

MEDICAL CO-PRESCRIPTION OF HEROIN

TWO RANDOMIZED CONTROLLED TRIALS

CENTRAL COMMITTEE ON THE TREATMENT OF HEROIN ADDICTS



To the Minister of Health, Welfare and Sports
P.O. Box 20350
2500 EJ The Hague

Utrecht, February 4, 2002

Re: submission of report

Your Excellency,

The Central Committee on the Treatment of Heroin Addicts (CCBH) has been installed by you and given the task of reporting to you, on the basis of a scientific investigation, on the desirable and undesirable effects of the medical prescription of heroin to heroin addicts who are resistant to current treatments, in order to improve the condition of their health and their social functioning. The Committee should at the same time be concerned with the ethical aspects of this administration and the consequences of the possible discontinuation of the treatment (Decree Centrale Commissie Behandeling Heroïneverslaafden 17 december 1996/nr. GVM/Vz/965074 and Decree hernieuwde instelling Centrale commissie behandeling heroïneverslaafden 26 september 2001/GVM/22/3937).

I am pleased to present to you the first report of the CCBH which incorporates these conclusions and recommendations. An executive summary of the report is available in the Dutch language, the full report is in English. The content of the report has been discussed with international experts, who advise the CCBH.

Following the preparation of the protocols and their approval by the Central Committee on Medical Ethics in the Netherlands, the investigation was implemented in good collaboration with the local authorities of six cities in the Netherlands. The investigation took place in the period between July 1998 - December 2001. From the report, it can be concluded that the investigation progressed smoothly, despite the need for great care, and the innovative aspects of an investigation concerning the medical prescription of heroin.

The CCBH concludes that in chronic, treatment-resistant heroin addicts who are already treated with methadone, the treatment with heroin in combination with methadone is more effective than the continuation of methadone alone. With this additional heroin therapy, the patients can benefit from the treatment with respect to their health and their social functioning. This applies to both intravenous and inhalation administrations of heroin. In a number of patients there is an indication for continuation of treatment. This is especially because discontinuation of the heroin prescription in most patients who benefited from the treatment resulted in a serious deterioration of the health status within two months of stopping. Undesirable effects with regard to the health of the patients and problems associated with control and management during the treatment were relatively scarce. This was also the conclusion of the National Safety Committee and the National Committee on Public Order and Controllability. Based on these grounds, the CCBH concludes that treatment with heroin is practicable, at least under the conditions described in the protocols of the CCBH. The costs of the treatment are presented in the report. Evaluation of the cost-effectiveness and cost-benefit is not yet available. The CCBH concludes that supervised medical co-prescription of heroin may be a useful supplement to the existing treatment options for chronic heroin addicts.

The CCBH advises you to facilitate the availability of prescribed heroin in the Netherlands for the treatment of chronic, treatment-resistant heroin addicts receiving methadone, as a last-resort pharmacotherapeutic option. To achieve this, the registration of heroin as a medicinal product (in both administration forms) is recommended. A good quality control of the implementation and execution of the treatment should be available. The CCBH emphasizes that the treatment with heroin can be implemented only under stringent conditions, this includes a state-of-the-art and accessible methadone maintenance treatment programme. Also treatment should be supervised and executed in separate treatment units which offer an adequate and state-of-the-art medical and psychosocial treatment. The financing of the treatment is a matter for attention. Since the future of the current treatment units is under consideration a decision would be appreciated at short notice. The CCBH is prepared to assist you in the development of these recommendations.

The Central Committee on the Treatment of Heroin Addicts,

Jan M.van Ree, chair

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ISBN 90-806932-2-7

NUGI 746

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Contents

Letter of submission		i
Note to the reader		ix
PART I	INTRODUCTION	
Chapter 1	Background, rationale and objectives of the study	13
1.1	Introduction	13
1.2	Good medical practice	14
1.3	Illicit heroin use in the Netherlands	15
1.4	Methadone treatment in the Netherlands	16
1.5	Prescription of opiates other than oral methadone in the Netherlands	19
1.6	Effectiveness of medically prescribed heroin	20
1.7	Rationale for the study	24
1.8	Objectives of the study	25
PART II	STUDY DESIGN AND METHODS	
Chapter 2	Methods	29
2.1	Study population	29
2.1.1	Target population	29
2.1.2	Selection criteria	29
2.1.3	Recruitment and selection procedure	32
2.2	Study design	33
2.2.1	Randomized controlled trial	33
2.2.2	Separate trials for injectable and inhalable heroin	35
2.2.3	Blinding	36
2.2.4	Randomization	36
2.3	Multicenter study	37
2.4	Stages of the study	37
2.5	Ethics, informed consent, and remuneration	38
2.6	Non-adherence to the protocol	39
2.7	Organization and responsibilities	39
2.8	Medication and treatment in the study	41
2.8.1	Objective of the treatment	41
2.8.2	Prescribed medications	41
2.8.3	Study supplies and drug accountability	43
2.8.4	Termination of the co-prescription of heroin	44
2.8.5	Concurrent treatments	44
2.8.6	Treatment units and dispensing procedures	45
2.9	Assessments	46
2.9.1	Instruments and outcome measures	46
2.9.2	Timing of the assessments	49
2.9.3	Primary outcome measure	49

2.10	Documentation of safety and public order aspects	50
	2.10.1 Adverse events, and serious/unexpected adverse events	50
	2.10.2 Public order and controllability	52
2.11	Data quality assurance	53
Chapter 3	Data analysis	57
3.1	Calculation of sample size	57
3.2	Statistical analysis of the primary study question	57
	3.2.1 Null hypothesis	57
	3.2.2 Primary assessment-points	58
	3.2.3 Study population in the primary analysis	58
	3.2.4 Missing endpoint-assessments	58
	3.2.5 Robustness of the findings	59
	3.2.6 Exploratory analyses of the validity of the findings	59
	3.2.7 Analysis model and statistical program	60
	3.2.8 Verification of self-report data	60
3.3	Statistical analyses of the secondary study questions	62
3.4	Supplementary analyses	63
Chapter 4	Protocol amendments	65
PART IIIA	STUDY FINDINGS INJECTABLE HEROIN TRIAL	
Chapter 5 ^A	Selection and disposition of patients	69
5 ^A .1	Selection procedure	69
5 ^A .2	Treatment participation and treatment completion	71
5 ^A .3	Adherence at two-monthly assessments	73
Chapter 6 ^A	Characteristics of the study population at baseline	75
6 ^A .1	Intention-to-treat population	75
	6 ^A .1.1 Baseline characteristics	75
	6 ^A .1.2 Inclusion profiles	78
	6 ^A .1.3 Comparability of the treatment groups	79
	6 ^A .1.4 Baseline characteristics across the six study sites	79
	6 ^A .1.5 Comparison of the study populations in the injectable and inhalable heroin trials	79
6 ^A .2	Treatment completers	79
Chapter 7 ^A	Effectiveness of co-prescribed injectable heroin versus methadone alone treatment	81
7 ^A .1	Treatment response after 12 months	81
	7 ^A .1.1 Treatment response after 12 months in the intention-to-treat population	81
	7 ^A .1.2 Treatment response after 12 months among the treatment completers	83
7 ^A .2	Treatment response after six months	84
7 ^A .3	Exploratory analyses of effectiveness	85
	7 ^A .3.1 Improvement and deterioration as components of treatment outcome	85
	7 ^A .3.2 Response at subsequent assessments	85

	7 ^A .3.3	Relative contribution of the outcome domains to response	86
	7 ^A .3.4	Sustained response	88
	7 ^A .3.5	Patients no longer meeting inclusion thresholds of the trial	89
7 ^A .4		Consequences of discontinuing the co-prescribed heroin treatment	90
Chapter 8 ^A		Safety of co-prescribed injectable heroin treatment	93
8 ^A .1		Focus of the evaluation	93
8 ^A .2		Serious adverse events in the experimental treatment phase of the trial	93
8 ^A .3		Drug overdoses, psychoses and seizures during the experimental phase	95
8 ^A .4		SAEs, drug overdoses, psychoses and seizures following the discontinuation of co-prescribed heroin treatment	96
PART IIIB STUDY FINDINGS INHALABLE HEROIN TRIAL			
Chapter 5 ^B		Selection and disposition of patients	99
5 ^B .1		Selection procedure	99
5 ^B .2		Treatment participation and treatment completion	102
5 ^B .3		Adherence at two-monthly assessments	103
Chapter 6 ^B		Characteristics of the study population at baseline	105
6 ^B .1		Intention-to-treat population	105
	6 ^B .1.1	Baseline characteristics	105
	6 ^B .1.2	Inclusion profiles	108
	6 ^B .1.3	Comparability of the treatment groups	109
	6 ^B .1.4	Baseline characteristics across the six study sites	109
	6 ^B .1.5	Comparison of the study populations in the injectable and inhalable heroin trials	109
6 ^B .2		Treatment completers	110
Chapter 7 ^B		Effectiveness of co-prescribed inhalable heroin versus methadone alone treatment	111
7 ^B .1		Treatment response after 12 months	111
	7 ^B .1.1	Treatment response after 12 months in the intention-to-treat population	111
	7 ^B .1.2	Treatment response after 12 months among the treatment completers	113
7 ^B .2		Treatment response after six months	114
7 ^B .3		Exploratory analyses of effectiveness	116
	7 ^B .3.1	Improvement and deterioration as components of treatment outcome	116
	7 ^B .3.2	Response at subsequent assessments	117
	7 ^B .3.3	Relative contribution of the outcome domains to response	118
	7 ^B .3.4	Sustained response	120
	7 ^B .3.5	Patients no longer meeting inclusion thresholds of the trial	121
	7 ^B .3.6	Underreporting of illegal drug use and treatment effect	122
7 ^B .4		Consequences of discontinuing the co-prescribed heroin treatment	123
Chapter 8 ^B		Safety of co-prescribed inhalable heroin treatment	125
8 ^B .1		Focus of the evaluation	125
8 ^B .2		Serious adverse events in the experimental treatment phase of the trial	125

