Statistical Issues in Planning a Randomised Controlled 'Heroin Trial'

Robyn G. Attewell* and Susan R. Wilson#

with a
Foreword on an evaluation strategy (Gabriele Bammer)
and an
Appendix on possible outcome measures
(Gabriele Bammer, Nova Inkpen and David McDonald)

Working Paper Number 12

Feasibility Research into the Controlled Availability of Opioids Stage 2

National Centre for Epidemiology and Population Health
The Australian National University

Australian Institute of Criminology

JULY 1994

ISBN 0 7315 2062 9
ISSN 1039–088X

*INTSTAT Australia Pty Ltd, and National Centre for Epidemiology and Population Health,
The Australian National University
Centre for Mathematics and its Applications, The Australian National University

Statistical Issues in Planning a Randomised Controlled 'Heroin Trial'
Robyn G. Attewell and Susan R. Wilson

Foreword - An Evaluation Strategy for a 'Heroin Trial'
Gabriele Bammer

Appendix - Responses of people currently on the ACT methadone program for a range of variables which measure health, HIV risk behaviours, criminal behaviour, social functioning and licit and illicit drug use
Gabriele Bammer, Nova Inkpen and David McDonald

Feasibility Research into the Controlled Availability of Opioids Stage 2
Working Paper Number 12
ISBN 0 7315 2062 9
ISSN 1039–088X

Published by the National Centre for Epidemiology and Population Health
The Australian National University
ACT 0200

July 1994

Acknowledgements

Financial support came from NCEPH, the Australian Institute of Criminology and The Australian National University's Strategic Development Fund.

Cover designed by Fran Smith, ANU Graphic Design, The Australian National University, ACT 0200. Based on an original design for the Feasibility Research Project by Kathie Griffiths.

Publications Officer: Jennifer Braid, NCEPH

Contents

Executive summary

This paper is concerned with the major statistical issues in planning a randomised controlled trial to compare two management regimes for the treatment of dependent heroin users. The background to the evaluation strategy is presented in the foreword. The primary purpose of the trial is to address the question (for people who are or have been on a methadone program):

> Does providing heroin as an optional addition to, or replacement for, methadone improve outcomes over and above improvements obtained with oral methadone alone? Outcomes include health, HIV risk behaviours, criminal behaviour, social functioning and licit and illicit drug use.

A trial would therefore have two arms: an *expanded availability* arm in which injectable heroin and oral methadone were both available and a *control* arm where only oral methadone was available.

This paper discusses, in this context, power and sample size considerations, the requirements for a good trial and issues associated with attracting and retaining volunteers from the study population.

A table is provided with a comprehensive range of values for determining whether the available study population size will be adequate for the level of effect in which one is interested. This table is used in conjunction with an appendix which lists, from surveys conducted with ACT methadone clients, likely *control* group values for various outcome measures. Suppose the sample size were to be 100 in each group (total 200). Then 80% of the time one would detect improvements as small as about 8% for outcome measures having frequencies around 10% (or 90%) in the *control* group, and this increases (decreases) to about 18% for outcome measures having frequencies around 50% in the *control* group.

There are four main requirements for a good trial, assuming the treatment groups, the participants, and the content of the outcome questions have been decided. They are absence of systematic error, precision, range of validity, and calculation of uncertainty.

Randomisation reduces the likelihood of systematic error, while lack of 'blinding', use of self-report data, and intermingling of study participants may contribute to such error. There is also discussion of randomisation of participants who are not independent, for example couples, and analysis of their data.

Precision can be increased by increasing the number of participants, by repeated observations of participants and by making concomitant observations of participants. Inclusion in the analysis of concomitant variables that strongly affect the 'outcome' variables, for example length of time on the methadone program, may (under certain conditions) increase the precision with which the effect of the treatment regime can be estimated, and increase the statistical significance of this effect.

The wider the range of conditions investigated in the trial, the greater is the confidence in the extrapolation of the conclusions. This is limited by the size of the study population. There is also subtle subjective bias which affects interpretation of the estimates of group differences. Extrapolation of the result to other situations and participants depends on one's point of view and this bias is neither fixed nor numerically measurable.

For this trial, there should not be any confounding factors at the initial design stage, but they may result as a consequence of differential retention of participants in the two treatment groups.

Attracting and retaining volunteers may well be the most challenging part of the trial. It can be feared that individuals who volunteer in the hope of access to heroin and who are then assigned to the 'methadone only' arm will drop out. 'Drop out' may be also related to concomitant variables. For example, one can imagine that those who have only been on the methadone program for a short length of time may be more likely to drop out. Dropping out would lead to a loss of power and dropping out related to concomitant variables would lead to confounding. A table is presented giving the maximum 'detectable as different' percentage for the *expanded availability* group, assuming a total original sample size of 200, no drop-outs in this group, and a 'reasonable' drop-out

rate of 50% from 100 to 50 in the *control* group, over a range of *control* group percentages. Slightly larger improvements would need to be seen to be 'detectable as different' at the same power. The table can also be used to show the effect of changing the ratio of assignment to the *expanded availability* group and the *control* group from 1:1 to, for example, 2:1 in order to increase a participant's odds of obtaining the *expanded availability* arm. The additional degree of improvement which would need to be seen to be 'detected as different' is relatively small. However, if such a recruitment strategy was used, retention rates, particularly in the *control* arm would have to be high.

Foreword—An Evaluation Strategy for a 'Heroin Trial'

The controlled provision of heroin to dependent users can be seen both as a treatment option and as a change in drug policy. Although such controlled availability is practised in the United Kingdom and is being trialled in Switzerland, there is not enough evidence to allow much to be said about whether or not heroin prescription 'works'.[1] There is a need for clear information about what controlled provision of heroin can and cannot achieve, therefore, if an ACT trial is found to be feasible and eventuates, rigorous evaluation will be central.

During Stage 1 of the feasibility investigations, a range of evaluation strategies were reviewed (Bammer *et al.* 1991). We decided to focus on the most rigorous, the randomised controlled trial. We have explored the possibilities and ramifications of using this strategy in the second stage of the feasibility study.

At a workshop held in June 1993 the advantages and disadvantages of modifying the standard randomised controlled trial design were discussed, as was the impact of choice of study population on the generalisability of the results and on types of outcome measures (Bammer and McDonald 1994). Particularly important was the handling of people who dropped out of a trial. A study by Hartnoll and co-workers (1980) which compared the then new oral methadone treatment with the then standard injectable heroin treatment was marred by a high drop-out rate from the oral methadone group. Twelve per cent of participants allocated to oral methadone left the trial immediately; by three months less than 50% were still in the trial and by 12 months this had fallen to 29%. In comparison, 74% of those allocated to injectable heroin maintenance were still in the trial at 12 months. Jarrett and Solomon (1994) explored statistical options to address this problem, particularly the effect of allowing participants to choose not to have certain treatments. Another option which may minimise drop-outs, at least initially, is a cross-over design, so that all trial participants will eventually be rotated through all possible treatment options (Bammer and McDonald 1994). However if strategies to minimise drop-outs are implemented, the number of drop-outs cannot be used as an outcome measure on which to compare the two arms of the trial. At the June 1993 workshop there was discussion about the value of using drop-outs as a meaningful and readily accessible outcome measure.

Other considerations which have fed directly into the development of the evaluation strategy have centred around the philosophy which would govern service delivery in a trial. Contradictions were identified between a randomised controlled trial and a health development[2] approach to service delivery (McDonald *et al.* 1994). Two particularly important issues are client choice and individualised treatment.

An evaluation strategy has now been developed which we believe meets as well as possible these various and sometimes conflicting demands.

The research questions:

1. Does providing heroin as an optional addition to, or replacement for, methadone improve outcomes over and above improvements obtained with oral methadone alone?

