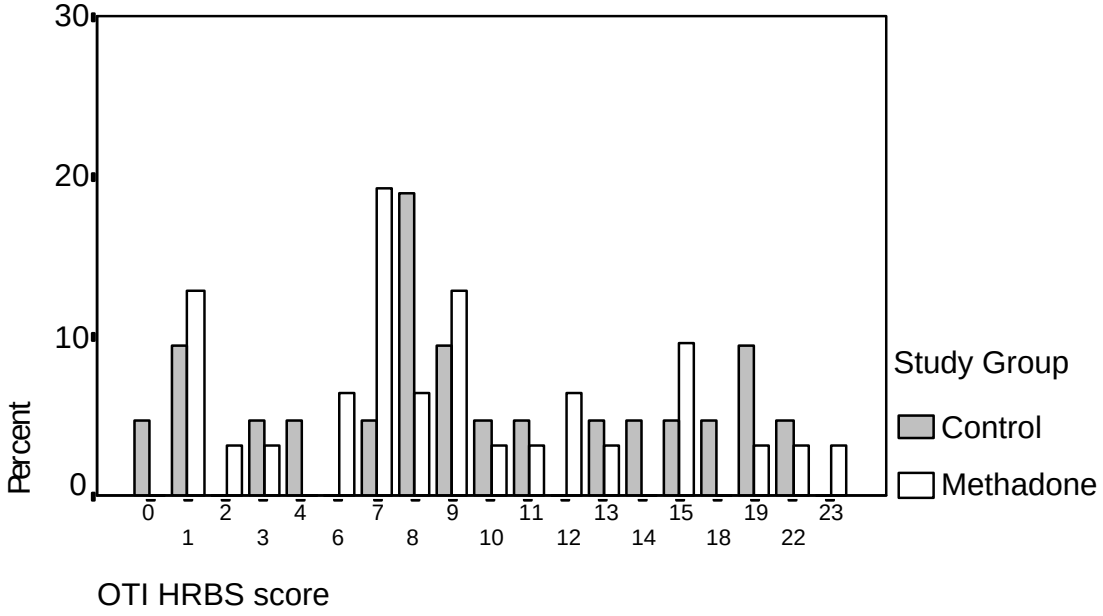
Figure 2 Frequency of self-reported heroin use at three-months by study group



A comparison of those reporting weekly use or less (including abstinence) with those using more frequently again failed to achieve statistical significance (control = 67%, treatment = 52%; $\chi^2 = 1.16$, df = 1, *p*, one-tailed = .140; RR = 0.69, 95% CI 0.34-1.40). A post-hoc power analysis indicated that, in the case of this test, there was sufficient statistical power (1-β = .81) to detect an effect should one exist in the data.

Figure 3 illustrates the relationship between HIV risk behaviour, as measured by the OTI HRBS at the follow-up interview, and study group. The lack of a relationship between study group and the OTI HRBS scores, as indicated by the result of the statistical analysis reported above, is confirmed by the similar distributions for treatment and control subjects evident in the figure.

Figure 3 OTI HRBS scores at three months by study group



When the outcomes on the binary variables were investigated, it was found that 52% per cent of the treatment group and 67% of the control group had morphine or its metabolites in their urine at their three-month interview, a difference which was not significant (χ^2= 1.16, df = 1, *p*, one-tailed = .281; RR = 0.69, 95% CI 0.34-1.40), thus supporting by an independent measure the null finding for heroin use. For needle sharing, 19% of the control group and 7% of the treatment group reported sharing at some time in the month prior to interview, a difference that was also not statistically significant (Fisher's exact test, *p*, one-tailed = .170; RR = 0.87, 95% CI 0.69-1.09).

Selective Attrition and Contamination Bias

Selective Attrition Bias

Although the randomisation was reasonably successful in creating two equivalent groups of subjects for the study, as noted above, there was a difference in the proportion of individuals followed-up in the two study groups, with 89% (n=31) of the treatment group and 66% (23) of the control group being interviewed at three months (χ^2= 7.48, df = 1, *p*, two-tailed = 0.006). This difference was further exacerbated after 2 additional subjects were excluded from the control group, because they had been in prison throughout the follow-up period. The presence of this differential loss to follow-up in a randomised experiment poses the threat of introducing bias into any conclusions that are drawn from comparisons between the two groups (Armitage, 1983; Cook & Campbell, 1979; Meinart & Tonascia, 1986)).

The procedure recommended by Cook and Campbell (1979) to deal with selective attrition, and the one followed here, involves a series of steps to determine to what extent bias may be present as a result of differential attrition. These analyses include:

a) a check to determine if the attrition rate is disproportionate across the treatment and control groups (see above);

b) a comparison between the two study groups for those remaining in the study at follow-up on baseline measures of demographic and important background variables; and,

c) a further comparison between the two study groups on baseline measures of the outcome variables, which Cook and Campbell (1979) suggest "provide the best single estimates of bias" (p. 361), because they presumably have the same underlying structure as the follow-up measures.

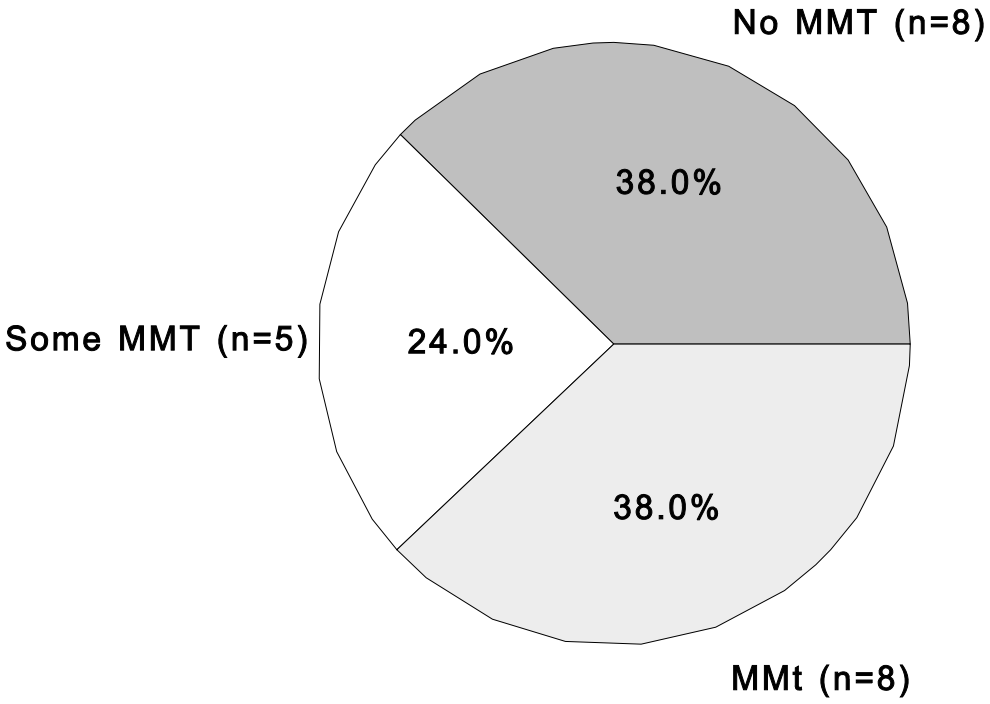
A series of comparisons were conducted following this procedure, and it was found that at three months the two groups differed on baseline measures of cocaine use, exposure to previous psychiatric treatment and OTI Health Scale scores. The treatment group had more cocaine users as measured by both self-report (65% versus 29%; χ^2= 6.47, df = 1, *p*, two-tailed = .011) and urinalysis (39% versus 11%; χ^2= 4.68, df = 1, *p*, two-tailed = .031)[2] than the control group, less individuals reporting previous psychiatric treatment (3% versus 28%; Fisher's exact test, *p*, two-tailed = .031), and lower average OTI Health Scores (mean = 16.4 versus mean = 20.9; *t* = 2.10, df = 50, *p*, two-tailed = .041). In the case of cocaine use, self-report recoded as a binary variable (reported use in month prior to study commencement = 1, no use = 0) was used rather than urinalysis, because it revealed more cocaine use and had no missing values.