8 ^B .3	Drug overdoses, psychoses and seizures during the experimental phase	127
8 ^B .4	SAEs, drug overdoses, psychoses and seizures following the discontinuation of co-prescribed heroin treatment	129
PART IV	FEASIBILITY OF HEROIN ON MEDICAL PRESCRIPTION	
Chapter 9	Public order and controllability	133
9.1	Focus of the evaluation	133
9.2	Events not attributed to individual patients	133
9.3	Events in the trial on injectable heroin	133
9.4	Events in the trial on inhalable heroin	135
Chapter 10	Contact dermatitis	137
Chapter 11	The costs of medical co-prescription of heroin	139
PART V	CONCLUSIONS AND RECOMMENDATIONS	
Chapter 12	Conclusions	145
Chapter 13	Recommendations	153
PART VI	REFERENCES	159
PART VII	APPENDICES	
1	Decision on the installation of the Central Committee on the Treatment of Heroin Addicts	167
2	Decision on the re-installation of the Central Committee on the Treatment of Heroin Addicts	169
3	Members of the Central Committee on the Treatment of Heroin Addicts, and Observers and advisors of the Central Committee on the Treatment of Heroin Addicts	171
4	Members of the National Research Board of the Central Committee on the Treatment of Heroin Addicts	172
5	Members of the National Safety Committee, and Members of the National Committee on Public Order and Controllability	173
6	International advisors	174
7	Statement of the National Safety Committee	175
8	Statement of the National Committee on Public Order and Controllability	176
9	Research projects related to the main study	177
10	Publications	180

Note to the reader

This report is divided into seven parts. Following the introduction (part I), and description of the study design and methods (part II), part III consists of two parallel sections, in which the study findings of the trial on injectable heroin (part IIIA) and on inhalable heroin (part IIIB) are presented separately. The numbers of the chapters and paragraphs in the injectable heroin section, marked with "A", correspond with those in the inhalable heroin section, marked with "B". To further assist the reader in distinguishing between the two trials, a different marker is placed on the top corner of the pages in the injectable heroin section (short green marker), and in the inhalable heroin section (long green marker). In the subsequent parts, the feasibility of co-prescribed heroin treatment is discussed for both trials combined (part IV), and the conclusions and recommendations are formulated for both trials combined (part V). Lastly, part VI and VII contain the references and appendices, respectively.

PART I

INTRODUCTION

Chapter 1

Background, rationale and objectives of the study

1.1 Introduction

In 1995, the Dutch Minister of Welfare, Health and Cultural Affairs asked the Health Council of the Netherlands for advice about the prescription of heroin to chronic heroin addicts as an additional medical treatment for this population, and about the conditions under which this type of treatment could be regarded as good clinical practice. In the report written in response to this request, the Committee on Medical Interventions in Heroin Addicts of the Health Council concluded that the medical prescription of heroin to heroin dependent patients could have positive effects on their physical and mental condition, as well as on their social functioning and addictive behavior (Health Council of the Netherlands, 1995). According to the Council, medical treatment with heroin would be expedient if sound medical-scientific research would establish a positive balance between the beneficial and harmful effects associated with such treatment. In order to obtain the necessary information, the Health Council recommended to conduct a trial in the Netherlands, involving severely heroin dependent patients who did not respond (sufficiently) to the currently available medical interventions.

The government adopted the Health Council's conclusion, and, in accordance with the Dutch parliament, decided to prepare and conduct the proposed study (Ministry of Health, Welfare and Sports, 1995). In December 1996, the Minister of Health, Welfare and Sports installed the Central Committee on the Treatment of Heroin Addicts (CCBH), assigning this Committee the task to develop and conduct the study, and subsequently to report about the intended and unintended effects of medical treatment with heroin.

Following extensive discussions, the CCBH developed two parallel protocols for the study of the effects of the medical prescription of heroin to severe, treatment-resistant heroin addicts: one protocol for the investigation of the effectiveness of intravenously injected heroin, and one protocol for the trial involving inhaled heroin. In addition, separate study-protocols were written for the development and testing of a stable and efficient inhalable form of heroin administration. All protocols were developed in compliance with the international guidelines for Good Clinical Practice, the Dutch law, and common medical-ethical standards regulating the conduct of medical-scientific research.

The protocols were subsequently submitted to several international experts in the field of addiction research in order to obtain their feedback. In addition, views and experiences were intensively exchanged between the CCBH and several members of the research group involved in the Swiss study investigating medical heroin treatment. Lastly, extensive discussions took place with the Central Committee on Medical Ethics in the Netherlands. The results of these and other contacts were incorporated in the final version of the study-protocols (CCBH, 1997).

In August 1997, the final study-protocols were presented to the Minister of Health, Welfare and Sports. According to these protocols, a total of 750 patients would be included in the study, which would be conducted in eight treatment units situated in six Dutch cities. In September 1997, the parliament of the Netherlands approved the execution of a test period of three months, during which a total of 185 patients, of whom 50 would actually receive heroin, would be studied. Following the three month test, the study would be extended to its intended size if no unacceptable

medical or public order problems would have occurred. In January 1998, the International Narcotics Control Board (INCB) of the United Nations confirmed the estimates of the amounts of heroin needed to sustain the study. In July 1998, the first treatment units opened in Amsterdam and Rotterdam, the cities selected for the test. Following a positive evaluation of the test period by the National Safety Committee (LVC) (1998), and the National Committee on Public Order and Controllability (LCB) (1998), the study was extended to its full size in the course of the year 2000, involving a total of eight treatment units in six cities (CCBH, 1999a). Table 1 provides an overview of the most important events and dates in the development of the study.

Table 1. Events and dates in the development of the study

<i>Event</i>	<i>Date</i>
- appearance of the advisory report of the Health Council of the Netherlands	June 1995
- decision of the Dutch government to develop the study	June 1996
- installation of the Central Committee on the Treatment of Heroin Addicts	December 1996
- approval of the study protocols by the Central Committee of Medical Ethics, and presentation of the final study protocols to the minister of Health	July 1997
- approval of the government's decision to conduct the study by the Dutch Parliament	September 1997
- installation of the National Safety Committee (LVC) and the National Committee on Public Order and Controllability (LCB) by the minister of Health	June 1998
- start of the test period of the study in Amsterdam (July) and Rotterdam (August)	July 1998
- positive evaluation of the test period by the CCBH, LVC and LCB	November 1998
- decision of the Dutch government and Parliament to continue and extend the study	February 1999
- extension of the study to the cities of Groningen, Heerlen, The Hague, and Utrecht, and second treatment units in Amsterdam and Rotterdam	April 2000

1.2 Good medical practice

In its advisory report, the Committee of the Health Council emphasized the medical context of the advice. A physician has the obligation to provide every patient with treatment, aimed at improving the patient's medical situation. In all cases, the starting point is to avoid harm to the patient. According to the Health Council, the following hierarchy of – sometimes overlapping – goals of (pharmacological) treatment of addiction can be distinguished:

- treatment of acute intoxication symptoms;
- achieving abstinence;
- prevention of relapse;
- stabilization (harm reduction, risk reduction);
- palliation.

Given these goals, and provided that the treatment is intended to bring about an improvement of the patient's medical status and has a starting point not to harm the patient, the Committee considered the prescription of substances such as heroin by a medical doctor in the context of medical treatment to be good clinical practice. In addition, good clinical practice, by means of an individual approach of addicts as patients, has public health implications, and medical professionals have a responsibility in the area of public health as well (Health Council, 1995).

Hence, a clear distinction is made between the medical concepts of 'prescription' and 'dispensing' on the one hand, and 'free supply' on the other. Whereas the first two concepts refer to a situation in which a medical doctor attempts to cure the patient or alleviate his symptoms or

disorder by means of medical treatment and on medical indication, the latter term refers to the provision of substances at the patient's request without medical indication (Health Council, 1995). Given the medical context of the advice, the Committee of the Health Council did not make any statements with regard to the public discussion on any form of legalization of heroin.

1.3 Illicit heroin use in the Netherlands

Heroin was introduced as a street drug in the Netherlands in the autumn of 1972. During the first few years, its use was largely limited to the ethnic Dutch population and the route of administration was mainly through intravenous injection. A rapid upsurge in the number of heroin users occurred around 1975 when Surinam, a former Dutch colony in the north of South-America, became independent. At that time, almost half of the Surinamese population emigrated to the Netherlands, settling mainly in Amsterdam, Rotterdam, The Hague and some other urban areas. Young Surinamese men came to play a major role in the street trade of heroin in the big cities, and many of them became heroin users themselves.

In this process, many Surinamese heroin users adhered to their own way of administering the drug, by means of inhalation instead of injection (Korf, 1995), using a technique called "chasing the dragon", or - revealing its Eastern origins - "chinesing", the common name used in the Netherlands. When chasing, the heroin is placed on a piece of aluminum foil, and heated with a cigarette-lighter from below. The heroin fumes are then inhaled by the person through a straw. Originating in Hong Kong in the 1950's, chasing the dragon subsequently spread to other countries in South East Asia in the 1960's and 1970's as well as to the Netherlands in the early 1970's, where it became widespread in the course of the 1980's not only among Surinamese heroin users, but also in the ethnic Dutch heroin using population (Grund and Blanken, 1993; Strang et al., 1997). Currently, chasing the dragon has become an established route of heroin self-administration in not only many Asian countries and the Netherlands, but also in certain parts of Spain (among others Andalucia) and regions in the United Kingdom (among others London) (Strang et al., 1997). As for the Netherlands, epidemiological studies in both treatment and non-treatment samples of Dutch heroin users have consistently indicated that chasing has been the predominant route of heroin self-administration in the Netherlands in the past two decades (Cruts et al., 1997). Currently, it is estimated that 75-90% of the Dutch heroin users predominantly or exclusively inhale their heroin (IVV, 2000; NDM, 2001).