---

[1] There will be a review of heroin, morphine and other short-acting psychoactive drug prescription in a forthcoming working paper.

[2] Health development concepts arise from a program of research being undertaken at NCEPH by David Legge (personal communication; see also McDonald *et al.* 1994). Four principles of health development are that:

- service delivery is undertaken in a respectful collaboration with the people whose health it is (at both the clinical and community levels)
- service delivery addresses the micro and immediate needs of sick care and public health in ways that also contribute to redressing problems understood in terms of macro-level structures and longer time horizons
- service delivery addresses the technical tasks of sick care and public health in ways that also strengthen our ability to manage existential challenges, and
- service delivery conceives the functions of sick care and public health as continuous with the broader domains of living a fulfilling life and contributing to building a better society.

Outcomes include health, HIV risk behaviours, criminal behaviour, social functioning and licit and illicit drug use, and

2. Does the provision of an injectable heroin option attract back into treatment people who have dropped out of oral methadone treatment?

The study population

The study population will be drawn from volunteers from two groups:

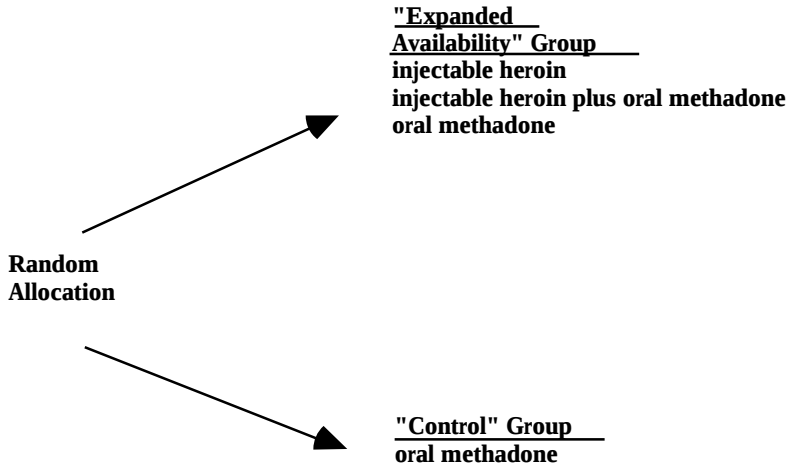
- clients of the ACT methadone program, and
- people who have dropped out of the ACT methadone program.

To deter immigration to Canberra, volunteers will also need to prove ACT residency since at least 1993.

Randomised controlled trial

Volunteers would be randomly allocated to one of two groups.

- The ***control*** **group** would receive oral methadone, the current 'gold standard' for the treatment of heroin dependence.
- The ***expanded availability*** **group** would have a choice between injectable heroin only, injectable heroin and oral methadone and oral methadone only, and can move at will (within limits of safety) between these choices. This is summarised in the following diagram:



It is likely that by confining trial participants to people who have had experience with methadone treatment, either because they are currently on methadone or because they have previously dropped out of methadone treatment, drop-outs will be minimised. In particular, for people currently on a methadone program (whom we expect to be the bulk of participants), the control group option is no worse than the treatment they are currently receiving. A two-phase trial is also being considered. After the randomised controlled trial has run for a sufficient length of time to allow outcomes to be clearly measured, possibly around 12 months, all participants would have the expanded availability option available to them for a further 12 months. During this time the results of the randomised controlled trial would be analysed and it would be a further check on how well controlled availability worked over an extended time period.[3]

[3] It seems likely that in the initial few months at least, participants in the expanded availability arm might be on their 'best behaviour' because they might be anxious to make a trial succeed. In terms of trial evaluation it would be important to see to what extent behavioural change could be maintained over the longer term.

The element of choice in the expanded availability arm meets, to some extent, the desire to run a trial according to health development principles. Allowing participants choice in the expanded availability arm means that the question being addressed is about the effects of expanded options and choice. It does not allow for direct comparison between heroin and methadone treatments. While some would prefer a more straight-forward comparison between groups (e.g. injectable heroin compared with oral methadone), it can be argued that oral methadone is known to be an effective long-acting stabilising drug and that the option of this treatment should not be denied to any trial participant. A potential problem with injectable heroin is that it is a short-acting drug and that some participants may not be able to be stabilised on it. From a treatment perspective it makes sense that these participants should be offered oral methadone either alone or in conjunction with injectable heroin. In addition, it is likely that it would not be acceptable to the wider community for heroin to be made available on a take-away basis. Allowing participants to take oral methadone, which can be prescribed on a take-away basis, would allow them to travel interstate or to simply not visit the clinic for a short time. It would also be an option which would allow people to give their veins a 'rest' from injecting.

The question could then be asked: why are there only three options in the expanded availability group? Why not allow, for example, smokable heroin and/or injectable methadone? We are, of course, interested in analysing what happens in the expanded availability group, with regard to tracing the choices participants make. The more options available, the more difficult this tracing would become. Coupled with this, our surveys of current dependent heroin users showed a very clear preference for injectable heroin over any other route of administration and for injectable heroin over injectable methadone (to be published in a forthcoming working paper).

The restriction of participants to current or former clients of the ACT methadone program also has other advantages. Because the identities of eligible participants are known, it should reduce the likelihood that dependent heroin users from elsewhere in Australia will migrate to the ACT in order to attempt to get a place on a trial. This should be strengthened by the additional restriction that those eligible for a trial will need to have been resident in the ACT since at least 1993 (Bammer *et al.* 1994).

In our analysis of the ACT illicit drug market we concluded that 'there are potential dangers in perturbing a system which is poorly understood' and that 'a trial should be structured to have minimal impact on the illicit drug market' (Bammer and Sengoz 1994:vi). The restriction on eligible participants will go some way towards achieving this aim.

The third advantage of limiting participation to people with experience with methadone relates to trial termination. If a trial has to be terminated early because of unexpected negative effects or is shown not to be effective in improving outcomes, participants will be transferred to oral methadone-only treatment. Because they have all had experience with this treatment, there are fewer ethical problems in exercising this option.

The disadvantage is that a trial would not be able to address the question of whether or not an injectable heroin option attracted to treatment people who had never been in treatment before. However it would assess if people who had dropped out of methadone treatment could be attracted back to treatment and this would give some insights into the relative attractiveness of a heroin option over methadone alone.

An essential step in assessing the evaluation strategy outlined above is to determine if there is enough power to measure the hypothesised changes in outcomes. That was the starting point for the current working paper. Results from possible quantitative measures of outcome taken from people currently on the methadone program were taken as indicators of the results which might be found in the control group. This study investigated a large number of potential outcome measures and they are listed in the Appendix. In addition, a total sample size of 200 was used as the basis for the calculations. This was also derived from the survey of current ACT methadone program clients. Two-thirds of those surveyed reported that they would be interested in a place on a trial (to be reported in a forthcoming working paper). The program currently has around 300 clients, thus

around 200 may be interested in a place on a trial. This does not take into account methadone treatment drop-outs who may wish to participate in a trial, so that 200 participants may be a conservative estimate.

Using sample sizes of 100 in each group (total 200), Attewell and Wilson report the following: 80% of the time one would detect improvements as small as about 8% for outcome measures having frequencies around 10% (or 90%) in the control group, and this increases (decreases) to about 18% for outcome measures having frequencies around 50% in the control group.

These are relatively large changes and it is not clear whether or not they are likely to be attainable. However, it can be argued that the provision of an injectable heroin option is likely to be significantly more expensive than the provision of oral methadone alone[4] and that this would need to be justified by marked improvement in outcomes.