Contamination Bias

A major confounding influence on the estimates of the effectiveness of the KRC pilot methadone program was the extent to which members of the control group were exposed to methadone treatment during the three-month study period. Figure 4 illustrates the extent of this exposure.

[2]Five missing observations, n = 47.

Figure 4 Exposure to methadone treatment during the follow-up period for controls (n=21)



As can be seen from the above figure, 76% of the control group were exposed at some time during the follow-up period to methadone treatment, and 38% of these were still in treatment at the time of interview.

To control for contamination bias, the number of weeks spent in methadone treatment in the follow-up period was entered into regression models along with the three variables identified through the examination of the consequences of selective attrition. It should be noted that this variable (weeks spent in methadone treatment) may have suffered differential measurement error to some extent, because information was derived from clinic records for the methadone treatment group and self-report for the control group.

Treatment versus Control: Adjusting for Bias

To adjust for selective attrition and contamination bias, the following full regression model was fitted to each of the outcome variables, using linear regression for continuous outcomes and logistic regression for binary outcomes:

> Outcome = Constant + Study group + OTI Health + Cocaine + Previous psychiatric treatment + Weeks spent in methadone treatment + (Study group * OTI Health) + (Study group * Cocaine) + (Study group * Any psychiatric treatment).

This model controls for each of the variables identified as possible sources of bias and for likely interactions between study group and self-reported cocaine use, health and past psychiatric treatment. Each of the models was reduced and checked for adequacy of fit to the data and violation of assumptions, using the hierarchical backward elimination procedures recommended by Kleinbaum (1994). All four outcome variables were analysed in this fashion, because bias may suppress an effect of treatment as well as produce one.

Heroin use

The OTI heroin use scores were heavily skewed to the right with a substantial number of zeros. An initial model developed on the raw scores was rejected, because the residuals were not normally distributed. The heroin scores were transformed by taking the natural logarithm of each of the scores after adding 1 to each observation (thereby eliminating zero scores). This resulted in a more satisfactory multiple regression model (less outliers, normally distributed residuals and better fit to the data as indicated by higher R^2). This model is set out below in Table 3

According to this model, there is a statistically significant relationship between study group and heroin use in the presence of an interaction between cocaine use at baseline and study group. The other notable feature of the regression model in Table 3 is that there is also a statistically significant relationship between weeks spent in methadone treatment during the follow-up period and the OTI heroin score, with increasing time in methadone treatment being associated with less heroin use. There was no interaction between group and time spent in methadone treatment during the follow-up period.

Table 3 *Multiple linear regression model predicting heroin use[a] at three-month follow-up from study group while adjusting for bias (N=52)*

Variable	***b***	***SE***	***t***	***p***[b]

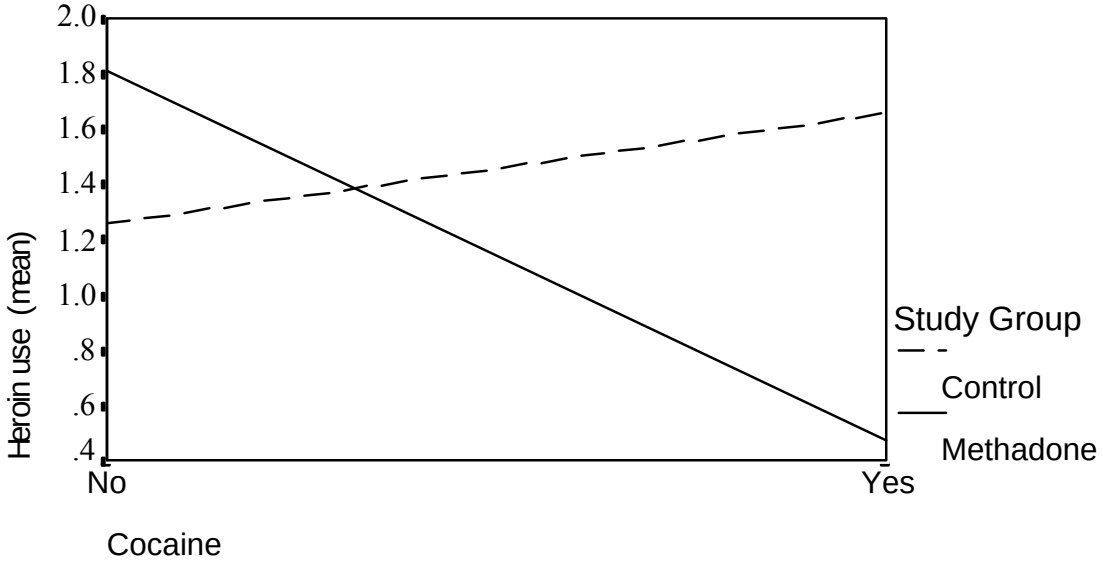
Study group (1=KRC MMT)	.382	.208	1.84	.073
Cocaine[c](yes=1)	.359	.275	1.31	.198
OTI Health score[c]	.002	.009	0.17	.863
Past psychiatric treatment (yes=1)	-.243	.251	-0.97	.338
Time in methadone treatment (weeks)	-.054	.015	-3.53	.001
Study group * Cocaine[c]	-.821	.330	-2.49	.017
$F = 4.35$, $p = .002$				
$R^2 = 0.37$				

Note. b=unstandardised regression coefficient.