Since the introduction of heroin in the Netherlands, the estimated number of heroin users has increased from 10,000 in 1977 to 20,000 in 1979 and 30,000 in 1983 (Schreuder and Broex, 1998). Since 1984, the total number of heroin addicts in the Netherlands seems to be rather stable, with probably some decrease in the last few years (Hoekstra and Derks, 1991; Van Brussel et al., 1996). The total number of heroin addicts in the Netherlands is currently estimated to be approximately 25.000 (Schreuder and Broex, 1998).

The general epidemiological picture of heroin use in the Netherlands is that of a relatively stable population, with a low incidence of new cases and a low mortality rate (NDM, 2001). This is also reflected in the fact that the mean age of the methadone maintenance population in Amsterdam has increased by approximately 10 months each year since 1984 (the mean age in 1984 was 28.2, whereas the mean age in 1997 amounted to 38.8 years), and in the fact that the percentage of heroin addicts in methadone maintenance who are younger than 26 years dropped from 28% in 1985 to 3% in 1997 (Buster and Reurs, 1997). A similar pattern emerged in Rotterdam, where 28% of the methadone maintenance patients were under the age of 25 years in 1988, whereas only 13% belonged to this age category in 1995 (they had a mean age of 29.3 in 1988 and 34.2 in 1995 (Toet, 1996).

This stable, aging population of heroin addicts is served by a comprehensive treatment and health care system that provides services free of charge and has little or no waiting lists. The system includes various kinds of abstinence oriented treatment facilities (e.g. inpatient and outpatient detoxification, methadone reduction, residential treatment, therapeutic communities) as well as a wide range of facilities which do not focus on abstinence but rather on stabilization and harm reduction (e.g. methadone maintenance, needle and syringe exchange, work projects, sheltered housing, user rooms). It is estimated that, depending on the local circumstances, 65-85% of the heroin addicts in the Netherlands is currently in some form of contact with the treatment system in the course of one year (Gageldonk et al., 1997; Schreuder and Broex, 1998; NDM, 2001).

Patients often begin treatment with the objective of becoming abstinent. In the course of their addiction and treatment career, however, many of those who did not quit the habit switch from abstinence treatment to some kind of harm reduction, primarily through participation in a methadone maintenance program, with or without the additional use of other pharmacological treatments (e.g. triple therapy for AIDS, antidepressants for a comorbid affective disorder) and psychotherapeutic (e.g. counseling, skills training) or psychosocial (e.g. budgeting, housing assistance, work projects) interventions.

Against this background, the medical prescription of heroin is considered as a final treatment option, which is intended only for those chronic heroin addicts who have repeatedly failed in other available treatments, including a state of the art treatment in a methadone maintenance program. In the context of medical heroin prescription, it is therefore crucial to have an adequate understanding of methadone treatment in the Netherlands and the results that have been achieved with it.

1.4 Methadone treatment in the Netherlands

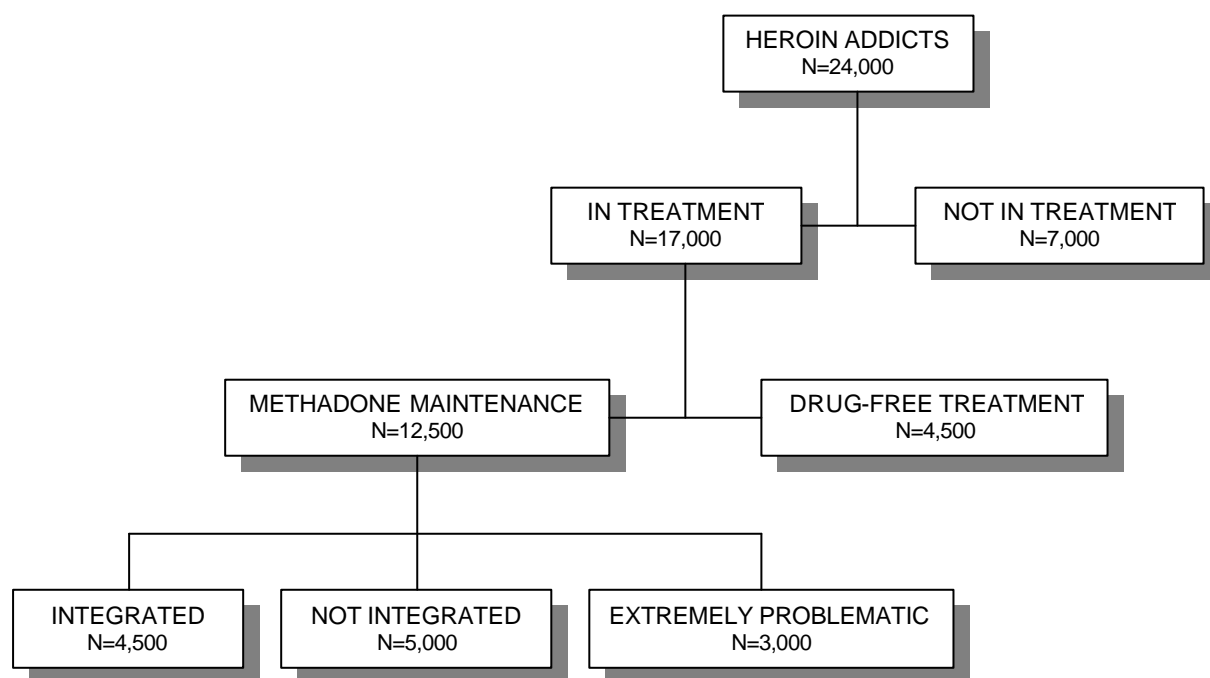
The prescription of methadone as a treatment method began in the Netherlands in 1968. During the first few years, methadone was prescribed to morphine dependent patients. Following the introduction of heroin in the Netherlands in 1972, treatments with methadone were primarily directed towards achieving abstinence from heroin addiction. Generally, these methadone reduction programs suffered from high drop-out rates, and there was a serious threat that they would lose contact with many addicts. Paralleling the rapid increase in the number of heroin addicts during the 1970s, and the introduction of HIV/AIDS in the mid 1980's, the aim of oral methadone prescription in the Netherlands shifted from achieving abstinence towards achieving stabilization and the reduction of drug related harm. Prevention of risk-behaviors and the provision of medical care through regular contact with the addict became the primary objective of methadone maintenance programs for those patients who refused counseling and continued their use of illicit drugs. In this period of increasing risk of infection and increasing necessity – for the purpose of AIDS-prevention – to at least stay in contact with the addict, the high drop-out rates in the methadone reduction programs were considered unacceptable by both treatment agencies and policy makers.

Currently, many of the Dutch methadone programs can be referred to as so-called "low-threshold" maintenance programs, characterized by the absence of mandatory counseling, absence of sanctions in case a urine test reveals illicit substance use, and relatively low dosages of methadone. These programs are aimed at the reduction of health risks and improvement of the quality of life of those addicts who are unable or unwilling to give up their drug use. Due to their low-threshold character, a high percentage of heroin addicts in the Netherlands (50-80%), including "poor performers", are reached by these programs (Bieleman et al., 1995; NDM, 2001).

Although no controlled studies on the effectiveness of the methadone treatments have been conducted in the Netherlands, there is extensive clinical experience with dispensing methadone, and

naturalistic follow-up studies provide some insight into their outcomes. In 1988, a survey was conducted on the dispensing of methadone in the Netherlands (Driessen, 1990). According to this study, the estimated number of heroin addicts in the Netherlands then was 24,000¹. Of these, an estimated 17,000 addicts (71% of the total) had been in contact with a treatment program at least once during the previous year (Figure 1). Among this group, approximately 4,500 had been in drug-free treatment (e.g. inpatient and outpatient detoxification, residential treatment centers, therapeutic communities, and drug-free prison programs). Approximately 12,500 had received methadone on a regular basis, most of them for many years (the average time in treatment amounted to approximately 8 years). According to the treatment staffs of the methadone maintenance programs, 36% of the 12,500 methadone patients (4,500 persons) were well regulated, meaning that they exhibited little or no drug use, were compliant with treatment efforts and showed some degree of social integration. Another 40% (5,000 persons) were not adequately regulated, meaning that they had frequently used illicit drugs, had been less than compliant with treatment efforts and achieved low levels of social integration. Finally, 24% (3,000 persons) were considered as being extremely problematic. These persons used various illicit substances on a daily basis, manifested symptoms of physical and/or mental problems, exhibited high levels of criminality, and showed no evidence of social integration.

Figure 1. Treatment situation in the Netherlands



Source: Driessen, 1990

Data from 1991 indicate that three-quarters (78%) of all methadone maintenance patients had continued using heroin, and more than a third (37%) were still using heroin on a daily basis (Driessen, 1992). At that time, nearly all methadone maintenance programs offered a broad spectrum of additional services, including psychosocial counseling, medical counseling and treatment, social work and – in some centers – psychotherapy. Despite their availability, however, only 49% of these clients took advantage of social work assistance, 28% took part in medical counseling, 13% in

¹ It should be noted that this estimate by Driessen (1990) is slightly lower than the estimate by Schroeder and Broex (1998) in paragraph 1.3.

psychiatric counseling, 2% in psychotherapy, 2% in family therapy and 6% in group therapy (Driessen, 1992).