Attewell and Wilson also highlight a number of other statistical issues which a trial would need to consider. They suggest an option for increasing trial participation, namely allocating twice as many people to the expanded availability arm as to the control arm. However, the effect of any drop-outs from the control arm would then be quite critical.

Feedback on the design outlined in this foreword and on the working paper would be very welcome.

Gabriele Bammer PhD
Feasibility Research Co-ordinator

References

Bammer, G. and D. N. McDonald (1994) 'Report on a workshop on trial evaluation'. In *Issues for designing and evaluating a 'heroin trial' Three discussion papers.* Feasibility Research into the Controlled Availability of Opioids Stage 2 Working Paper Number 8, 1-10. Canberra: National Centre for Epidemiology and Population Health, Australian National University and Australian Institute of Criminology.

Bammer, G. and A. Sengoz (1994) *How would the controlled availability of heroin affect the illicit market in the Australian Capital Territory? An examination of the structure of the illicit heroin market and methods to measure changes in price, purity and availability, including heroin-related overdoses.* Feasibility Research into the Controlled Availability of Opioids Stage 2 Working Paper Number 10. Canberra: National Centre for Epidemiology and Population Health, Australian National University and Australian Institute of Criminology.

Bammer, G., Douglas, R. and P. Dance (1991) 'Evaluation by a randomised controlled trial' In National Centre for Epidemiology and Population Health *Feasibility Research into the Controlled Availability of Opioids Stage 1 Volume 2 Background Papers* 279-286. Canberra: National Centre for Epidemiology and Population Health, Australian National University.

Bammer, G., Tunnicliff, D. and J. Chadwick-Masters (1994) *How could an influx of users be prevented if Canberra introduces a trial of controlled availability of heroin?* Feasibility Research into the Controlled Availability of Opioids Stage 2 Working Paper Number 9. Canberra: National Centre for Epidemiology and Population Health, Australian National University and Australian Institute of Criminology.

Hartnoll, R. L., Mitcheson, M. C., Battersby, A., Brown, G., Ellis, M., Fleming, P. and N. Hedley (1980) 'Evaluation of heroin maintenance in a controlled trial' *Archives of General Psychiatry* 37: 877-884.

Jarrett, R. G. and P. J. Solomon (1994) 'An evaluation of possible designs for a heroin trial (draft)'. In *Issues for designing and evaluating a 'heroin trial' Three discussion papers.* Feasibility Research into the Controlled Availability of Opioids Stage 2 Working Paper Number 8, 11-30. Canberra: National

[4] Costing will be presented in a forthcoming working paper.

Centre for Epidemiology and Population Health, Australian National University and Australian Institute of Criminology.

McDonald, D., Bammer, G., Legge, D. G. and B. M. Sibthorpe (1994) 'Service provision considerations for the evaluation of a 'heroin trial'. A discussion paper'. In *Issues for designing and evaluating a 'heroin trial' Three discussion papers.* Feasibility Research into the Controlled Availability of Opioids Stage 2 Working Paper Number 8, 31-34. Canberra: National Centre for Epidemiology and Population Health, Australian National University and Australian Institute of Criminology.

Introduction

This paper is concerned with the statistical issues to be considered in planning a randomised controlled trial to provide heroin in a controlled manner to dependent users. First, the proposal is summarised as follows (see Bammer 1994, Foreword):

The research questions:

1. Does providing heroin as an optional addition to, or replacement for, methadone improve outcomes over and above improvements obtained with oral methadone alone? Outcomes include health, HIV risk behaviours, criminal behaviour, social functioning and licit and illicit drug use, and
2. Does the provision of an injectable heroin option attract back into treatment people who have dropped out of oral methadone treatment?

The study population

The study population will be drawn from volunteers from two groups:

- clients of the ACT methadone program, and
- people who have dropped out of the ACT methadone program.

To deter immigration to Canberra, volunteers will need also to prove ACT residency since at least 1993.

Randomised controlled trial

Volunteers would be randomly allocated to one of two groups.

- The ***control* group** would receive oral methadone, the current 'gold standard' for the treatment of heroin dependence.
- The ***expanded availability* group** would have a choice between injectable heroin only, injectable heroin and oral methadone and oral methadone only, and can move at will (within limits of safety) between these choices.

To focus the statistical discussion, it is beneficial first to define a principal purpose for the trial, even though the trial may have more than one purpose. (This was emphasised by Sackett 1983 in the context of trials having both 'explanatory' and 'management' purposes.) The two research questions above have different purposes. The first question is 'explanatory', in the sense of evaluating how a change in treatment regime might 'cause' a change in the outcome variable/s. The second question concerns 'catchment', in the sense of evaluating whether choice in the treatment management will attract more clients. This paper will concentrate on discussion of statistical issues that arise in planning a trial to answer the first question.[5] Mainly it is concerned with evaluation of how much power the randomised controlled trial design might have, given the likely size of the study population. This relatively straightforward aspect of trial planning is the subject of the next section.

However, the planning of a trial such as the one proposed raises more complex issues than power and sample size considerations. The requirements for a well-executed trial (*see* Cox 1958) are as follows:

- the group comparisons (between the *control* and *expanded availability* groups) should, as far as possible, be free from systematic error;
- the group comparisons should be made sufficiently precisely;
- the conclusions should have a wide range of validity, and
- the uncertainty in the conclusions should be assessable.

[5] We have not yet been able to obtain information about the number of drop-outs from methadone treatment in the ACT, and this makes it difficult to examine the second question in any but the most superficial way.

These considerations are the focus of the third section. The fourth section discusses briefly some statistical issues associated with attracting volunteers to the trial and retaining them in the study.

These last two sections do not claim to give a completely comprehensive coverage of *all* relevant factors to be considered when undertaking this type of trial in this context. Rather, these sections form a base for further discussion. Finally, it is beyond the scope of this paper to consider other important aspects of the trial, such as methods of analysis, multiple tests, and multiple end-points.

Sample size and power

In Table 1 we present a comprehensive range of values for determining whether the available study population size will be adequate for the level of effect in which one is interested. The numbers are based on the formula given in Wilson and Gordon (1986). Since the first research question essentially asks whether outcomes in the *expanded availability* group will 'improve' over and above improvements obtained in the *control* group, a one-sided testing approach has been assumed, with significance level, α, of 5% (or less), for three different sizes of study population (150, 200, 250; equal numbers in each group) over three different power levels (70%, 80%, 90%). The values are the maximum 'detectable as different' percentages in the *expanded availability* group for assumed *control* group percentages in the range 10% to 95% in 5% steps. (Potential study size numbers are too small to evaluate percentages as low as about 5%.) Table 1 can be used in conjunction with the Appendix, which summarises from surveys conducted with ACT methadone clients, likely *control* group values for various outcome measures. This allows determination of what level of change (improvement[6]) between the two groups can be detected, and with what probability.