[a]Ln(OTI Heroin + 1). [b]Two-tailed. [c]Measured at baseline.

Figure 5 depicts the relationship between study group, cocaine use at baseline and heroin use.

Figure 5 Heroin use: interaction between cocaine use at intake and study group



This figure suggests a crossed interaction in which individuals who reported using cocaine at baseline reported using less heroin at follow up in the methadone treatment group than those

in the control group, while those that did not report cocaine use reported more heroin use in the methadone treatment group than the control group. There is, therefore, a treatment effect for those who reported cocaine use at entry to the study, but not for those who did not.

Crime

The distribution of the OTI Crime Scale scores did not allow for the use of either the untransformed or transformed scores in a linear regression analysis, due to the large proportion of individuals (48%) who scored zero. An examination of crime as a binary variable, to see if the difference between the two groups was maintained after dichotomising the scores, revealed that 71% of controls compared with 39% of those in the treatment group reported some crime in the month prior to interview and that this difference retained statistical significance (χ^2= 5.37, df = 1, *p*, one tailed = .010). The final logistic regression model predicting any crime in the month prior to interview is set out below in Table 4.

Table 4 *Multiple logistic regression model for predicting crime by study group while adjusting for selective attrition and contamination bias (n=52)*

Variable	Odds ratio	95% confidence interval
Study group (methadone=1)	0.99	0.18-5.39
Cocaine[a] (yes=1)	0.62	0.14-2.87
OTI Health score[a]	1.07	0.98-1.17
Past psychiatric treatment (yes=1)	6.40	0.49-84.39
Time in methadone treatment (weeks)	0.79	0.67-0.93**
Model χ^2 = 20.09, p = .001 Hosmer & Lemeshow χ^2= 5.42, p = .608		

[a]Measured at baseline.

**p, two tailed < .01

As was the case with heroin use, number of weeks spent in methadone treatment in the follow-up period was a statistically significant predictor of crime. However, none of the other variables in the model were statistically significant, including study group. An examination of each of the predictor variables alone, and in combination with other variables in the model, in a series of logistic regression models indicated that adjusting for time spent in methadone treatment alone was sufficient to reduce the relationship between study group and crime to statistical insignificance. For the other predictors, no single variable alone was sufficient to alter this relationship, but any two of the variables in combination was. After adjusting for selective attrition and/or contamination bias, it is concluded that there is no effect of study group on crime. However, there is a relationship between amount of methadone treatment received, regardless of site, and reduced reporting of crime.

Health

The distribution of the OTI Health Scale scores was suitable for linear regression analysis. The multiple linear regression model adjusting for bias is set out below.

Table 5 *OTI Health Score at three months: multiple regression model for study group adjusting for possible selective attrition and contamination bias (n=52)*

Variable	*b*	*SE*	*t*	*p*[a]
Study group	-2.77	2.00	-1.39	.172
OTI Health at baseline	0.71	0.10	6.79	.000
Cocaine	-0.65	1.77	-0.37	.715
Psych. treatment	0.95	2.60	0.37	.716
Time in MMT (weeks)	-0.15	0.17	-0.90	.373
$F = 13.61$, $p = .000$ $R^2 = 0.60$				

Note. b=unstandardised regression coefficient.
[a]Two-tailed.

This model suggests that after adjusting for selective attrition and contamination bias, there is no longer a statistically significant effect of study group on health. However, the one-tailed *p* value for study group (.086) is close to the criterion level and, given the small sample size, the result must be interpreted with caution.

An analysis to determine which variables in the model altered the statistical significance of the relationship between study group and health, indicated that exposure to methadone was the key variable involved. When duration of methadone treatment is excluded from the model, the partial regression coefficient for study group retains a statistically significant relationship in the prediction of OTI Health Scale scores ($t = -1.71$, *p*, one-tailed = .047). This suggests that the effect of study group on health status remains after adjusting for selective attrition bias, but not after additionally adjusting for contamination bias.

HIV Risk Behaviour

It was not possible to arrive at a satisfactory multiple linear regression model that included study group as a term (i.e. the F-test for all models was non-significant). Thus, it is concluded that, after adjusting for bias, there is no relationship between study group and the OTI HRBS scores.

In summary, after adjusting for selective attrition and contamination bias using appropriate statistical procedures, there is no unequivocal relationship between study group and any of the four major study outcomes. However, this seems to be due to the confounding influence of amount of exposure to methadone treatment, suggesting that, while it is difficult to arrive at an unconfounded estimate of the effectiveness of the KRC methadone program in isolation, there is evidence supporting the general effectiveness of methadone maintenance treatment.

Within Groups: Pre-post Comparisons

Reductions in OTI scores for heroin use, HIV risk behaviour and drug-related health problems from baseline to three months were observed in both the treatment and control group. However, a reduction in the OTI crime score was only observed in the treatment group. These findings are set out below in Table 6.

Table 6 *Results of Wilcoxon matched-pairs signed-ranks tests for comparisons between baseline and 3-month follow-up assessments for treatment and controls*

OTI Scale	**Baseline** (median)	**3-months** (median)	***z*** **statistic**	***p***[a]
Control Group (*n*=21)				
Heroin	3	0.8	-2.88	.004
Crime	2	1	-1.15	.249
Health	23	17	-2.50	.012
HIV Risk	15	9	-3.04	.002
Treatment Group (*n*=31)				
Heroin	3	0.1	-4.34	.000
Crime	1	0	-2.03	.042
Health	17	10	-3.77	.000
HIV Risk	13	8	-3.95	.000

[a]Two-tailed.

Both the treatment and control groups reduced their heroin use as measured by urinalysis at three months compared with baseline. However, while the reduction in the treatment group from 90% morphine-positive to 52% was statistically significant (3 missing observations; McNemar χ^2 binomial equivalent, *p*, two-tailed = .006), the reduction from 89% to 67% in the control group was not (2 missing observations; McNemar χ^2 binomial equivalent, *p*, two-tailed = .125). For the sharing of injecting equipment a similar result was found, with the treatment group significantly reducing sharing from 52% to 7% (McNemar χ^2 binomial equivalent, *p*, two-tailed = .008), compared with a non-significant reduction from 32% to 19% for the control group (McNemar χ^2 binomial equivalent, *p*, two tailed = .092).

In summary, an analysis of changes in behaviour over the three-month study period within the two study groups revealed that statistically significant reductions in measures of heroin use, HIV risk behaviour and health status were observed in both groups, but that in the case of crime such a reduction was only observed in the treatment group. The differential

reduction observed in morphine positive urine test results was not supported by the results for self-reported heroin use and an examination of the percentages involved suggest that the finding may be due to chance. This also holds true for the differential reduction in needle sharing. However, for crime, the difference observed between the two groups in favour of treatment is supported by a differential reduction in crime observed in the two groups.