In 1993-1994, the cohort of methadone clients interviewed in 1991 was again approached, to obtain information about the developments in their status after 2-2.5 years (Driessen et al., 1999). In the course of this follow-up period, nine of the original 599 subjects had died (1.5%), of whom one person due to a drug overdose, 8.4% was found to be abstinent (for at least three months), and by far the largest group (90.1%) was still using illicit drugs and/or methadone. From this latter group (of whom 96% had participated in a methadone maintenance program in the year before the follow-up interview), 32% was considered to be integrated, 61% not integrated, and 7% very problematic drug users (Driessen et al., 1999).

These early data (Driessen, 1990, 1992, 1999) are supported by a more recent study, conducted in Amsterdam (Buster and Van Brussel, 1996). This study found that 5,545 heroin addicts living in Amsterdam had received methadone between 1994 and 1995. Based on the results of urinalysis tests, 65-70% of them were found to still be using heroin regularly or even daily. This high level of illegal heroin use cannot be explained (as it sometimes has been) as a byproduct of low methadone dosages (less than 50 milligrams), however, because in 1995 in Amsterdam, the average daily methadone dose amounted to almost 60 milligrams (Van Brussel et al., 1996).

In addition to the 11,500 patients in methadone maintenance programs in 1995, there were more than 1,400 drug-related admissions to a general psychiatric hospital and more than 3,000 drug-related admissions to addiction treatment clinics in the Netherlands (Gageldonk et al., 1997). Finally, some outpatient drug-free treatment is provided by the Dutch Consultation Centers for Alcohol and Drugs. It should be noted that these numbers can not be simply added to obtain figures for the Netherlands as a whole, because some patients use more than one of the above services during the registration period and therefore could be counted more than once. It is, however, quite certain that the amount and the types of services, which are currently provided to heroin addicts, are very similar to those in 1988 (Driessen, 1990).

In 1993, the Netherlands Institute of Mental Health (NcGv) surveyed 1,900 patients and ex-patients from the Consultation Centers for Alcohol and Drugs (Jongerus et al., 1994). The results of this survey indicated that 62% of the methadone patients were (very) satisfied with the treatment they had received. Almost 60% reported a reduction in their heroin use as a result of this treatment, and nearly one third reported abstinence in terms of illicit drug use. Despite these positive outcomes, 47% of the patients reported that methadone had made it more difficult for them to achieve abstinence, and 10% reported that methadone treatment had not had any positive impact on them. These data are very similar to those collected earlier by Driessen (1992), in which 47% reported one or more major complaints, especially regarding dispensing times, the lack of take-home prescriptions and the undesired contact with other drug addicts.

In the Netherlands, there are many different regimes offered by methadone programs, but no data are available on the relationship between methadone dose-levels, the various forms of counseling provided in the programs, and the results of the treatment. However, data provided by the Amsterdam Municipal Health Service indicate that there has been an increase in the average daily methadone dosage from 43 milligrams in 1989 to 56 milligrams in 1995 (Van Brussel et al., 1996), and similar developments have been reported in other cities in the Netherlands (NDM, 2001). This average is, however, still lower than the recommended dose-level used in programs in the United States (Parrino, 1992). According to the American guidelines, the effective daily methadone dosage should be about 80 milligrams plus or minus 20 milligrams. However, a national survey showed in the US indicated that many programs had dose limits below these effective ranges and that many programs applied time limits regarding the maximum length of stay allowed in the program (D'Aunno and Vaughn, 1992). Given the fact, that most patients who receive methadone in the Netherlands are

either unable or unwilling to give up their heroin use, higher methadone doses, which would prevent them from experiencing the euphoric effects of heroin (Korf et al., 1998), are often unacceptable to the patient. Consequently, prescribing higher doses of methadone is likely to promote elevated drop-out rates, thereby undermining one of the main aims of the Dutch methadone treatment system – to reach as many addicts as possible for prevention, medical supervision and treatment.

The effectiveness of this pragmatic approach is evidenced, among other measures, by the relatively small proportion of injecting drug users who are AIDS patients in the Netherlands (12%) compared to the United States (24%) and Europe at large (38%) (Van Laar et al., 1995). In addition, deaths attributable to drug addiction (as a primary or secondary cause) of death remain quite low in the Netherlands, where only 33 drug-related deaths of Dutch residents were registered in 1995 (De Zwart and Van Wamel, 1998). In Amsterdam and Rotterdam, the cities with by far the largest population of heroin users and addicts, 16 and 14 deaths occurred respectively in 1996 (De Zwart and Van Wamel, 1998).

Taken together, these findings suggest that methadone maintenance treatment is widely available in the Netherlands. At least 50% of all heroin addicts are currently enrolled in one of these programs, which serve a stable and aging population of chronic heroin addicts with long addiction and treatment careers. It was also observed that a substantial number of the methadone patients regularly use illegal heroin and other illegal drugs. Approximately 8,000 of the 12,500 methadone maintenance patients function at less than optimal levels, exhibiting low levels of medical and psychosocial functioning, and about 3,000 of them are engaged in high levels of criminal behavior.

There has been a growing awareness of the limited success of the treatment efforts in these sub-populations, despite extensive attempts by professionals to improve the living conditions of these chronically addicted patients. In addition, there have been repeated calls for reductions in the public nuisance which results from their criminal behavior. These aspects have led to various attempts to prescribe opioids other than oral methadone for the treatment of chronic, and especially treatment-resistant heroin addicts in the Netherlands. These efforts are briefly discussed in the next paragraph.

1.5 Prescription of opiates other than oral methadone in the Netherlands

In the Netherlands, there have been three small-scale experiments – all in the city of Amsterdam – involving the prescription of opioids other than oral methadone in the substitution treatment of heroin users. In 1983, the Minister of Health, Welfare and Sports approved a small-scale morphine dispensing program for heroin addicts in Amsterdam. At the same time, the city council of Amsterdam announced its plans for the initiation of a large-scale heroin dispensing program for approximately 300 drug users. This latter plan was not approved by the Dutch government, however, and the program was never implemented (Brussel, 1997a; Derks, 1997).

The morphine dispensing program started at the end of 1983 with a group of 37 very problematic heroin addicts, and was to run for an experimental period of two years. Most of these patients received a combination of intravenous morphine along with a basic dose of oral methadone. The results of the study suggested a beneficial effect (reduced levels of illegal heroin use and criminality) for approximately half of the participants. However, these results could not simply be attributed to the co-prescription of intravenous morphine, because the study lacked a control group. In addition, 11 participants abandoned the treatment program within the first year because they were dissatisfied with morphine and/or were suffering from histamine reactions following its administration (Derks, 1984, 1990). By 1993, ten years after the start of the project – which was supposed to run for only two years – seven of the original 37 patients were still receiving intravenous

morphine, 14 patients had returned to oral methadone maintenance treatment, one was known to be drug-free and 15 had died (five committed suicide, six died from AIDS, two had developed lung cancer, and two died of a drug overdose). These data clearly indicate a high mortality rate, although most of these deaths were not considered to be related to the program itself, but instead reflected the severity of the patients' level of pathology at treatment entrance. Nevertheless, the experimental program demonstrated that prescription of injectable opioids is feasible, that very little morphine leaked to the black market and that some of the patients did improve. When the experiment ended, no new patients were recruited because when given a choice, most patients preferred injectable methadone.

In 1990, the Amsterdam Municipal Health Service started a second quasi-experiment, involving the prescription of intravenous methadone to 30 severely addicted AIDS patients, all suffering from a very poor health condition. The treatment had to be terminated for nearly half of the patients, however, because they failed to comply with the treatment regimen. From the remaining group, many patients subsequently died. Among the patients who continued treatment, clear improvements were reported in the therapeutic relationship with the treatment staff. In addition, the heroin use of these patients decreased considerably, although it did not stop (Van Brussel et al., 1996).

In 1995, the Amsterdam Municipal Health Service started a third experimental program, involving the prescription of oral dextromoramide (Palfium^R) in addition to oral methadone to 53 severely addicted non-injecting heroin users with an average addiction career of 21 years, who had not responded well to earlier methadone treatment. The goal of this treatment was to alleviate the patients' suffering and to stabilize their heroin use. Unfortunately, the experimental program was not systematically evaluated. The general impression of the project staff was that the treatment with Palfium resulted in improved social functioning of the patients, and in a better relationship with the treatment services. A clinical evaluation suggested that heroin use had decreased among most patients, and that one patient had actually stopped his heroin use. In addition, urinalysis tests revealed no increase in the use of cocaine. Lastly, the termination of the Palfium prescription to those patients who had not benefited from the treatment did not cause problems (Van Brussel, 1997b).

To summarize, while reflecting an active debate regarding the medical prescription of opioids other than oral methadone to chronic, treatment-resistant heroin addicts, the three experimental treatment programs described above all involved very small groups of heroin addicts with rather specific needs, lacked a control condition, and the results were not adequately documented. Given these limitations regarding the effectiveness of the treatments, the generalizability of their results, and the absence of data in the Netherlands regarding the medical prescription of heroin, the Health Council of the Netherlands (1995) had to turn to scientific evaluations of experiments with heroin in other countries, including the United Kingdom (Hartnoll et al., 1980) and Switzerland (Uchtenhagen, 1996a), when discussing the desirability of medical prescription of heroin to Dutch heroin addicts. These evaluations are summarized in the next paragraph.