A typical use of Table 1 in conjunction with the Appendix can be detailed as follows. The percentage in the *control* group who had a *'Total drug use in the last month (not including alcohol and tobacco;*

Table 1
Maximum 'detectable as different' percentages in the *expanded availability* group with various powers (70%, 80%, 90%) at one-sided 5% significance for total sample sizes of 150, 200 and 250 (equal numbers in each group) for a range of *control* percentages (10%–95%)

	n=150			n=200			n=250		
	70%	80%	90%	70%	80%	90%	70%	80%	90%
Control %									
10	2.2	1.4	*	2.9	2.2	1.1	3.5	2.7	1.7
15	4.9	3.8	2.2	6.0	4.9	3.5	6.7	5.7	4.4
20	8.1	6.7	4.8	9.4	8.1	6.4	10.3	9.1	7.5
25	11.6	10.0	7.8	13.2	11.6	9.6	14.2	12.9	11.0
30	15.4	13.6	11.1	17.1	15.5	13.2	18.4	16.8	14.7
35	19.4	17.4	14.7	21.3	19.5	17.0	22.7	21.0	18.7
40	23.7	21.5	18.5	25.7	23.7	21.1	27.1	25.3	22.9
45	28.1	25.8	22.6	30.2	28.2	25.4	31.7	29.9	27.3
50	32.7	30.3	26.9	34.9	32.8	29.8	36.5	34.5	31.9
55	37.5	34.9	31.5	39.8	37.6	34.5	41.3	39.4	36.6
60	42.4	39.8	36.3	44.8	42.5	39.4	46.4	44.4	41.6
65	47.6	44.9	41.3	49.9	47.7	44.5	51.5	49.5	46.7
70	52.9	50.3	46.6	55.3	53.0	49.8	56.9	54.8	52.0
75	58.5	55.9	52.2	60.8	58.6	55.4	62.4	60.4	57.6
80	64.3	61.8	58.1	66.6	64.4	61.3	68.1	66.2	63.5
85	70.5	68.1	64.5	72.7	70.6	67.6	74.1	72.3	69.7
90	77.3	75.0	71.6	79.2	77.3	74.5	80.5	78.8	76.4
95	84.9	82.8	79.7	86.5	84.8	82.3	87.5	86.1	84.0

* indicates power unattainable even with 0% in the *expanded availability* group.

[6] Improvement will mean an increase in scores on some variables and a decrease on others.

OTI)' outcome of *'daily or more than daily'* can be taken to be 20% (Appendix). If one had 100 participants in each group (total 200) and a fixed level 0.05 (i.e. 5%) significance test, the probability that if the true percentage in the *expanded availability* group is 8.1% one will reject the null hypothesis (that the value has not changed from that for the *control* group) is 0.8 (Table 1). If the true percentage is 6.4% then this probability increases to 0.9, while if the true value is 9.4% the probability drops to 0.7. Further, suppose one is satisfied with a power of 80%, then if the sample size fell to 75 in each group (150 total), one could detect a drop in the percentage having this outcome from 20% to 6.7%. While, if the sample size increased to 125 in each group (250 total) one could detect a lesser decrease in this percentage to 9.1%. Given the (relatively) small sample sizes on which the percentages in the Appendix are based, rounding the percentages having each of the outcomes to the nearest 5% suffices, (although the pedantic could extrapolate within the table!). So then the above argument goes through, basically *mutatis mutandis*, for the outcomes *'High crime score (OTI)'* and *'Shoplifted in last month (OTI)'*, and the resultant values should be rounded to the nearest percentage point.

Table 1 can be used in the 'reverse' direction in the following way. Consider the health outcome variable *'Rate self as happy or very happy'*, and round the percentage in the *control* group from 58% to 60% (Appendix). Then the 'mirror-image' outcome would have a (rounded) percentage of 40%. Next assuming, say, a total sample size 200, power 80%, the 'mirror-image' outcome percentage would be 23.7% in the *expanded availability* group, giving a final (rounded) estimate for the outcome of interest in the *expanded availability* group of 76%.

Now some values for other outcome variables of particular interest will be presented. Further, it will be assumed that the sample size is 100 in each group (total 200) and the chosen power is 80%. Then, for each of the outcome variables the observed *control* group percentage followed by the maximum 'detectable as different' percentage in the *expanded availability* group (using the above rounding procedure) are given. In other words, if 19% of the *control* group had a crime score on the Opiate Treatment Index which rated as high (*'High crime score (OTI)'*), this would have to be reduced to 8% or less in the *expanded availability* group for a 'statistically significant' improvement to be seen.

1. Health

High score for health problems (OTI)	(34%, 19%)
High score on GHQ (OTI)	(17%, 5%)
Rate health as poor or fair	(68%, 53%)
Rate self as happy or very happy	(58%, 76%)

2. HIV Risk

High HIV risk score (OTI)	(10%, 2%)
Injected in the last month (OTI)	(59%, 42%)

3. Criminal behaviour

High crime score (OTI)	(19%, 8%)
Committed a property crime in last month (OTI)	(27%, 12%)
Shoplifted in last month (OTI)	(21%, 8%)
Sold drugs in last month (OTI)	(42%, 24%)

4. Social functioning

Low social functioning score (OTI)	(28%, 15%)
Income from illegal sources in last 6 months	(32%, 16%)

5. Drug use in last month (OTI)

Total drug use (not including alcohol and tobacco):	
daily or more than daily	(20%, 8%)
Heroin use: daily or more than daily	(11%, 2%)
Alcohol use: daily or more than daily	(30%, 15%)

Cannabis use: daily or more than daily	(43%, 28%)
Tranquillisers use: daily or more than daily	(20%, 8%)

In summary: suppose the sample size were to be 100 in each group (total 200). Then 80% of the time one would detect improvements as small as about 8% for outcome measures having frequencies around 10% (or 90%) in the *control* group and this increases (decreases[7]) to about 18% for outcome measures having frequencies around 50% in the *control* group.

Further topics for consideration

This section discusses the requirements for a good trial, assuming the treatment groups, the participants and the content of the outcome questions have been decided on. The four main requirements will now be discussed in turn.

Absence of systematic error

This means that if a trial of the given design were conducted using a large number of individuals, it would almost certainly give a correct estimate of each group comparison. Randomization to groups should achieve this, in that the individuals allocated to the *control* group should differ in no systematic way from those allocated to the *expanded availability* group. In other words, there should be no bias.

A possible source of systematic error (or bias) for this trial might arise from it being virtually impossible to have any blinding (of volunteers or workers with the study). So the social context in which the trial is taking place and the fact that the data are mainly "self-reported" may introduce systematic error into the results. Trial participants and researchers may consciously or unconsciously be wanting to achieve a particular outcome in favour of one of the treatment regime groups. Ashery and McAuliffe (1992) discuss in the context of trials of treatments for drug users the difficulties of maintaining uniform psychosocial interventions by different counsellors. Further, differences between groups may be attenuated because participants in different conditions intermingle when away from the treatment site/s. Aiken (1986) discusses how clients can distort their self-presentation in order to gain access to desired treatment. This can then obscure true gains during treatment. Ball (1967) suggested that the social situation and auspices under which interviews are obtained affect the participant's motivation to be either candid, equivocal or deceitful. Finally, as Chalmers (1983) notes: 'The influence of bias is pervasive. Its complete elimination is impossible, but all practical efforts must be made to minimize it' (p. 125).

Further, the participants need to respond "independently" of one another. This raises the question of couples (or family/household units) who might be expected to respond similarly, compared with individuals from different households. Experimental design principles would suggest assigning at random one of each couple to the *control* arm, the other to the *expanded availability* arm, that is, treat each couple as a "block". However, there may be psychosocial and other reasons to allocate couples to the same treatment arm. Discussion of just what might be the proper unit for ethical attention— individual or family— needs more development (Bailar 1983).

At this stage of planning it is recommended that the volunteers be stratified separately as singles or couples. Then for sample size and power considerations, a conservative approach is to assume each couple provides a single unit for analysis. (The result for one person in the couple is selected randomly.) So, using for illustrative purposes our example discussed at length in the previous section, where the *control* group outcome percentage is about 20% and taking a power of 80%, suppose we have 200 volunteers, consisting of 100 individuals and 50 couples. Conservatively this should be treated as a sample of overall size 150, rather than 200, giving a lower detectable percentage in the *expanded availability* group of 6.7% rather than 8.1%; the true value will, of course, lie somewhere between these

[7] Obviously 18% is an increase over 8%, but actually is a decreasing value relative to the *control* group percentage.

two values. At the analysis stage, the full data for couples/household units would be used. It is noted that appropriate analyses may not be particularly straightforward if done properly.