Self-selected Methadone Treatment

As a result of the extent of exposure to methadone in the control group, it is likely that an unconfounded estimate of the effectiveness of the KRC methadone program, when compared with untreated controls, is not possible on the basis of the data collected. However, the basic research question of whether methadone would improve the specified outcomes for clients attending the KRC was answerable to some extent. The accumulated evidence about the effectiveness of methadone treatment suggests that for most individuals, and certainly for those similar to the "at-risk" group attending the KRC, methadone treatment reduces heroin use and crime only for as long as it is being administered (Ward, Mattick & Hall, 1992). In the light of this evidence, it was decided to repeat the comparative analyses of treatments versus controls comparing those receiving methadone at the time of their follow-up interview with those who were not.

At follow-up, 77% of the KRC methadone treatment group were still receiving treatment, and these were combined with the 38% of the controls who were in methadone treatment elsewhere. The 23% of the treatment group, and the 62% of the controls who were not in treatment at three months, were combined to form a no-treatment comparison group. Both the between- and within-groups comparisons comparing the treatment and control groups as defined by randomisation were repeated comparing those receiving and not receiving methadone at three months. These two groups are hereafter referred to as the methadone and no-methadone groups respectively. It is recognised that this comparison is not equivalent to that made on the basis of randomisation and would have to take into account other plausible alternative explanations for any differences that were found (Cook & Campbell, 1979).

One likely alternative explanation is that there are systematic differences between those who decide to enter and stay in treatment, compared with those who do not (Cook and Campbell, 1979). These subjects may be more motivated to change their behaviour, and better off at any time, than their counterparts. That is, they would look better off three months later even without treatment. In order to investigate this possibility, the procedure outlined in the previous section for checking for bias due to selective attrition advocated by Cook and Campbell (1979) has been followed in this case as well. This had two aims, to attempt to detect if there were any indications of bias and, if there was, in which direction it might influence the results of statistical analyses.

A series of comparisons were performed which compared the methadone and no-methadone groups on key predictor variables and baseline measures of the outcome variables. The only difference found was for age first charged with a criminal offence which has been shown to be a strong predictor of outcome during treatment (Ward et al., 1992). Subjects not receiving methadone treatment at three months (n=16) were first charged at a mean age of 14.8 years, while those receiving methadone (n=29; seven individuals had never been charged hence reduced total n = 45) were first charged at a mean age of 17.9 years (Mann-Whitney test; z =

-2.50, *p*, two-tailed = .013).
Individuals who had never been charged were evenly distributed between the two groups, with four not receiving and three receiving methadone. Where possible (given distributional assumptions of appropriate tests), all between-group comparisons have been repeated controlling for age first charged. In order to do this satisfactorily and include all subjects in the analysis, a procedure recommended by Cohen and Cohen (1983) for replacing missing values and still testing for their influence was employed. Following this procedure, the scores for subjects who had never been charged were replaced with the median for the whole group, and a further binary variable was created which was scored zero for those who had been charged at some time and one for those who never been charged, thereby allowing for the inclusion of all subjects and estimating the influence of whether they had ever been charged or not.

Unadjusted comparisons between those receiving methadone at three-month follow-up and those not receiving methadone are set out below for the continuous outcomes. Compared to those not receiving methadone at three months, those who were receiving methadone showed significantly less heroin use, crime and HIV risk behaviour.

Table 7 *Results of Mann-Whitney tests comparing those receiving and not receiving methadone treatment at three-month follow-up*

OTI Scale	**No MMT** (n=20) (median)	**MMT** (n=32) (median)	***z*** **statistic**	***p***[a]
Heroin	1.50	0.10	-2.91	.001
Crime	1	0	-2.36	.009
Health	15	10	-0.79	.214
HIV Risk	11	8	-1.94	.026

[a]One-tailed.

The statistically significant difference in self-reported heroin use, as measured by the OTI, was confirmed by the finding that 75% of those not in methadone treatment returned a morphine-positive urine sample at their three-month interview compared with only 47% of those in methadone treatment, a finding that was statistically significant (χ^2= 3.99, df = 1, *p*, one-tailed = .023). The finding of less HIV risk behaviour was reflected in there being less needle sharing among those in treatment (6% compared to 20%). This difference was not statistically significant (Fisher's exact test, *p*, one-tailed = .144), but the proportions involved are very small. Comparisons between the two groups on the sexual (*z* = -1.43, *p*, one-tailed = .076) and injecting sub-scales (*z* = -1.44, *p*, one-tailed = .075) of the OTI HIV Risk-taking Behaviour Scale did not achieve statistical significance in either case, although both were close to being significant, suggesting a combined effect of the two sub-scales on the outcome.

To further explore the nature of the differences between those receiving and not receiving

methadone at their three-month follow-up interview, a further series of within-groups comparisons between baseline and three-month follow-up OTI scores were performed. The results of these comparisons are summarised below in Table 8 for the no-methadone group and the methadone group. Statistically significant reductions were observed for both groups on all outcomes, except for crime where those not receiving methadone treatment reduced their scores on the OTI Crime Scale but this difference was not statistically significant.

Table 8 *Results of Wilcoxon matched-pairs signed-ranks tests for comparisons between baseline and follow-up for those receiving and not receiving methadone*

OTI Scale	**Baseline** (n=20) (median)	**3-months** (n=20) (median)	***z*** **statistic**	***p***[a]
No MMT (n=20)				
Heroin	3	1.5	-1.79	.037
Crime	3	1	-0.97	.165
Health	18	15	-2.01	.022
HIV Risk	15	11	-2.22	.013
MMT (n=32)				
Heroin	3	0.1	-4.62	.000
Crime	1	0	-2.31	.010
Health	18	10	-4.18	.000
HIV Risk	13	8	-4.54	.000

[a]One-tailed.

Pre-post comparisons for the presence of morphine in the urine samples collected revealed that for those not receiving methadone treatment there was no difference between baseline (88% - 3 missing observations) and follow-up (75%; McNemar χ^2 binomial equivalent, *p*, one-tailed = .188). For the group receiving methadone, a reduction was observed from 90% (2 missing observations) at baseline to 47% at follow-up (McNemar's χ^2 test binomial equivalent, *p*, one-tailed = .000). For needle sharing, a statistically significant reduction was again found for the group receiving methadone (from 40% to 6%; McNemar χ^2 binomial equivalent, *p*, one-tailed = .001) but not for the no-methadone group (from 40% to 20%; McNemar χ^2 binomial equivalent, *p*, one-tailed = .172).

The results of comparisons between those in methadone treatment at three-month follow-up and those who were not found methadone treatment to be associated with less heroin use, crime and HIV risk behaviour. No advantage was observed for health status. However, statistically significant reductions in measures of heroin use, HIV risk behaviour and health status over the three month study period were found for both groups. In the case of crime, such a reduction was only observed for the methadone group.