1.6 Effectiveness of medically prescribed heroin

In the past decades, several countries have gained experience with the prescription of heroin to heroin addicts. This experience goes back to as far as the 1920's, when physicians in the United States and the United Kingdom started to prescribe heroin to morphine addicts for both detoxification and maintenance purposes (Drucker and Vlahov, 1999; Zador, 2001). With the

'heroin epidemic' in the late 1960's, the National Health Service (NHS) drug clinics in the United Kingdom took over the responsibility for prescribing injectable heroin from individual physicians, who were no longer allowed to prescribe heroin to heroin addicts. During the following years, the NHS clinics began to switch the prescribed substance from injectable heroin to injectable methadone and since the mid-1970's to oral methadone (Mitcheson, 1994). During this period of transition (1972-1975), a randomized clinical trial was conducted, comparing the effectiveness of medical prescription of injectable heroin (the former standard treatment) with a medical prescription of oral methadone (the new treatment) (Hartnoll et al., 1980).

The study of Hartnoll, Mitcheson and their colleagues represents the only controlled trial that has been conducted with heroin, prior to the current Dutch trials (Hartnoll et al., 1980). The study population consisted of 96 clients, with a mean age of 23.9 years (range 18-32 years), an average duration of opiate addiction of 5.9 years, and a history of daily heroin injection for at least three months. All participants were strongly committed to continue their drug use. After an extensive intake procedure (during which the patients were not informed about their participation in a trial), the patients were randomly assigned to either treatment with injectable heroin (44 persons), or treatment with oral methadone (52 persons), both prescribed on an outpatient maintenance basis. The prescribed daily heroin doses ranged from 30 to 120 mg, with most prescriptions ranging from 40 to 80 mg, and the daily methadone doses ranged from 10 to 120 mg.

The study produced equivocal results, in that no clear indications were obtained that one treatment produced better overall results than the other. Both treatments showed positive outcomes in certain areas, and negative ones in others. For example, treatment compliance was considerably higher among the patients in the heroin condition than among those in the methadone condition, and they also demonstrated a greater reduction in their illegal heroin use and criminal activities. On the other hand, more patients in the methadone condition had reached abstinence at the one-year follow-up assessment, compared to their heroin condition counterparts. No differences were found with respect to the other areas under investigation, including work performance, housing status, diet or physical complications arising from the patients' drug use, neither from pre- to post-treatment status, nor between the two treatment groups. In addition, no pre-treatment patient factors could be detected, which were clearly indicative for the patients' status after treatment. In addition to these results, most patients in the heroin prescription group could be successfully persuaded after completion of the trial to convert from prescribed injectable heroin to oral methadone, which led the investigators to conclude that a maintenance dose of injectable heroin for a limited period of time does not have adverse consequences on the long-term status of the patients.

Based on the results of this early study, the investigators argued that the (differential) results suggest that the choice for one or the other treatment approach depends on the priorities assigned to the various outcome domains: either helping a minority of heroin addicts to terminate their drug use (by means of methadone maintenance), or helping as many addicts as possible to improve their situation (by means of injectable heroin maintenance). Nevertheless, the findings were used by many to infer that injectable heroin maintenance treatment should be dropped in favor of oral methadone maintenance. Following a heated debate, many of the clinics shifted towards a more interventionist therapeutic approach, and new patients were refused prescribed injectable heroin (Mitcheson, 1994). In 1994, only 1-2% of the estimated 75,000-150,000 heroin users in the United Kingdom had actually received a prescribed supply of any injectable drug, and only a small proportion had received injectable heroin (Strang et al., 1994). Based on a postal survey of community pharmacies in the United Kingdom, heroin accounted for less than 1.7% of all prescriptions in 1995 for treatment of opiate dependence (Strang et al., 1996). More recently, the number of heroin addicts who had received injectable heroin on medical prescription in the year

2000 had dropped to an estimated 400 persons, the majority of whom received their prescriptions from a total of 20 licensed physicians (Metrebian, 2000).

Despite this trend towards decreasing injectable opiate prescriptions, Metrebian and her colleagues (1998), when investigating the prescription of injectable opiates to opiate dependent drug users in the mid 1990's, concluded that the prescription of injectable heroin and methadone is a feasible treatment option for long-term injecting drug users, who had previously tried and failed oral methadone and who were unable or unwilling to give up injecting (Metrebian et al., 1998).

The most recent experience with the prescription of opioids other than oral methadone derives from Switzerland. In 1994, the Swiss started a large-scale study into the effects of prescribing injectable and smokeable heroin, injectable and oral morphine, and injectable and oral methadone, as part of a comprehensive national treatment strategy. Based on the positive results of this study, involving a total of 1,969 opiate dependent drug users who began medical treatment with heroin between January 1994 and December 2000 (Rehm et al., 2001), as well as the support which the prescription practice received in a national referendum on the issue, the medical prescription of heroin continues to be an established treatment at the time of writing this report.

According to the reports produced by the investigators (Uchtenhagen et al., 1996a, 1996b, 1997, 1999; Rehm et al., 2001), and an independent process evaluation conducted by the World Health Organization (WHO, 1999), the results of the Swiss heroin experiment have indeed been positive, with high treatment retention rates (86% after three months, 70% after 12 months, and 50% after 30 months), considerable reductions in the use of illegal drugs (heroin and cocaine) and in the level of the participants' criminal activities, substantial and stable improvements in the domains of physical health, psychological well-being, housing and employment, and a substantial reduction in the number of contacts with drug users and the drug scene in general (Rehm et al., 2001) (see Table 2).

Table 2. Changes in the patients' status in the Swiss heroin study ($n = 237$)

<i>Variable</i>	<i>Baseline</i>	<i>6 months</i>	<i>12 months</i>	<i>18 months</i>
- (nearly) daily consumption of illicit heroin	82 %	9 %	4 %	6 %
- (nearly) daily consumption of cocaine	29 %	7 %	4 %	5 %
- (nearly) daily consumption of benzodiazepines	19 %	12 %	15 %	9 %
- unstable housing situation	43 %	31 %	24 %	21 %
- homeless	18 %	8 %	1 %	1 %
- unemployed	73 %	48 %	44 %	45 %
- receiving welfare payments	63 %	60 %	61 %	54 %
- financial debts	74 %	74 %	73 %	67 %
- illegal income	69 %	17 %	14 %	11 %
- severe physical health problems	22 %	12 %	13 %	13 %
- severe psychiatric problems	37 %	20 %	17 %	19 %

In addition to these findings, it is important to note that no public order problems were encountered, and no fatalities could be attributed to the study medications used. Finally, the cost-benefit analysis revealed an overall net economic benefit of € 35 (approx. 45 Swiss Francs) per patient per day, compared to treatment as usual (mainly methadone maintenance).

Although the Swiss experiment has clearly shown that medical prescription of heroin is feasible, and that methadone with co-prescribed heroin, combined with adequate psychosocial support, can lead to considerable improvements in the medical, psychiatric, and social condition of highly dysfunctional

opiate addicts, the study has some important limitations from a scientific point of view, which prevent a conclusive answer to the question whether the medical prescription of heroin itself caused the observed improvements.

First, the results are based on a single group pre-post design, i.e. without a control condition, and hence, without reference to the development in similar patients in non-experimental treatment conditions. Within that design, it should be noted that the presented follow-up data were obtained from only 237 of the 385 patients (62%) who entered the project until March 1995 and remained in the program for at least 18 months (Uchtenhagen et al., 1999; Rehm et al., 2001). Although the Swiss collected data at a later stage on patients in various standard methadone programs, and conducted ad hoc comparisons of the treatment results of these patients with those of the experimental group, these comparisons – which involved statistical matching procedures to control for differences between the experimental and comparison groups – lack the strengths of a randomized design. In addition, it should be noted that the Swiss study did include four rather small randomized trials, in some of which a double-blind procedure was used. Three of these studies were, however, not intended to evaluate the long-term effects of heroin prescription, but to investigate the short-term effects associated with the different experimental substances (intravenous heroin, intravenous methadone, and intravenous morphine) on patient recruitment, treatment retention, treatment compliance, and side-effects. The only randomized trial examining the long-term effects of heroin prescription was a small study conducted in Geneva (Perneger et al., 1998). In this study, 51 treatment-resistant heroin addicts were randomly assigned to either intravenous heroin, combined with additional health and psychosocial services or to some other type of conventional drug treatment, usually oral methadone maintenance. After six months, almost all of the patients using prescribed heroin had stopped their illegal heroin use, and their psychological and social functioning (as measured by the frequency of suicide attempts and the level of criminal activities) was much better than that of the patients in the control group.

Second, it is important to note that no attempts were made in the Swiss study on the long-term effects of medically prescribed heroin to investigate the effects of the prescription of heroin alone, i.e. without mandatory counseling and other psychosocial interventions. Hence, the Swiss experiments do not provide information about the effect of the prescription of heroin per se, but about the effect of a combined package of pharmacological (heroin) and psychosocial interventions, compared to more usual treatment (methadone maintenance without obligatory counseling and less psychosocial support) or no treatment at all. Consequently, it is possible that the benefits of the Swiss heroin maintenance programs could at least be partially attributable to the additional and sometimes mandatory psychosocial interventions (Perneger et al., 1998).

Third, it should be noted that the Swiss experiment with smokeable heroin, in the form of heroin reefers (surrogate cigarettes), failed due to the low bio-availability (10-15%) of the heroin from these cigarettes: due to pyrolytic degradation, an average of 85-90% of the heroin in the cigarette did not enter the body of the patient (Seidenberg and Honegger, 1998).