Precision

If the absence of systematic errors is achieved by randomisation, the estimate of a group contrast obtained from the trial will differ from its true value only by random errors. (It is noted that the term "random" is used in its technical statistical sense. Roughly speaking it means that the variations will show no reproducible pattern.) The calculations given in the previous section assume these conditions hold, in the context of, essentially, comparing percentages.

As noted by Ashery and McAuliffe (1992) the within groups variation is likely to be greater in a trial such as the one being planned here because outpatient settings do not permit tight control of exogenous variables directly affecting outcomes (e.g., drug use, crime, social functioning). Since so many things that affect outcomes, besides the intervention, can occur over six months or more, there can be a lot of variance which is not accounted for by differences in treatment regimes. Also, variation in reporting (see, for example, Mieczkowski *et al.* 1991) will further increase the within groups variation.

Our requirement about precision is, roughly speaking, that the standard error should be sufficiently small and also sufficiently precise, when dealing with, say, binomial variation and assuming homogeneity within groups, for us to be able to draw cogent conclusions.

Increasing the number of individuals increases precision, and so may taking repeat observations on individuals. Another method is by improved design. Supplementary observations may be used to increase precision. Such observations are classically termed *concomitant* observations (Cox 1958). The essential point in our assumptions about these observations is that the value for any unit must be unaffected by the particular assignment of individuals to treatments. In particular this means that either

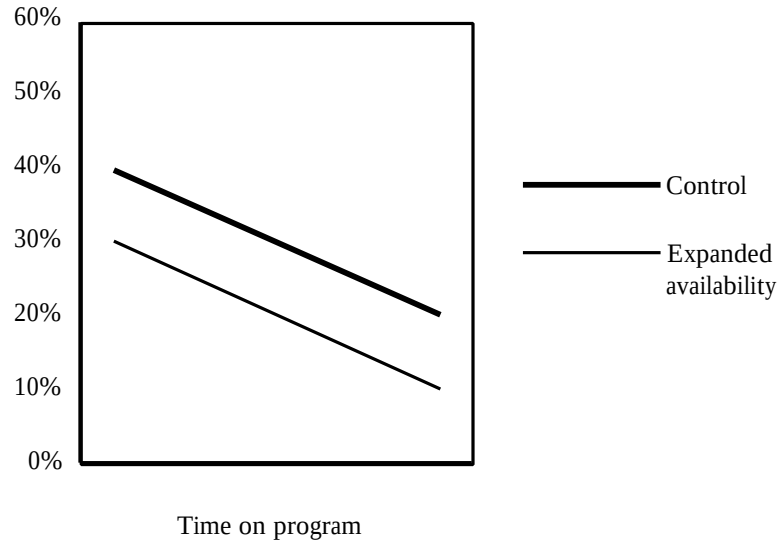
(a) the concomitant observations are taken before the assignment of individuals to groups is made; or

(b) the concomitant observations are made after the assignment to groups, but before the effect of the treatment regimes has had time to develop; or

(c) we can assume from our knowledge of the nature of the concomitant observations concerned, that they are unaffected by treatment regime differences.

For example, the "demographic" variables (sex, age, marital status, dependent children, education, occupation, income sources) and variables such as clinic attended (if there is more than one clinic), time on program and number of times on methadone treatment, should be treated as concomitant variables.

If those concomitant variables that strongly affect the "outcome" variables are included in the statistical analysis, this may (under certain conditions) increase the precision with which the effect of the treatment regime can be estimated, and increase the statistical significance of this effect. An example from the above list, of a concomitant variable that has been shown to be related to many of the proposed "outcome" variables to be investigated, is length of time on program (see e.g. Gottheil *et al.* 1993; Simpson 1981). To give a simple, hypothetical example, suppose the *control* group and *expanded availability* group outcome percentages were 30% and 20% respectively. Then based on group sizes and power given in Table 1, such a result may not be statistically significant. However, there may be a statistically significant difference between the two groups if the outcome percentages and the concomitant variable values cluster reasonably closely around a smooth curve (drawn here simply as a straight line), and these curves differ between the two groups; see diagram.



Range of validity

When the data which are (finally) collected are analysed, the conclusions refer to the particular individuals who participated in the trial, to the social and cultural context and to the specific conditions investigated in the trial. If the conclusions are to be applied to new conditions or individuals, some additional uncertainty is involved over and above the uncertainty measured by the standard error.

So, for example, the trial as it is currently formulated cannot form conclusions like: 'Injectable heroin has better outcomes (/worse outcomes) than oral methadone'. A previous proposal of a three-arm design (Jarrett and Solomon 1994) involving injectable heroin, injectable heroin plus oral methadone, and oral methadone, would better address this type of statement. As it is formulated, this trial will be aiming to gain insight into a specific situation where two realistic treatment regimes are being compared.

The wider the range of conditions investigated in the trial, the greater is the confidence we have in the extrapolation of the conclusions. However, the available study population is not large enough to warrant division into more than two groups. Sub-analyses may throw some light on sub-hypotheses. For example, further evaluation of those in the *expanded availability* arm *may* indicate a relationship between the outcome measures and, say, the choice of injectable heroin only, or the percentage of time on injectable heroin, and so forth (given that this group will have a choice between injectable heroin only, injectable heroin and oral methadone and oral methadone only, and can move at will, within limits of safety, between these choices).

Bailar (1983) draws to our attention the second type of bias which may be called inferential, interpretive, or subjective bias. It tends to be more subtle. It affects our interpretation of the estimates of (here) group differences. The identification and meaning of such bias is no longer fixed and numerically measurable; it depends on one's point of view. Suppose those in the *expanded availability* arm are measured to have better "outcomes". How far could such results be extended to other situations?, to other patients?, and so on. The answers to questions such as these depend on our subjective interpretation of the range of validity.

Calculation of uncertainty

The above discussion in this section, on the requirements for a good trial, has not been particularly statistical. The previous section was concerned with determination of likely detectable levels of difference between the two groups in the percentages having a particular outcome, given the

likely size of the study population as well as power. The section *Precision*, discussed the possibility of increasing precision using concomitant observations. It is worth noting here the possibility of confounding factors. Confounding factors are those which are related to both the outcome variable and 'treatment' group. If account must be taken of a confounding factor, at the design stage, the main conclusion (Breslow and Day 1987) is that unless the confounding factor and treatment group are strongly related, or the confounding factor is strongly related to outcome (meaning by 'strongly related' an odds ratio of ten or more), an increase of more than 10% in the sample size is unlikely to be needed. For this trial, there should not be any confounding factors at the initial design stage, but they may result as a consequence of differential retention of participants in the two treatment groups; see next section.

Finally, we reiterate that discussion of final approaches to analysis is outside the scope of this paper. However, it is worthwhile to note in passing that Meier (1983) illuminates a broad range of issues in the statistical analysis of clinical trials, including the problems of multiplicity, that is, the complications that arise from examining the same body of data, or its subsets, in many different ways.