Given the reductions observed for both groups on most variables and the possible confounding influence of age first charged, analyses were carried out to estimate the extent of influence of baseline measures and age first charged on the differences observed for each group. However, because of the nature of the distributions of each of the variables, a different solution was used for each variable.

The OTI Crime Scale scores presented little difficulty and were transformed to a binary variable indicating whether any crime was reported in the month prior to interview with little loss in information because of the large number of zero responses and few scores in the higher ranges. An unadjusted estimate for the influence of receiving or not receiving methadone was obtained by computing the unadjusted odds ratio which was found to be 0.20 (95% CI 0.06, 0.69), and this was compared to the odds ratio obtained in a logistic regression model which included whether any crime was reported at baseline, age first charged, whether the individual had been charged and whether the individual was receiving methadone at the time of interview or not. This adjusted odds ratio (OR = 0.20, 95% CI 0.05, 0.77) did not differ markedly from the unadjusted estimate, suggesting that the difference in crime between the two groups was not influenced by crime at baseline or age first charged.

Heroin use was transformed initially to a binary variable indicating whether or not the person reported any heroin use or not in the month prior to interview. However, it was found that 85% of those followed-up as whole reported some heroin use and there was no difference between the two groups in this regard (χ^2= 0.72; df = 1, *p*, two-tailed = .395). A second binary transformation was attempted that would retain the differences between the methadone and no-methadone groups which coded those who used heroin more than weekly (1) as opposed to those who used heroin on a weekly basis or less (0). The unadjusted odds ratio for the methadone versus no-methadone groups on this variable was 0.19 (95% CI 0.05, 0.71). When adjusted for baseline OTI heroin use scores in a logistic regression model the odds ratio remained 0.19 (95% CI 0.05, 0.71), and when the age-first-charged variables were added the odds ratio was 0.17 (95% CI 0.09, 0.69), although the latter model did not fit the data well. These results suggest that the association between using heroin and being in methadone treatment persisted after adjusting for baseline differences in extent of heroin use. It is unlikely that age first charged has any influence on this relationship.

The results for HIV risk behaviour were inconsistent. Although there was a statistically significant difference between the methadone and no-methadone groups on the OTI HIV Risk-taking Behaviour Scale, this difference was not reflected in differences in needle sharing or the injecting and sexual sub-scales. There was, however, a significant reduction in needle sharing in the methadone group. These findings overall suggest a trend towards methadone being associated with less needle sharing, but the finding is not robust enough to draw confident conclusions in this regard.

KRC Versus Public Methadone Clinics

In a further attempt to clarify the extent of the effectiveness of methadone maintenance at the KRC, a further set of comparisons on the four major outcomes (heroin use, crime, HIV risk behaviour, and drug-related health problems) were made with the data collected for an evaluation of public methadone clinics which is described in detail in Ward (1995). Two sets

of comparisons were performed: one that compared those in treatment at the KRC at three months with those in the three public clinics who had been in treatment for three months or less, and one that compared those in treatment at the KRC with those in treatment for three months or less at a methadone clinic located in the same area of Sydney where data was collected during the same period (August-September, 1993). If methadone maintenance at the KRC is as effective as that provided through special purpose, public clinics, then similar, or better, levels of effectiveness should be achieved on the four major study outcomes. All statistical tests have employed two-tailed *p* values, because the direction of the outcome is unknown.

Comparisons between those in methadone treatment at the KRC at follow-up and those in treatment for three months or less at both the three public methadone clinics and Clinic B examined separately revealed a statistically significant difference for heroin, with more heroin use being evident at the KRC. There were no such differences for HIV risk-taking behaviour, crime or drug-related health problems. These findings are summarised below in Table 9.

Table 9 *Results of Mann-Whitney tests comparing those in KRC methadone treatment at 3-month follow-up (n=24) with patients in treatment for three months or less at the three public methadone clinics (n=36) and Clinic B (n=19)*

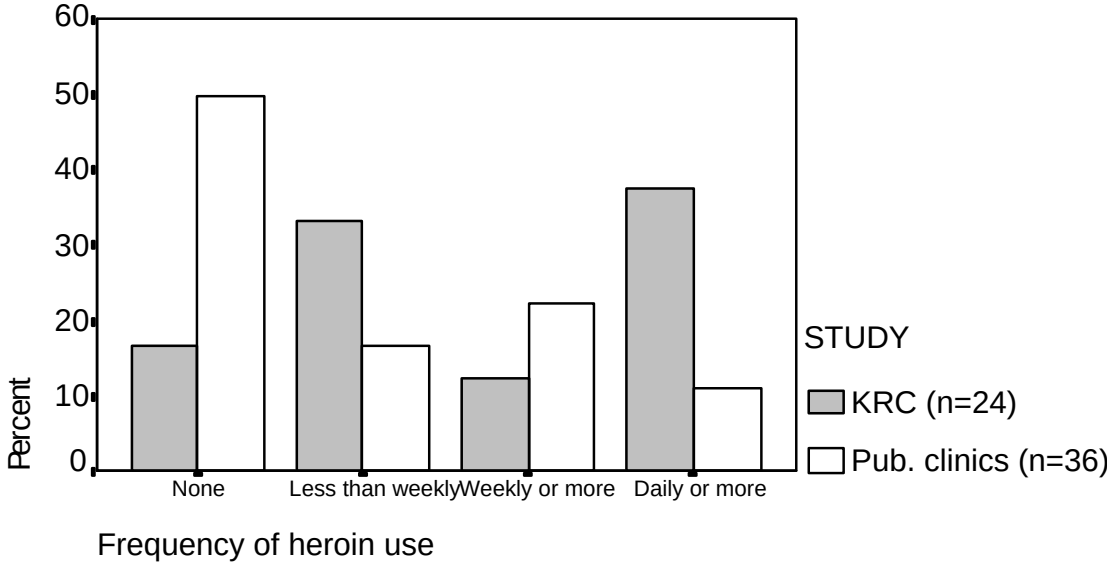
OTI Scale	**Median**	**Median**	***z* statistic**	***p*[a]**
	KRC (n=24)	*3 Clinics (n=36)*		
Heroin	0.14	0.02	-2.38	.017
Crime	0	0	-1.41	.159
Health	9	13	-1.58	.114
HIV Risk	8	6	-1.53	.126
	KRC (n=24)	*Clinic B (n=19)*		
Heroin	0.14	0.04	-2.52	.012
Crime	0	0	-1.21	.228
Health	9	13	-1.66	.097
HIV Risk	8	6	-1.82	.070

[a]Two-tailed.