In summary, the Swiss experiences suggest that the medical prescription of injectable heroin is both feasible, medically safe, and potentially effective in chronic, treatment-resistant heroin addicts, at least under the investigated circumstances, i.e. when the prescription is medically controlled, no take-home heroin is provided, and if psychosocial services are provided (e.g. Wodak, 1998). Important questions, however, remain unanswered, particularly pertaining to the causal attribution of the observed improvements to the experimental treatment, the relative contribution of the prescription of heroin in a combined pharmacological and psychosocial treatment program, and the effects and effectiveness of medically prescribed inhalable heroin. In line with this point of view, a special committee of the World Health Organization (WHO, 1999) concluded in its independent process

evaluation, that the Swiss studies "(...) have shown that it is medically feasible to prescribe intravenous heroin as a maintenance drug, at least under the conditions that prevailed during the studies." (p. 10), but also that "The Swiss studies were not able to examine whether improvements in health status or social functioning in the individuals treated were causally related to heroin prescription per se or a result of the impact of the overall treatment programme." (p. 1).

1.7 Rationale for the study

The review of the available information regarding the results of methadone maintenance treatment in the Netherlands indicates that, although heroin addicts have a wide range of treatment modalities at their disposal and the treatment provided is adequate for a large number of addicts, there is also a considerable number of addicts for whom stabilization or improvement is difficult or impossible, despite intensive participation in methadone maintenance and/or other treatment. From a total of 24,000 heroin addicts in the Netherlands, it was estimated that approximately 8,000 addicts fall into this category (Driessen, 1990).

To meet the treatment needs of these addicts, for whom previous treatment has not yielded sufficient results, supplementary types of treatment are needed. On a limited scale, experiments have been conducted with injectable morphine, injectable methadone and oral Palfium, but these interventions lacked a scientific evaluation, and produced inconsistent results (morphine) or were aimed at palliation (injectable methadone and Palfium). Another option which has been under consideration is the prescription of increased dose levels of oral methadone, but since heroin addicts in the Netherlands generally reject high methadone dosages (Korf et al., 1998), this approach holds the risk of low compliance. To investigate the effects of such an approach, a randomized study is currently being conducted in the Netherlands into the effectiveness of medically prescribed oral methadone in dose levels of at least 80 mg a day in chronic, treatment-resistant heroin addicts (Driessen, 2000), the results of which are expected to be available in the year 2002. Prior to the start of the current study, there have been no experiences with the medical prescription of heroin to heroin addicts in the Netherlands.

Nearly all of the experience with the prescription of heroin stems from the United Kingdom and Switzerland. In the United Kingdom, however, the randomized trial by Hartnoll and his colleagues involved a small number of participants, who were quite young (mean age of 24 years), had a short addiction career (average of six years), and who all injected their heroin. In addition, the study was conducted in the early 1970's, when the heroin epidemic was at a much earlier stage, and methadone maintenance treatment was a new type of treatment. In the following decades and up till recently, only a small proportion of the heroin users in the United Kingdom received heroin maintenance treatment. In addition, the results of these treatments have been poorly documented, and no systematic scientific evaluation has taken place. The Swiss experiment has indicated that medical prescription of heroin is feasible and potentially effective in highly dysfunctional opiate addicts, but questions remain with regard to the causal attribution of the improvements, the relative contributions of the heroin component and the psychosocial component to the results of the combined treatment, and the effectiveness of medical treatment with inhalable heroin.

Given the existence of a sizeable group of heroin addicts in the Netherlands whose treatment needs are insufficiently met, and against the background of the positive experiences obtained in Switzerland, the medical prescription of heroin to treatment-resistant heroin addicts merits further

investigation in a randomized controlled study. Starting points of this study are the utilization of randomized group assignment and subsequent comparison of patients in oral methadone maintenance treatment with similar patients in oral methadone and co-prescribed heroin treatment, who receive a similar offer of psychosocial counseling and support in both treatment conditions. In addition, given the predominance of heroin inhalation among Dutch heroin addicts, a new effort should be made to study the effectiveness of the medical prescription of inhalable heroin to non-injecting heroin addicts. Finally, it is important to note that neither in the United Kingdom, nor in Switzerland, nor in the sparse literature on treatment with heroin in earlier years, any indications have been found that the prescription of heroin to heroin addicts on a medical basis would harm those involved to such an extent that an experiment with this type of treatment would be ethically unacceptable.

1.8 Objectives of the study

The primary objective of the study was to evaluate the beneficial and harmful effects of 12 months of maintenance treatment with oral methadone and co-prescribed heroin, compared with standard maintenance treatment with oral methadone alone. The study population consisted of chronic, treatment-resistant heroin addicts who were currently enrolled in methadone maintenance programs. The main effect of the medical co-prescription of heroin was evaluated in terms of (1) improvements in the physical and mental status of the patients, (2) improvements in their social integration and social functioning, and (3) changes in the patient's illicit drug use. The primary study question was investigated separately for the prescription of injectable and inhalable heroin.

The secondary study objectives included (a) a comparison of the effects of co-prescribed heroin given for six months and 12 months duration, (b) an evaluation of the effects of the discontinuation of co-prescribed heroin after six and 12 months of treatment with co-prescribed heroin, (c) an evaluation of the effect of co-prescribed heroin on patient satisfaction, and (d) an investigation of prognostic factors for positive treatment outcome, in order to generate hypotheses for future patient-treatment matching strategies.

In this report, the findings are presented with regard to the primary study objective, and first two secondary objectives. In subsequent reports, the last two secondary study objectives will be investigated.

PART II

STUDY DESIGN AND METHODS

Chapter 2

Methods

2.1 Study population

2.1.1 Target population

According to the advisory report of the Health Council of the Netherlands (1995), the study should be directed to the treatment of severely addicted heroin users who have not (sufficiently) responded to currently available medical interventions. To qualify for participation, patients are required to have repeatedly and unsuccessfully participated in treatment programs, aimed at – by means of medication in adequate dose levels and dose frequency – stabilization and the prevention of relapse (Health Council, 1995). The Dutch government added to this description that the study should be restricted to “older patients with a long addiction career, whose psychosocial condition is without perspective” (Ministry of Health, Welfare and Sports, 1995). According to the Committee of the Health Council, other categories of addicts would in principle qualify for a medical-scientific study with heroin as well. These addicts may be "difficult or impossible to reach", not (yet) as severely addicted to heroin, have not "repeatedly but unsuccessfully" participated in treatment programs aimed at relapse prevention and stabilization, and may still have a genuine possibility to stop their heroin use. Although neither the literature, nor past experiences contain convincing arguments against the prescription of heroin to this group in a controlled trial, the Committee of the Health Council argued that current knowledge provides insufficient arguments to justify, in ethical terms, the recruitment of patients who have not first tried the currently available treatment modalities in the first clinical trial with medically prescribed heroin.

Hence, the target population has been operationally defined in the study protocol (CCBH, 1997, 1999a) as the sub-population of chronic heroin addicts who have been treated repeatedly but unsuccessfully in methadone maintenance programs. In addition, the decision to limit the study population to this group of patients was based on the following considerations: (1) a considerable number of patients in methadone maintenance programs fit the description of the target group; these patients have been described earlier in this report as "not integrated" and "extremely problematic", (2) the problems of methadone maintenance patients in the Netherlands are quite similar to those of heroin users currently not in contact with the treatment system (Eland-Goossensen, 1997); this, in turn, may be related to the "low threshold" character of most Dutch methadone maintenance programs, (3) the registration systems of the methadone programs provide a clear sampling frame for the selection of study subjects, and (4) a combination of data from the methadone and the heroin registration systems can prevent the prescription of double (methadone and heroin) dosages. With regard to the validity of the study findings, the decision to limit the study population to treatment-resistant methadone maintenance patients may increase the internal validity.

2.1.2 Selection criteria

Following the study protocol, all study subjects were selected from the local methadone maintenance treatment registration systems, according to a predefined set of inclusion and exclusion criteria. These criteria are described in Table 3.

Table 3. Inclusion and exclusion criteria of the study

<i>Inclusion criteria</i>	<i>Exclusion criteria</i>
1. Treatment-resistant heroin dependency, as indicated by: <ol style="list-style-type: none"> a. a history of heroin dependency (DSM-IV) of at least five years; b. a minimum dose level of 50 mg (inhaling) or 60 mg (injecting) of methadone per day for an uninterrupted period of at least four week in the previous five years; c. in the previous year registered in a methadone program, and during the previous six months in regular contact with the methadone program; d. chronic heroin addiction and unsuccessfully treated in methadone maintenance treatment; e. daily or nearly daily use of illicit heroin; f. poor physical, and/or mental, and/or social functioning; 	1. Not meeting all inclusion criteria
2. Heroin is used through intravenous injection or inhalation	2. Severe medical, psychiatric or psychosocial problems which constitute a contra-indication for participation
3. At least 25 years old	3. Severe medical, psychiatric or psychosocial problems which may interfere with the conduct of the study
4. Citizen or legal resident in the Netherlands	4. A history of aggressive behavior which is expected to interfere with the conduct of the study and/or the participation in the study of other subjects
5. Registered as a resident in the city area of the treatment site for at least three years	5. Pregnancy or continued lactation
6. Willing and able to attend the treatment site for the required study assessments and other procedures	6. Unwilling or unable to attend the treatment site for the required assessments
7. Willing to attend the treatment site at least three days a week	7. A life expectancy not exceeding the study duration
8. Written informed consent	8. The heroin dependency is of secondary importance compared to an existing non-opiate dependency
	9. The patient is unwilling to use the prescribed heroin in the treatment site
	10. A period of voluntary heroin abstinence of at least two months in the previous year
	11. Patients requiring an oral dose of methadone exceeding 150 mg per day
	12. Patients requiring a dose of prescribed heroin exceeding 1000 mg per day
	13. Patients who currently participate in another trial involving anti-addiction treatment, or have participated in such a trial in the previous six months
	14. Patients unable to understand the Dutch language