Attracting and retaining volunteers from the study population

Attracting and retaining volunteers from the study population may well be the most challenging part of the trial. The essential difficulty is that the study is not 'blind', and so it can be feared that individuals who volunteer in the hope of access to heroin and who are then assigned to the 'methadone only' arm will drop out. This, one can argue, provides an indirect and partial answer to Question 2. However this 'answer' will not be satisfactory, particularly in terms of generalizability (i.e. range of validity). More importantly, the cost is high: Question 1 may no longer be able to be properly evaluated. The power may become very low indeed. Also, the 'drop out' may be related to some (or all) of the concomitant variables. For example, one can imagine that those who have only been on the methadone program for a short length of time may be more likely to drop out. This will lead to a further loss of power (and the variable becomes a confounder; see previous section). In Table 2 we give the maximum 'detectable as different' percentage for the *expanded availability* group, assuming a total original sample size of 200, no drop-outs in this group, and a 'reasonable' drop-out rate of 50%[8] from 100 to 50 in the *control* group, over a range of *control* group percentages. Using the example of the *Sample size and power* section, with a percentage in the *control* group of 20% and power 80%, the maximum 'detectable as different' percentage in the *expanded availability* group is 6.2%, compared with 8.1% if there had been no drop-outs. However, when there is differential (i.e non-random) drop-out, the statistical data analysis and its interpretation also become more complex (see for example, Armitage 1983). Desland and Batey (1991) found that retention rates are higher if interviews are held every few months, with a flexible research procedure maintained over time.

Table 2
Maximum 'detectable as different' percentages in the *expanded availability* group, with various powers (70%, 80%, 90%) at one-sided 5% significance for a sample of 50 in the *control* group and 100 in the *expanded availability* group for a range of *control* percentages (10%-95%)

	Expanded availability %		
	Power 70%	**Power 80%**	**Power 90%**
Control %			
10	1.9	1.2	0.4
15	4.5	3.4	2.2
20	7.6	6.2	4.5

[8] In 1988 51% of Australian methadone clients had been on the program for more than one year (National Campaign Against Drug Abuse 1989).

25	11.0	9.4	7.3
30	14.7	12.8	10.4
35	18.6	16.6	13.9
40	22.9	20.6	17.6
45	27.1	24.8	21.6
50	31.7	29.2	25.8
55	36.4	33.7	30.2
60	41.3	38.6	34.9
65	46.3	43.6	39.8
70	51.7	48.9	45.0
75	57.2	54.4	50.5
80	63.0	60.2	56.3
85	69.1	66.5	62.7
90	76.0	73.3	69.6
95	83.3	81.0	77.6

One way around the problem of differential retention rates between the two groups might be a cross-over design. However there are two obvious draw-backs to this design. First there would be carry-over effects from one time period to the next. Second, individuals assigned to the methadone-only arm in the second time period might drop out of the trial at this stage.

In reviewing nine randomised clinical trials of outpatient psychosocial treatments for drug use, Ashery and McAuliffe (1992) found the most common problem was participant recruitment. They found that randomisation itself often causes problems. One partial solution is to change the ratio of assignment to the *expanded availability* group and the *control* group from 1:1 to, for example, 2:1 in order to increase a participant's odds of obtaining the preferred (*expanded availability*) arm. This would reduce the statistical power of the study. The results in Table 2 can be used to give examples. Suppose our study population size is 150 and we assign 50 to the *control* group and 100 to the *expanded availability* group. Then, continuing the above example, taking power of 80% and a percentage in the *control* group of 20%, the maximum 'detectable as different' percentage in the *expanded availability* group is 6.2% compared with 6.7% if the 150 had been allocated on a 1:1 basis. Increasing the percentage in the *control* group to 70% (e.g. *Rate health as poor or fair*) the 2:1 allocation gives a maximum 'detectable as different' percentage in the *expanded availability* group of 48.9% compared with 50.3% for the 1:1 allocation. Such differences are not great, and so a 2:1 allocation may be attractive for participant recruitment. Then, however, one could not afford to have retention rates that are too low.

Conclusion

This paper discusses the basic statistical issues that need to be considered when planning a two group randomised control trial. At this stage of the feasibility research it is beneficial to define a major purpose for the trial. Here we have chosen to evaluate the 'explanatory' question, namely whether the two management routines produce essentially the same outcomes or not. In this context, power and appropriate sample sizes are relatively straightforward to calculate and relevant tables are provided. Further, the following requirements for a good trial are discussed: there should be no systematic error; precision should be as high as possible; conclusions should be as widely valid as possible, and the uncertainty in the conclusions should be assessable. We discuss problems associated with couples (or family/household units) who volunteer together and recommend they be stratified separately and be allocated (at random between couples) to the same arm of the trial. Finally there is discussion of problems associated with both attracting and retaining volunteers from the eligible population. Some consideration is given to the possibility of changing the assignment ratio from (the usual) 1:1.

Appendix

Responses of people currently on the ACT methadone program for a range of variables which measure health, HIV risk behaviours, criminal behaviour, social functioning and licit and illicit drug use[9]

Gabriele Bammer, Nova Inkpen and David McDonald
Data collected by Aaron Stowe, Iain Anderson and Corinna Lee

1. Health

Outcome factor	*n*[10]	*Expected 'control' level (%)*[11]
High score for health problems (OTI)[12]	56	34
High or above average score for health problems (OTI)	56	64
High score on GHQ[13] (OTI)	54	17
High or above average score on GHQ (OTI)	54	30
Had abcesses or infections related to injecting in last 6 months[14]	62/29	3/7
Rate health as good or excellent	62	32
Rate health as poor or fair	62	68
Rate self as happy or very happy	62	58
Rate self as unhappy or very unhappy	62	26[15]

[9] There will be a more detailed presentation of responses to variables which could be used as outcome measures in a forthcoming working paper. This will include qualitative data, full presentation of methods and discussion of the variables. The intention of this Appendix is to present information on a range of variables to allow the adequacy of the likely sample size to be assessed (in conjunction with Table 1 in Attewell and Wilson).

[10] Of around 260 people on the methadone program, 65 were interviewed. The representativeness of this sample will be discussed in the forthcoming working paper mentioned above.

[11] These scores were calculated for people currently on the methadone program. Assuming that the sample was representative, similar scores would be expected for trial participants allocated to the control (methadone only) treatment.

[12] These variables are taken from the Opiate Treatment Index (OTI, Darke *et al.* 1991). The other variables are taken from a questionnaire designed specifically for this study. In the OTI, participants were asked about symptoms and their responses were given a score which was summed. Darke and colleagues (1991) provide categorisations of scores into 'high', 'above average', 'average', 'below average' and 'low'.

[13] General Health Questionnaire

[14] Measures over the last six or 12 months may be problematic as many participants have been on methadone for less than six or 12 months. Two scores are therefore given along with the corresponding n's. First the scores for everyone on methadone and then for those who have been on methadone for more than six months (or 12 months as appropriate).

[15] Ten per cent rated themselves as both happy and unhappy and seven per cent responded 'don't know'.

2. HIV Risk

Outcome factor	*n*	*Expected 'control' level (%)*
High HIV risk score (OTI)	48	10
High or above average HIV risk score (OTI)	48	23
Injected in the last month (OTI)	49	59
Injected more than once a week in the last month (OTI)	49	20
Injected in the last week	64	52
Injected 3 or more times in the last week	64	16
Injected more than once a day on day that injected	64	20
Believe at risk of contracting HIV through injection	61	8
Believe been at risk of contracting HIV through injection in last 12 months	58	22
Believe at risk of contracting HIV through sexual practices	57	11

3. Criminal behaviour

Outcome factor	*n*	*Expected 'control' level (%)*
High crime score (OTI)	48	19
High or above average crime score (OTI)	48	27
Committed a property crime in last month (OTI)	48	27
Committed a property crime once a week or more in last month (OTI)	48	15
Shoplifted in last month (OTI)	44	21
Sold drugs in last month (OTI)	48	42
Sold drugs once a week or more in last month (OTI)	48	29
Committed fraud in last month (OTI)	48	6
Committed crime involving violence in last month (OTI)	48	2
Currently facing charges (OTI)	46	4
Involved in property crime in last 6 months	59/26[16]	44/35
Involved in fraud in last 6 months	59/26	20/15
Involved in dealing in last 6 months	59/26	53/54
Been arrested in last 12 months	61/15	33/40
Been arrested more than once in last 12 months	61/15	11/20
Been arrested in ACT in last 12 months	60/15	23/40
Been arrested more than once in ACT in last 12 months	60/15	8/20
Had convictions in last 12 months	58/15	21/20
Had more than one conviction in last 12 months	58/15	10/13
Had convictions in ACT in last 12 months	58/15	12/20
Had more than one conviction in ACT in last 12 months	58/15	7/13

4. Social functioning

		Expected 'control' level (%)

[16] All people on methadone/people on methadone for more than six months (or 12 months as appropriate)– see footnote 6.