The findings concerning self-reported heroin use were reflected in the proportion using any heroin at all in the month prior to interview in the three groups. Eighty-three per cent of the KRC group reported using some heroin in comparison to 50% of patients attending the three

clinics (χ^2= 6.89, df = 1, *p*, two-tailed, = .009; OR = 0.20, 95% CI 0.06-0.70) and 51% attending Clinic B (χ^2= 7.37, df = 1, *p*, two-tailed, = .007; OR = 0.21, 95% CI 0.06-0.69). Figure 6 further clarifies this relationship, and illustrates the tendency for KRC patients to use heroin more frequently than public sector methadone patients, especially at daily levels of use.

Figure 6 Frequency of self-reported heroin use among KRC and public methadone study subjects (N=60)



An examination of crime recoded as a dichotomous variable, indicating whether or not the individual concerned reported any crime in the month prior to interview, revealed slightly more crime among the KRC sample (38%) when compared with the three clinics group (22%; χ^2= 1.66, df = 1, *p*, two-tailed, = .198; OR = 0.48, 95% CI 0.15-1.49) and Clinic B (26%; χ^2= 1.17, df = 1, *p*, two-tailed, = .278; OR = 0.57, 95% CI 0.20-1.59), but these differences were not statistically significant. When the sharing of injecting equipment was examined separately, the rates across the three samples were found to be roughly equivalent (KRC = 8%, three clinics = 11%, and Clinic B = 5%), thus confirming the non-significant result of the comparisons on the OTI HRBS. Finally, while the KRC group had lower average scores on the OTI Health Scale indicating less health problems reported, this difference was not statistically significant.

Overall, the results of comparisons between those in treatment at the KRC at three months with comparable groups of patients attending three public methadone clinics suggest that the KRC patients use heroin more frequently but that this difference is not found for the other three study outcomes (crime, HIV risk behaviour and drug-related health status). However, the typical level of heroin use among the KRC patients, as indicated by the median OTI heroin use score (once a week), represents a significant reduction from the daily use observed

in the KRC study group at intake. Thus, it can be concluded that the KRC methadone program led to reductions in heroin use.

Dose-Response Analysis

To the extent that methadone is the active ingredient of treatment at the KRC, it is reasonable to expect on the basis of prior evidence that a dose-response phenomenon should be observed such that as daily methadone dose increases, heroin use decreases. The relationship between these two variables is depicted in the scatter plot below for those individuals still receiving methadone treatment at the time of their follow-up interview. The regression line has been fitted using the robust procedure known as "lowess smoothing," with the smoothing parameter set at 50% of points (Chambers, Cleveland, Kleiner & Tukey, 1983).

Figure 7 Smoothed scatterplot of heroin use by methadone dose for those receiving methadone at follow-up (N=32)

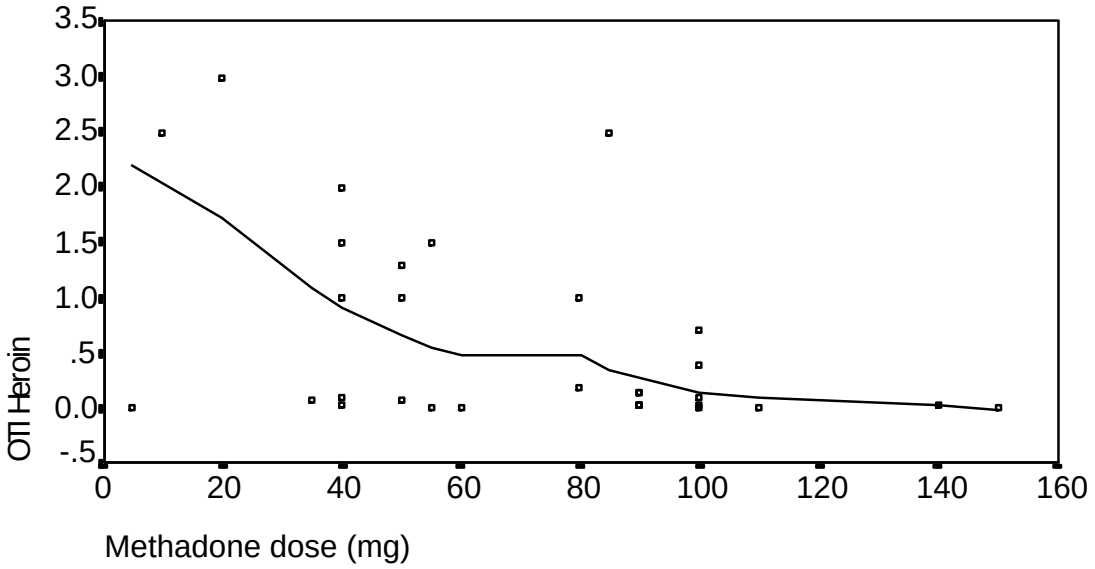


Figure 7 clearly shows a tendency for heroin use to decrease as methadone dose increases. This suggests a dose-response relationship between the amount of methadone ingested and heroin use.

Are KRC Clients Different From Their Methadone Clinic Counterparts?

The argument suggesting a need for a methadone program at the KRC was based on a number of beliefs that KRC staff held about their clientele. Essentially, KRC staff believed that their clients were younger and more "at-risk" than clients applying for treatment at traditional methadone clinics. Table 10 below summarises a series of comparisons made

between volunteers for the KRC methadone study and the volunteers from three public methadone clinics who participated in the study described in Ward (1995) and were in treatment for three months or less.

Table 10 *Comparisons between volunteers for the KRC methadone study and patients in treatment for three months or less at the public methadone clinics on age and indicators of "at-risk" status*

Variable	KRC (n=70) (mean)	Public MMT (n=36) (mean)	*t*	*p*
Age (years)	25.1	30.9	-3.87	.000
Age first heroin addiction (years)	18.0	20.1	-2.52	.013
Education (years)	9.2	10.4	-2.73	.008
Previous MMT (months)	7.0	24.0	-2.86	.007
Years since first heroin addiction at commencement of current MMT episode	7.1	10.8	-2.61	.011
Age first charged with a criminal offence (years)[a]	16.4	18.0	-1.41	.164

[a] Excluding those never charged; for KRC n=60, and for Public MMT n = 31.

As can be seen from this table, the KRC study subjects are younger and, on various measures of known prognostic indicators, can be considered to be worse off. They reported being addicted to heroin at a younger age, had an average of one year less of education and were earlier on in their addiction careers. They had also been exposed to less months of methadone treatment in the past, a fact that was born out by a smaller proportion of the KRC subjects having been in previous methadone treatment at all (47%) when compared with the clients at the three public methadone clinics (72%; χ^2= 6.06, df = 1, *p*, two-tailed = .014; OR = 2.92, 95% CI 1.22-6.94).