From the inclusion criteria, the items 1a-1f refer to the severity and chronicity of the addiction problems, despite the patient's regular participation in a methadone maintenance program in which methadone has been prescribed in adequate dose levels. With regard to inclusion criterion 1a, the cut-off point of five years was chosen on the basis of a systematic review by Cramer and Schippers (1994) regarding the course and outcome of heroin addiction. They found that a major shift from drug use towards abstinence occurred in the first five years of the addiction career. Generally, after

five years approximately 20% of the population of problematic drug users had reached abstinence, and this percentage did not change much in the following five to 10 years (see also: Hser et al., 2001). Regarding inclusion criterion 1b, it is important to note that a methadone dose of 80 milligrams plus or minus 20 milligrams per day has been recommended as an effective dose in the American State Methadone Maintenance Treatment Guidelines (Parrino, 1992). Therefore, a daily dose of 60 milligrams can be regarded as the minimum dose level for methadone maintenance to become effective and a minimum requirement for the decision regarding treatment resistance. For methadone maintenance patients who inhale their heroin, given their usually lower methadone dose level (Buster and Van Brussel, 1996) and the lower bioavailability of inhaled heroin compared to that of injected heroin, the methadone dose level required for entering the study was adapted to a minimum of 50 milligrams per day.

In inclusion criterion 1c, the "regular" attendance of the methadone program was operationalized in terms of at least 50 visits during the previous six months for patients in a five-day per week methadone program, and at least 30 visits for patients in a three-day methadone program.

In inclusion criterion 1e, daily or nearly daily use of illicit heroin was operationalized analogous to the definition used in the Addiction Severity Index (McLellan et al., 1980, 1992; Hendriks et al., 1989) for regular heroin use. To be eligible for entering the study, subjects had to use illicit heroin at least three days a week during the previous month.

With regard to the operationalization of inclusion criteria 1f, the physical condition of the patient was assessed by means of the Maudsley Addiction Profile Health Symptoms Scale (MAP-HSS; Marsden et al., 1998). For entering the study, the patient had to have a MAP-HSS total score of at least 8 (see paragraph 2.9.1). The psychiatric status of the patient was measured by means of the Symptoms Checklist (SCL-90; Derogatis, 1983; Arrindel and Ettema, 1986). Based on the (different) distributions of the SCL-90 in male and female populations, a cut-off score of at least 41 was used for male patients and at least 60 for female patients for entering the study (see paragraph 2.9.1). With respect to the domain of social functioning, the patient should have had at least six days in the previous month in which he was involved in criminal activities, and/or at least six days without personal contact (of at least half an hour duration a day) with a non-drug-using person, in order to be eligible for the study. This criterion of "at least six days in the previous month" in the social domain was based on the face value of a threshold of at least 20% of the maximum possible score on these items (i.e. 30 days).

With regard to the exclusion criteria, it is important to note that the items 2, 3, and 4 were purposely described in general terms, i.e. without explicit operationalization, because these items were intended to exclude only those patients who *a priori* would be very likely to jeopardize a successful conduct of the study. On the basis of information about the target population, no more than 2-3% of the recruited patients were expected to be excluded from participation in the study. With respect to exclusion criterion 4, the history of aggressive behavior should have been indicated by the patient having repeatedly been expelled from a methadone program prior to the start of the trial. In criterion 5, the pregnancy should have been confirmed by urine screening. Exclusion criterion 6 included those patients who – on the basis of sentences that still have to be executed – anticipated to be incarcerated for a duration of at least three months during the study period. Exclusion criterion 10 was specifically aimed at excluding patients from participating in the study, who still had a genuine possibility to terminate their heroin addiction. Lastly, in exclusion criterion 11, the maximum methadone dosage was based on the maximum dose levels allowed in most Dutch methadone programs, which generally range from 70-120 mg a day, but occasionally involve higher dosages.

2.1.3 Recruitment and selection procedure

On the basis of the inclusion and exclusion criteria described above, the potential candidates for participation in the trials were recruited in a selection procedure which, in broad terms, involved the following steps:

1. pre-selection of a source population on the basis of the available information from the methadone treatment *registration system*;
2. patients in the source population were invited in a random order to an *initial meeting* with the physician of the local treatment unit; subsequent screening on various selection criteria and provision of oral and written information;
3. candidates who met the initial selection criteria and who provided initial informed consent entered the qualification period; an *initial screening* took place in which all selection criteria were examined;
4. four to eight weeks later a *final screening* was conducted among the candidates who had passed the initial screening; during this final screening, the most important selection criteria were again assessed, and final informed consent was obtained;
5. randomization took place with all patients who met all inclusion criteria and were not barred by any of the exclusion criteria at the final screening.

Step 1. Registration system

In the first selection step, the available information from the methadone maintenance treatment registration system was examined, with regard to the following selection criteria:

- heroin dependency of at least five years;
- registered in a methadone program and regular contact with the program;
- minimum daily methadone dose level of 50 mg (inhalation) or 60 mg (injecting) for at least four consecutive weeks in the previous five years;
- at least 25 years old;
- at least three years registered in the city area of the treatment site.

Step 2. Initial meeting

All patients who met the criteria described above received a randomly assigned patient identifier number, and were invited to an initial meeting with the physician of the local treatment site in the order of their identifier number. During this meeting, the patient received extensive oral and written information about the objectives and procedures in the study, the potential benefits and risks for the patient, and the expected co-operation during the study. In addition, the following selection criteria were examined:

- daily or nearly daily use of illicit heroin;
- the use of heroin through intravenous injection or inhalation;
- the ability to understand the Dutch language;
- the ability and willingness to participate in the study according to the requirements (e.g. life expectancy, visits required for the assessments, use of the prescribed heroin in the treatment site, an anticipated incarceration of no longer than three months).

Step 3. Initial screening

Patients who met the criteria described in step 2 and who were not barred by exclusion criteria were referred to the local research team and the physician for an initial screening assessment in the four to eight weeks qualification period of the study. Prior to the screening assessment, the physician obtained initial written informed consent from the patient. During this initial screening, the following selection criteria were examined:

- Dutch nationality or legally residing in the Netherlands;
- examination of the entry criteria concerning poor physical health, and/or mental health, and/or social functioning (see paragraph 2.1.2):
 - MAP-HSS score ≥ 8 ;
 - SCL-90 score ≥ 41 (male) or ≥ 60 (female);
 - at least six days of illegal activities in the previous month;
 - at least six days in the previous month without personal contact with a non-drug-using person;
- medical screening:
 - contra-indication for health reasons;
 - pregnancy or continued lactation;
 - life expectancy shorter than one year;
- contra-indication for aggressive behavior;
- otherwise not able to participate in the study (including expected incarceration \geq three months);
- voluntary heroin abstinence \geq two months in the previous year;
- requiring a daily dose of more than 150 mg of methadone and/or 1000 mg of heroin;
- participation in another clinical trial, directed at addictive behaviors.

Step 4. Final screening (baseline assessment)

Four to eight weeks after the initial screening, patients who met the criteria described in step 3 and who were not barred by exclusion criteria received their final screening assessment. Prior to the final screening, patients were asked to provide final written informed consent. The following selection criteria were examined:

- final informed consent;
- daily or nearly daily use of illicit heroin;
- examination of the entry criteria concerning poor physical health, and/or mental health, and/or social functioning:
 - MAP-HSS score ≥ 8 ;
 - SCL-90 score ≥ 41 (male) or ≥ 60 (female);
 - at least six days of illegal activities in the previous month;
 - at least six days in the previous month without personal contact with a non-drug-using person;
- medical screening (including psychiatric evaluation):
 - contra-indication for health reasons;
 - pregnancy or continued lactation;
 - life expectancy shorter than one year;
- heroin addiction of secondary importance compared to an existing non-opiate dependency.

Step 5. Randomization

Within three to four days after the final screening (baseline assessment), all patients who had provided informed consent, met all inclusion criteria, and who were not barred by any of the exclusion criteria were randomized to one of the treatment conditions. Within days following the outcome of the randomization procedure, all patients were orally informed by the local treatment staff about the treatment condition they were randomized to.

2.2 Study design

2.2.1 Randomized controlled trial

The study is a multicenter trial, including a total of 625 patients¹ who are treated in eight treatment units located in six cities in the Netherlands. After an intensive debate, the CCBH decided to develop

¹ In the original study protocol, three treatment conditions were distinguished for both injectable and inhalable heroin (CCBH, 1997), but given the low prevalence of intravenous injecting among heroin users in the Netherlands, the third treatment condition (group C) was omitted from the injectable protocol. As a consequence, the intended total sample size of the study decreased from $n=750$ to $n=625$ (see chapter 4).

the study as a traditional randomized controlled trial and not along the lines of a so-called pre-randomization or Zelen design (CCBH, 1997, 1999a).

The study was developed as a randomized controlled trial (see Figure 2). Three consecutive phases are distinguished in the study. During the four to eight weeks qualification period (phase I), the potential participants initially selected from the methadone treatment registration systems were screened on all selection criteria (see paragraph 2.1.2). At the end of the qualification period, and following the baseline assessment, a decision was made as to which trial (injectable or inhalable heroin) the patient would participate in, and all eligible patients were randomized to one of two (trial on injectable heroin: group A or B) or three (trial on inhalable heroin: group A, B or C) treatment groups (see chapter 4).