Outcome factor	*n*	
Low social functioning score (OTI)	50	28
Low or below average social functioning score (OTI)	50	50
In last 6 months living all the time with someone who uses heroin (OTI)	49	35
In last 6 months living half or more of time with someone who uses heroin (OTI)	49	51
All people hang around with now are users (OTI)	49	8
Half or more of people hang around with now are users (OTI)	49	47
No income from paid employment in last 6 months	65/29[17]	66/76
Income from government benefits in last 6 months	65/29	85/93
Government benefits were main source of income in last 6 months	65/29	71/83
Income from illegal sources in last 6 months	65/29	32/28
Illegal sources were main source of income in last 6 months	65/29	5/7
Mentioned drug taking as an important activity	52	12
Been violent to someone because of drug use in last 6 months	55/23	20/17

5. Licit and illicit drug use

Outcome factor	*n*	*Expected 'control' level (%)*
Total drug use in the last month (not including alcohol and tobacco; OTI)		
- abstinence	50	26
- daily or more than daily	50	20
- more than daily	50	14
Heroin use in the last month (OTI)		
- abstinence	46	65
- daily or more than daily	46	11
Other opiate use in the last month (OTI)		
- abstinence	50	96
- daily or more than daily	50	2
Alcohol use in the last month (OTI)		
- abstinence	47	51
- daily or more than daily	47	30
- more than daily	47	23
Cannabis use in the last month (OTI)		
- abstinence	47	47
- daily or more than daily	47	43
- more than daily	47	38
Amphetamines use in the last month (OTI)		
- abstinence	50	92
- daily or more than daily	50	2
Cocaine use in the last month (OTI)		
- abstinence	50	96
- daily or more than daily	50	2

Continued over

5. Licit and illicit drug use: continued

Tranquillisers use in the last month (OTI)		
- abstinence	49	69
- daily or more than daily	49	20
- more than daily	49	20

[17] All people on methadone/people on methadone for more than six months– see footnote 6.

Barbiturates use in the last month (OTI)	49	0
Hallucinogens use in the last month (OTI)		
- abstinence	48	98
- daily or more than daily	48	2
Inhalants use in the last month (OTI)	48	0
Tobacco use in the last month (OTI)		
- abstinence	48	8
- more than daily	48	92
Heroin use in the last week		
- abstinence	64	58
- daily or more than daily	64	3
Benzodiazepines use in the last week		
- abstinence	64	67
- daily or more than daily	64	27
- more than daily	64	19
Cannabis use in the last week		
- abstinence	64	41
- daily or more than daily	64	38
- more than daily	64	24
Alcohol use in the last week		
- abstinence	62	41
- daily or more than daily	62	18
- more than daily	62	12
Tobacco use in the last week		
- abstinence	62	5
- daily or more than daily	62	92
- more than daily	62	90
Analgesic use in the last week		
- abstinence	64	84
- daily or more than daily	64	5
Injected their methadone	64	6
Amount spent on heroin last week		
$100 or more	64	19
$200 or more	64	8
$400 or more	64	2
Binged in the last 6 months	64/28[18]	69/64
More than one binge in the last 6 months	64/28	47/43
Binged on heroin in the last 6 months	64/28	52/39
Binged on amphetamines in the last 6 months	64/28	13/21
Binged on alcohol in the last 6 months	62/28	24/18
Binged on other drugs in the last 6 months	64/28	33/43

[18] All people on methadone/people on methadone for more than six months– see footnote 6.

References

Aiken, L.S. (1986) Retrospective self-reports by clients differ from original reports: implications for the evaluation of drug treatment programs, *International Journal of the Addictions*, **21**, 767-788.

Armitage, P. (1983) Exclusions, losses to follow-up, and withdrawals in clinical trials. In Shapiro, S. H. and T. A. Louis (eds), *Clinical Trials: Issues and Approaches* Marcel Dekker, New York, 99-113.

Ashery, R.S. and W.E. McAuliffe (1992) Implementation issues and techniques in randomised trials of outpatient psychosocial treatments for drug abusers: recruitment of subjects, *American Journal of Drug and Alcohol Abuse*, **18**, 305-329.

Bailar, J.C. III (1983) Introduction In Shapiro, S. H. and T. A. Louis (eds), *Clinical Trials: Issues and Approaches* Marcel Dekker, New York, 1-12.

Ball, J.C. (1967) The reliability and validity of interview data obtained from 59 narcotic drug addicts, *American Journal of Sociology*, **72**, 650-654.

Breslow, N.E. and N.E. Day (1987) *Statistical Methods in Cancer Research Volume II. The Design and Analysis of Cohort Studies.* IARC Scientific Publications No. 82, Lyon.

Chalmers, T.C. (1983) The control of bias in clinical trials. In Shapiro, S. H. and T. A. Louis (eds), *Clinical Trials: Issues and Approaches* Marcel Dekker, New York, 115-127.

Cox, D.R. (1958) *Planning of Experiments* John Wiley, New York.

Darke, S., Ward, J., Hall, W., Heather, N. and A. Wodak (1991) *The Opiate Treatment Index (OTI) Manual. Technical Report Number 11* National Drug and Alcohol Research Centre, University of New South Wales.

Desland, M. and R. Batey (1991) High retention rates within a prospective study of heroin users. *British Journal of Addiction*, **86**, 859-865.

Gottheil, E., Sterling, R.C., and S.P. Weinstein (1993) Diminished illicit drug use as a consequence of long-term methadone maintenance. *Journal of Addictive Diseases*, **12**, 45-57.

Jarrett, R.G. and P.J. Solomon (1994) An evaluation of possible designs for a heroin trial (draft). In National Centre for Epidemiology and Population Health and Australian Institute of Criminology, *Issues for Designing and Evaluating a 'Heroin Trial': Three Discussion Papers.* Feasibility Research into the Controlled Availability of Opioids Stage 2 Working Paper Number 8. National Centre for Epidemiology and Population Health, The Australian National University, Canberra.

Meier, P. (1983) Statistical analysis of clinical trials. In Shapiro, S. H. and T. A. Louis (eds), *Clinical Trials: Issues and Approaches* Marcel Dekker, New York, 155-189.

Mieczkowski, T., Barzelay, D., Gropper, B. and E. Wish (1991) Concordance of three measures of cocaine use in an arrestee population: hair, urine and self-report, *Journal of Psychoactive Drugs*, **23**, 241-249.

National Campaign Against Drug Abuse (1989) *National Drug Abuse Data System, Statistical Update, Clients of Methadone Programs*, Number 9.

Sackett, D.L. (1983) On some prerequisites for a successful clinical trial. In Shapiro, S. H. and T. A. Louis (eds), *Clinical Trials: Issues and Approaches* Marcel Dekker, New York, 65-79.

Simpson, D.D. (1981) Treatment for drug abuse. Follow-up outcomes and length of time spent. *Archives of General Psychiatry*, **38**, 875-880.

Wilson, S.R. and I. Gordon (1986) Calculating sample sizes in the presence of confounding variables, *Applied Statistics*, **35**, 207–213.