Retention for KRC and Non-KRC Methadone Treatment

A further belief held by KRC staff was that these younger, more "at-risk" clients would be retained in a methadone program at the KRC. In order to test this hypothesis, a comparison was made between the retention rates for the group receiving methadone at the KRC and that proportion of the control group who entered methadone treatment elsewhere. Although a further comparison with patients attending the three public clinics would also have been desirable, information on three-month retention rates for these individuals was not available. The results reported below suggest that, for the three-month study period, that there are no differences between retention rates at the KRC and elsewhere.

An examination of the retention rates for the treatment group revealed that at three months 77% were still in treatment. This was compared to the proportion of the sub-group of the controls who had accessed methadone treatment elsewhere (n = 13) and were still in treatment at three months (62%) and was found to be not statistically significant (Fisher's

exact test, $p = .236$). However, unlike the treatment group who all entered methadone treatment at the beginning of the three-month study period, the controls could have entered treatment at any time during this period. To explore whether this might be the case the average length of stay was computed for the treatment group (8.9 weeks) and the sub-group of controls exposed to non-KRC methadone treatment (8.2 weeks) and no difference was found between the two groups ($t = -0.23$, $p = .817$).

In interpreting the results in this section regarding retention, it has to be acknowledged that the comparison group is self-selected and the sample size small. Therefore, the result should be interpreted with some caution.

Examining the Influence of Couples

One possible confounding influence on the comparisons between the treatment and control groups was the randomising of couples as a unit or cluster to each group (Donner, Brown & Brasher, 1990). While this avoided the unwanted situation of having one individual in each group who were living together, it posed another type of problem for the statistical analysis. The problem is that for each couple the observations made on the two individuals are not independent of each other. This correlation between the behaviour of couples poses a possible problem for the statistical analyses reported above, because the variation within the couple will be less than that between any other two non-couple individuals and this might unduly influence comparisons between groups.

Eight couples joined the study, of which five were assigned to the treatment group and three to the control group. At three-month follow-up, seven couples were re-interviewed and of these six remained intact (one member of the other couple had been imprisoned), leaving four couples in the treatment group and two in the control group. The uneven distribution of couples across the two groups indicated that the possibility of bias should be investigated. In order to check for any such bias that might have arisen as a result of the assignment of couples in pairs to study conditions, all of the comparisons reported above were repeated after one randomly selected member of each couple had been deleted, which is a procedure commonly employed in such a situation (Glynn & Rosner, 1992). The results of these analyses did not differ from those reported above, suggesting that the results were not unduly influenced by the assignment of couples as pairs to treatment condition.

Discussion

The unique features of the study described in this report were the site at which the methadone was dispensed, the composition of the treatment population and a liberalisation of the usual methadone program rules. The site was a primary health care centre which integrated the dispensing of methadone into its routine activities, and the population was more "at-risk" than that usually attending a traditional methadone maintenance clinic. Due to selective attrition and the exposure of control subjects to the treatment under investigation, the results of this study address more clearly questions concerning the effectiveness of methadone maintenance with this more "at-risk" client than those concerning the treatment setting.

Interpretation of Study Outcomes

An intention-to-treat analysis, which compared subjects as assigned to study groups, found statistically significant effects of treatment in terms of improved health and reduced criminal activity. No such effects were found for heroin use or HIV risk behaviour, although the differences observed were in the expected direction. However, when adjustments were made to control for bias introduced into the study by selective attrition and exposure to methadone treatment among controls, the statistically significant effects on health and crime were not sustained. The number of weeks spent in methadone treatment was a strong source of bias in the intention-to-treat analysis, and the entry of this variable into the statistical models for predicting health and crime rendered the relationship between study group and these outcomes statistically insignificant. By itself, the number of weeks spent in methadone treatment was a significant predictor of heroin use and crime.

The importance of methadone itself was further confirmed when the relationship between methadone dose and heroin use was examined and found to exhibit a typical dose-response relationship in which heroin use decreased with increasing doses of methadone. The relationships between weeks spent in methadone treatment and heroin use and crime might also be interpreted in this dose-response fashion. These findings are consistent with the large number of studies that have found increasing methadone doses and increasing time in treatment to be associated with better outcomes (Ward et al., 1992).

The more general question of whether methadone treatment itself might help this population was addressed by comparing subjects who entered, and were in, treatment at the time of their three-month follow-up interview with those who were not. This was based on the accumulated research evidence reviewed in Ward et al. (1992), which suggests that methadone treatment is only effective for clients with a clinical profile similar to that of the KRC study participants while it is being delivered. This analysis of self-selected methadone treatment entrants versus those who chose not to attend found significant associations between being in methadone treatment and reduced heroin use, crime, and HIV risk behaviour.

Comparisons with Self-Selected Samples

The extent to which comparisons between self-selected groups of subjects is valid is debatable. It may be the case that the subjects who elected to enter and remain in methadone treatment would have been better off at follow-up with or without treatment (although given the demonstrated potency of methadone maintenance treatment this is unlikely). Similarly, it may be the case that such subjects are more motivated to change and that some of the effect of treatment is due to this motivation rather than treatment. The problem of drawing inferences from self-selected samples is not restricted to methadone maintenance treatment and is met with in other research situations (Wainer, 1986).

Singer (1986), who considers the problem of self-selection in relation to the evaluation of methadone treatment, has argued that if one wishes to compare methadone treatment to what would happen in the absence of treatment, then it will only be possible on the basis of a comparison of individuals who elect to enter and remain in treatment with those who do not elect to do so. Singer goes on to argue that such a comparison is not feasible because a control group consisting of opioid addicts who do not wish to enter, and therefore do not apply for, treatment is not feasible for practical reasons, heroin users being a hidden

population.
The regrouping of the subjects in the KRC methadone study into two self-selected groups goes some way towards achieving a comparison of the kind described by Singer. However, there is an important caveat. *All* of the subjects who volunteered for the study wanted to enter methadone treatment, but 50% were unable to enter the program of their choice. This had a number of practical consequences. It may be the case that more individuals in the control group entered methadone treatment than might have happened in the absence of participation in the study. Having come so far in terms of deciding to enter treatment, the experience of being assessed and discussing their problems with clinical staff may have prompted the further step of taking up the offer of immediate referral for treatment elsewhere. On the other hand, some members of the control group were clearly resentful about not being assigned to the treatment group and may have felt demoralised about their prospects. They may, therefore, have fared more poorly than they otherwise would have during the study period.

In the absence of the comparison of self-selected groups achieving the rigour necessary for drawing confident conclusions about the effectiveness of treatment, Singer (1986) argues that a further strategy may be useful for the evaluation of new methadone programs. This strategy involves comparing the new programs to existing methadone clinics, to determine if the new programs are as effective as their traditional counterparts. This strategy was adopted, and individuals assigned to the treatment group who were still receiving methadone at three-months were compared to participants in a study of three public clinics. The KRC methadone clients were found to be using more heroin than their public clinic counterparts, but were equivalent in terms of HIV risk behaviour, crime and health status. The level of heroin use among the KRC cohort, although higher than that found among the public sector patients, was reduced in comparison to that reported at intake. This finding based on self-report was consistent with the results of the urine tests.