Feasibility Research into the Controlled Availability of Opioids

The Feasibility Research into the Controlled Availability of Opioids arose from a request to the National Centre for Epidemiology and Population Health (NCEPH) from the Select Committee on HIV, Illegal Drugs and Prostitution established by the Australian Capital Territory (ACT) Legislative Assembly.

A first stage of research, conducted in collaboration with the Australian Institute of Criminology (AIC), found that a trial to provide opioids, including heroin, to dependent users was feasible in principle. It was recommended that a second stage of feasibility investigations to examine logistic issues be conducted.

The first stage investigations examined illegal drug use in the ACT, the arguments for and against the controlled availability of opioids as reviewed in the literature, the current Australian political context for a trial, the role of interest groups in social controversies, legal issues, possible options for a trial, ethical issues, attitudes to a trial in the general community and among key interest groups (police, service providers, and illegal drug users and ex–users), and evaluation by a randomised controlled trial.

In addition, a proposal for a trial was developed as the starting point for the Stage 2 investigations.

The research which needs to be conducted to determine Stage 2 logistic feasibility can be divided into five areas:

- core information (for example, estimating numbers of users, determining relevant characteristics of ACT–based users, documenting the known information about the psychopharmacological and toxicological effects of opioids);
- information relevant to trial design and evaluation;
- information relevant to service provision;
- information about relevant legal, law enforcement and criminological matters;
- community and key stakeholder acceptability of a specific trial proposal.

The Stage 2 research is also governed by the following principles:

- the research should have intrinsic value so that, regardless of whether or not a trial goes ahead, the research should be of value to treatment services or to drug policy generally;
- research should be conducted in all relevant disciplines and the disciplinary findings should be integrated to address the central problem;
- the process should involve to the greatest extent possible the key interest groups– illicit drug users, ex–users, service providers, police, policy makers and the community.

Stage 2 of the feasibility research into the controlled availability of opioids has many components. As significant advances are made in each particular substudy, we publish the results as a working paper, so that the information is available for discussion in the public arena.

Publications

Reports

* National Centre for Epidemiology and Population Health (1991), *Feasibility Research into the Controlled Availability of Opioids. Volumes 1 and 2.* NCEPH, The Australian National University, Canberra.

* Bammer, G. and Gerrard, G. (eds) (1992), *Heroin Treatment – New Alternatives*, Proceedings of a one-day seminar, Becker House, Canberra, November 1991.

Working papers

* Larson, A. (1992), *Estimating the numbers of heroin users in the ACT*, Feasibility Research into the Controlled Availability of Opioids Stage 2, Working Paper Number 1.

* Bammer, G. (ed) (1993), *Australian drug markets research: What are we doing? Where are we going? What are the gaps? Proceedings of a one–day workshop held at the Scarth Room, University House, The Australian National University, Monday 22 February 1993*, Feasibility Research into the Controlled Availability of Opioids Stage 2, Working Paper Number 2.

* Sibthorpe, B., Sengoz, A. and G. Bammer in collaboration with The Youth Affairs Network of the ACT (1993), *Drug use and HIV risk among homeless and potentially homeless youth in the Australian Capital Territory*, Feasibility Research into the Controlled Availability of Opioids Stage 2, Working Paper Number 3.

* Bammer, G. and S. Weekes (1993), *Becoming an ex–user: Would the controlled availability of heroin make a difference?* Feasibility Research into the Controlled Availability of Opioids Stage 2, Working Paper Number 4.

* Bammer, G. (ed) (1993), *Does childhood sexual abuse contribute to alcohol, heroin and/or other drug problems? Proceedings of a one–day workshop held at the National Centre for Epidemiology and Population Health, The Australian National University, Tuesday 22 June 1993*, Feasibility Research into the Controlled Availability of Opioids Stage 2, Working Paper Number 5.

* Humes, G; Moloney, M; Baas Becking, F. and G. Bammer, in collaboration with Winnunga Nimmityjah (1993), *'It will kill us faster than the white invasion': Views on alcohol and other drug problems and HIV/AIDS risk in the Canberra/Queanbeyan Aboriginal community and on the suitability of a 'heroin trial' for Aboriginal heroin users*, Feasibility Research into the Controlled Availability of Opioids Stage 2, Working Paper Number 6.

* Butler, J.R.G. and A.L. Neil (1994), *Economic issues in a trial of the controlled provision of heroin*, Feasibility Research into the Controlled Availability of Opioids Stage 2, Working Paper Number 7.

* National Centre for Epidemiology and Population Health and Australian Institute of Criminology (1994), *Issues for designing and evaluating a 'heroin trial': Three discussion papers*, Feasibility Research into the Controlled Availability of Opioids Stage 2, Working Paper Number 8.

* Bammer, G, Tunnicliff, D. and J. Chadwick–Masters (1994), *How could an influx of users be prevented if Canberra introduces a trial of controlled availability of heroin?* Feasibility Research into the Controlled Availability of Opioids Stage 2, Working Paper Number 9.

* Bammer, G. and A. Sengoz (1994), *How would the controlled availability of heroin affect the illicit market in the Australian Capital Territory? An examination of the structure of the illicit heroin market and methods to measure changes in price, purity and availability, including heroin-related overdoses.* Feasibility Research into the Controlled Availability of Opioids Stage 2, Working Paper Number 10.

* Cica, N. (1994), *Civil liability issues associated with a 'heroin trial'*. Feasibility Research into the Controlled Availability of Opioids Stage 2, Working Paper Number 11.

* Attewell, R.G. and S.R. Wilson (1994) *Statistical issues in planning a randomised controlled 'heroin trial'*

Feasibility Research into the Controlled Availability of Opioids Stage 2, Working Paper Number 12.

Published papers

Hartland, N; McDonald, D; Dance, P. and G. Bammer (1992), 'Australian reports into drug use and the possibility of heroin maintenance', *Drug and Alcohol Review*, 11, pp.175–182.

Bammer, G. (1992) 'A trial of controlled availability of heroin for the ACT?', in White, J. (ed) *Drug problems in our society: dimensions and perspectives* (Selected papers from the Window of Opportunity, First National Congress. An Intersectoral Approach to Drug Related Problems in Our Society, December 2–5, Adelaide), pp.57–62.

Bammer, G. (1993), 'Should the controlled provision of heroin be a treatment option? Australian feasibility considerations', *Addiction*, 88, pp.467–475.

McDonald, D; Stevens, A; Dance, P. and G. Bammer (1993), 'Illicit drug use in the Australian Capital Territory: Implications for the feasibility of a heroin trial', *Australian and New Zealand Journal of Criminology*, 26, pp.127–145.

Bammer, G; Douglas, B; Moore, M. and D. Chappell (1993) 'A heroin trial for the Australian Capital Territory? An overview of feasibility research', in Heather, N; Wodak, A; Nadelman, E.A. and O'Hare, P. (eds) *Psychoactive drugs and harm reduction: from faith to science* (Selected papers from the Third International Conference on the Reduction of Drug–related Harm), Whurr, London, pp.137–150.

Ostini, R; Bammer, G; Dance, P. and R. Goodin (1993) 'The ethics of experimental heroin maintenance', *Journal of Medical Ethics*, 19, pp.175–182.

Larson, A., Stevens, A. and G. Wardlaw (1994) 'Indirect estimates of "hidden" populations: capture-recapture methods to estimate the numbers of heroin users in the Australian Capital Territory', *Social Science and Medicine*, 39, pp.823–831.

Newsletters

Newsletters reporting project results are also published from time to time.

These publications are available free from:

Dr Gabriele Bammer
Feasibility Study Co–ordinator
National Centre for Epidemiology & Population Health
The Australian National University
ACT 0200
Phone: (06) 2490716
Fax: (06) 2490740

* These publications are for sale through:

Bibliotech
The Australian National University
ACT 0200