Methadone Maintenance and More "At-Risk" Populations

In terms of the original investigation of the extension of methadone treatment to a more "at-risk" population, it was confirmed that the KRC study subjects were younger and worse off on a number of prognostic indicators than the sample of recent entrants to the public methadone clinics. The extent to which methadone is effective with such a clientele is answerable to some extent from the analyses presented above, and it is concluded that it is possible to enrol and keep a significant proportion of such a population in treatment, but that the level of effectiveness in terms of reducing heroin use found in public methadone clinics is not achieved with this population. This may be due to the more "at-risk" status of the clientele, or it may be due to more liberal attitudes to continued drug use and attendance at the clinic. It is not possible, on the basis of the current study, to determine to what extent it is the nature of the environment, the population or the difference in treatment practices that are responsible for the observed difference.

One instigator of the current study was the failure to detect any influence of low threshold methadone programs on HIV infection and injection-related risk behaviours in Amsterdam (Hartgers et al., 1992; van Ameijden, 1994). The current study also found no difference between treatment and controls on HIV risk behaviour, as measured by the OTI HRBS and by rates of needle of sharing in the two groups. However, the initial high rate of needle sharing (43%) compared with other Australian samples of injecting drug users not in

treatment (e.g. Darke et al., 1990 = 20%; Darke et al., 1992 = 13%; Darke et al., 1994 = 15%) was dramatically reduced at follow-up for the study group as a whole (11%, n=6), resulting in very little risk behaviour to compare across the two study groups. While regression to the mean is to be expected, and was observed on most outcomes, such a substantial reduction is surprising. Two likely explanations are that subjects exaggerated their risk behaviour at intake to enhance their chances of being inducted into the study, or that the experience of a long assessment at induction which focussed on behaviours they knew put them at risk may have had some impact on their subsequent behaviour. The latter explanation seems more likely, because discussions with clinical staff, who also assessed needle sharing at intake, indicated that very little needle sharing was reported during clinical assessments. KRC clients may have been reluctant to reveal needle sharing to staff they were familiar with out of fear that they would disappoint them, whereas the research interviewer was unknown to the clients and stressed the independence and confidentiality of the research interview.

Study Limitations

The current study has a number of limitations which have to be taken into account in interpreting the findings. The study sample should not be regarded as necessarily typical of the heroin using population, the definition of which is unknown. As Singer (1986) has pointed out, heroin users seeking treatment are not typical of heroin users in general, and the study sample is not even typical of applicants for methadone treatment. This sample was younger and had more severe problems as indicated by a number of prognostic indicators. In this sense, the feasibility and effectiveness of methadone treatment in a primary health care setting was subjected to a more severe test than otherwise might have been the case.

The findings of the intention-to-treat analysis were strongly influenced by two sources of bias. Selective attrition across the two study groups introduced changes in the composition of the groups resulting from the randomisation. A significant proportion of the controls were exposed to the essential component (methadone) of the experimental condition, and this had a strong influence on the study outcomes. It has to be concluded that it was not possible to arrive at an unbiased estimate of the effect of methadone maintenance treatment at the KRC in comparison to what would happen in the absence of treatment.

The problem of unplanned treatment and the debate concerning intention-to-treat analyses versus analyses based on self-selection into treatment presents the data analyst with considerable difficulties in adopting an appropriate strategy. None of the strategies that exist, including the statistical adjustment used in this report, can fully control for the influence of unplanned treatment on the study outcome (Feinstein, 1985).

The results of the analysis based on self-selection into treatment and a non-equivalent control group have a number of likely alternative explanations that reduce confidence in the inference that methadone was responsible for the effects, despite the statistical adjustment employed. However, the findings are consistent with a substantial body of literature and are supported by the dose-response relationships observed between increasing exposure to treatment, both in terms of methadone doses and duration of treatment, and major study outcomes.

The Appropriateness of Randomisation Methadone Treatment Evaluations

This study raises two more general questions: Is a randomised design appropriate for evaluating new forms of methadone treatment? and, What is an appropriate control condition for studies of methadone maintenance? The design employed in the KRC study was adopted after considering a number of ethical issues and concluding that on balance these issues had been addressed. Randomisation was ethically justified by the excess of applicants to the small number of places available and the perceived fairness of randomly assigning individuals to these places. The assignment to the control group was augmented by an offer of referral to a traditional methadone clinic, because it was thought unethical to refuse access to a treatment of known effectiveness in its traditional setting to an at-risk population. The latter procedure, while necessary, resulted in a major threat to the randomised basis of the comparisons between the groups.

In a recent paper considering the ethical implications for the conduct of a randomised controlled trial of heroin maintenance, Ostini and colleagues (Ostini, Bammer, Dance & Goodin, 1993) note that an important aspect of the ethics of the use of randomised study designs is that it should be highly probable that the trial will be able to provide adequate answers to the study questions. An important, and perhaps unexamined, issue in this regard was the extent to which the control group subjects would gain access to methadone treatment elsewhere.

The effectiveness of traditional clinic-based methadone treatment has already been established in a small number of randomised controlled trials and a substantial number of observational studies that have employed a variety of more or less rigorous study designs. This evidence is biologically plausible in that it is consistent with what is known about the neurobiology of opioid dependence (Kreek, 1991). It is also highly likely, given the strong and consistent dose-response relationship between amount of methadone given and amount of heroin use observed, that a substantial amount of the variance in outcome during methadone maintenance is due to methadone itself. In the light of this evidence, the appropriateness and necessity of future randomised studies of methadone treatment that employ no-treatment control groups is questionable. The assessment of new forms of methadone treatment should, therefore, be compared to existing treatment practices and would perhaps best employ an observational study design to avoid resentful demoralisation if the new treatment is a highly desirable one, as was the case with the KRC study.

Conclusion

The study described in this report has highlighted the difficulties in conducting randomised controlled trials with opioid dependent individuals and, as has occurred previously (e.g. Bale et al., 1980), a quasi-experimental strategy had to be adopted to make sense of the results. The findings suggest that methadone treatment has some effect when extended to a younger and more troubled population, and that the outcomes achieved are slightly less impressive than those achieved in traditional methadone clinics with a usual treatment population. There may be a discernible benefit in encouraging a wider range of opioid dependent people to enter methadone treatment and adapting the treatment practices and settings to suit their needs. A major goal in this regard is to progress towards the "normalisation" of methadone treatment by integrating it into the primary health care system. The study reported in this report suggests that this is an attainable goal.

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