Figure 2. Design of the trials

<i>Qualification and randomization</i>			<i>Experimental study period</i>		<i>Follow-up period</i>
<i>Route of administration</i>	<i>Phase I 4 – 8 weeks</i>	<i>Group</i>	<i>Phase IIa 6 months</i>	<i>Phase IIb 6 months</i>	<i>Phase III 6 months</i>
INHALING	methadone	A	methadone	methadone	methadone + heroin
		B	methadone + heroin	methadone + heroin	most appropriate care *
		C	methadone	methadone + heroin	most appropriate care *
INJECTING	methadone	A	methadone	methadone	methadone + heroin
		B	methadone + heroin	methadone + heroin	most appropriate care *

* No medically prescribed heroin, except on individual medical indication.

Patients randomized to group A received oral methadone during the 12 months experimental phase of the study (phase II), in combination with a standard offer of psychosocial interventions. Patients in group B received a combination of oral methadone and heroin on medical prescription during the 12 months period of phase II, in combination with the same standard offer of psychosocial interventions. In group C, which is only applicable in the trial on inhalable heroin, patients received oral methadone alone during the first six months of the experimental phase (phase IIa), and a combination of oral methadone and co-prescribed heroin during the second six months of the study (phase IIb), both again with the same standard offer of psychosocial interventions. Major outcome assessments were conducted after six (end of phase IIa) and twelve (end of phase IIb) months of treatment, i.e. six and twelve months after randomization. The primary outcome assessment of the study took place at the end of the experimental study period, at the month 12 assessment-point.

Follow-up phase

Following the end of the experimental phase, all subjects entered a naturalistic follow-up period of six months (phase III). Patients who had been assigned to group A were then given the opportunity to receive the experimental treatment with methadone and co-prescribed heroin for a period of six months. The prescription of heroin in groups B and C was terminated at the end of phase IIb and replaced by an offer to return to the methadone maintenance treatment program or to any other form of standard addiction treatment ("most appropriate care"). This was true for patients who had been successfully treated with co-prescribed heroin ("responders"), and for those who had not benefited

from the experimental treatment with heroin ("non-responders"). For the group of non-responders in phase II, the termination of the prescription of heroin was final. A similar situation occurred for those responders to the experimental treatment who had not deteriorated two months after the termination of the heroin prescription: no further heroin was prescribed to these patients. Heroin prescription could, however, be reinstated in those responders to the experimental treatment who subsequently demonstrated substantial deterioration (i.e. $\geq 20\%$ of the problem severity at the time of the baseline assessment) in their functioning after two months following termination of the experimental treatment. In these cases, the treating physician had the possibility to offer co-prescribed heroin on medical indication in individual cases.

The decision to terminate the treatment with co-prescribed heroin at the end of the experimental phase for all patients was made on both medical-ethical and scientific grounds. If the experimental treatment has not been shown to be effective for a patient, there is no medical justification to continue the experimental treatment. If, on the other hand, the experimental treatment has been shown to be effective for a patient, it can not be excluded that there will be enduring stabilization or improvement after termination of the experimental treatment. In this case, continuation of the experimental treatment in these subjects would be unjustified. Hence, continuation of the experimental treatment only applied to patients who had benefited from the treatment and who showed considerable deterioration after stopping the treatment. To obtain information about these possible scenarios, the treatment must first be terminated, and the consequences of termination must be investigated. In addition, it is important to note, that the effectiveness of treatment with co-prescribed heroin was not (yet) demonstrated on the group level at the end of the experimental treatment period of a patient. In the absence of such evidence, and given that heroin is not yet registered as a medication for the treatment of heroin addiction, it is therefore not justified to continue the treatment with heroin, with the exception of heroin on medical indication and in individual cases as a form of compassionate use.

2.2.2 Separate trials for injectable and inhalable heroin

In the study, heroin was prescribed in an intravenous injectable and inhalable form. For the study on injectable and inhalable heroin, two separate protocols were developed. These protocols are identical, with the exception of those aspects which refer to the route of administration of the co-prescribed heroin (e.g. inclusion criteria). The rationale for conducting two separate trials, each requiring a separate randomization procedure and a separate control group, was that inhaling and injecting heroin addicts were expected to differ considerably in terms of – for example – ethnicity, pattern of drug use, and health status. Given these expected differences, it could not be assumed *a priori* that these two populations would respond similarly to the experimental treatment. In addition, it could not even be excluded *a priori*, that one group would respond favorably and the other group would not respond or even respond unfavorably to the experimental treatment. Lastly, route of administration is an important parameter in any clinical trial involving an investigational product.

The decision whether the patient should receive the co-prescribed heroin in inhalable or injectable form was made by the treating physician in agreement with the patient, on the basis of the patient's physical health condition and his past and current pattern of heroin administration. Patients who had been assigned to the injectable route of heroin administration in the trial had the opportunity to switch to medically prescribed inhalable heroin. Both forms of heroin, however, were not prescribed simultaneously to the same patient. If an injecting patient had switched to prescribed inhalable heroin, he was required to stay in the inhalable condition for a minimum period of two weeks before he was allowed to switch back to injectable heroin on medical

prescription. Participants who had been assigned to the inhalable condition at the start of the study were not allowed to switch to medically prescribed injectable heroin in the study. Lastly, it is important to note that the patients remained in the trial they were assigned to at the start of the trial, regardless possible switches in their route of administration of the medically prescribed heroin during the trial. Hence, patients in the injectable trial who had switched to prescribed inhalable heroin during the trial, were analyzed as participants in the injectable heroin trial.

2.2.3 Blinding

Because methadone maintenance treatment has been shown to reduce mortality due to natural causes and overdose in opiate addict populations (Grönbladh et al., 1990; Langendam et al., 2001), it would be unethical to use placebo in the control condition of the trials. Therefore, and since methadone maintenance treatment constitutes the most applied standard reference treatment for opiate addiction in the Netherlands, methadone was used as medication in the control condition. In the experimental condition of the trials, heroin was used as an add-on to methadone (add-on study). The rationale for prescribing methadone in combination with heroin in the experimental condition is that methadone, with its longer pharmacological action, prevents the occurrence of withdrawal symptoms during periods that the prescribed heroin is not available to the patient, e.g. when a patient is not able to visit the treatment site.

Given the nature of the medications under study – co-prescribed heroin and methadone in the experimental condition and methadone alone in the control condition – serious constraints are laid upon the use of the normally favored double-blind randomized, placebo-controlled study design (see also: Bammer et al., 1999). Application of the double-blind procedure – by the addition of a placebo treatment to methadone in the control condition of the trials – is problematic, because the psychopharmacological effects of heroin and methadone – versus placebo – are immediately recognized by opiate users. The blindness of the study would be compromised, because the subjects recognize immediately that they are receiving placebo, because they do not experience a "buzz" or "hit". For these reasons, the application of the double-blind placebo-controlled study design was rejected in this population of subjects, and with this pharmacological compound. The comparison between the control condition and the experimental condition was, therefore, made in a randomized, parallel groups design without blinding (open-label trial).

In order to reduce the risk of information bias, outcome assessments were conducted by independent assessors, who used standardized instruments and evaluation procedures. In addition, the validity of the self-report data was checked through the application of urinalysis, with regard to the concurrent use of illicit drugs, and collection of registered data from the police and justice system, with regard to committed offenses and periods of detention. These latter types of data are insensitive to information bias.

2.2.4 Randomization

The randomization was organized centrally by an independent monitoring organization, and conducted separately for the trials on injectable heroin and inhalable heroin. In order to maximize comparability of the treatment groups within the participating treatment sites and within gender and ethnic groups, the randomization was conducted for each treatment site separately, utilizing gender and ethnicity as stratification variables in randomization blocks of three (inhalable heroin trial) or two (injectable heroin trial) participants. To achieve the predetermined proportions of the treatment group sizes, the subjects within each block were randomized to the treatment conditions with a predetermined ratio of 135 : 115 : 125 for groups A, B, and C respectively in the inhalable

heroin trial, and with a ratio of 135 : 115 for groups A and B respectively in the injectable heroin trial (see paragraph 3.1)

Randomization took place at the end of the qualification period, following confirmation of the eligibility of the subject by means of the baseline assessment. To this end, the local study co-ordinator sent a request for randomization of the subject to the central monitoring organization by telefax, in which he confirmed the subject's eligibility. The monitoring organization subsequently assigned a randomization group code (A, B or C) to the subject, and telefaxed the group code to the local treatment site, and a copy to the local study co-ordinator. This procedure ensured that the randomization was conducted fully independently from both the treatment staff, local research teams, and the National Research Board.

2.3 Multicenter study

In their advisory report, the Committee of the Health Council of the Netherlands recommended to conduct the trials at several locations and in various cities simultaneously (Health Council, 1995). The study was, therefore, set up as a multicenter trial, both in order to recruit the necessary number of study subjects within a reasonable time-frame, to be able to practically manage the study and the treatment sites involved, and to provide a better basis for the generalization of the study findings. In addition, from the perspective of risk of public nuisance and manageability, large numbers of patients at one location had to be avoided.

For reasons of manageability and cost-effectiveness considerations, the optimal capacity for each treatment site was determined at 40-50 participants who would simultaneously receive co-prescribed heroin. Within each participating treatment site, the largest number of participants simultaneously receiving co-prescribed heroin would occur in the course of phase IIb of the study (see paragraph 2.2.1). Based on the power calculations and expected drop out rates, it was originally anticipated that a maximum of approximately 440 subjects would simultaneously receive co-prescribed heroin during this phase. Following the protocol amendment with regard to the removal of a treatment condition in the injectable heroin trial (see chapter 4), this number was anticipated to amount to 360 subjects. Hence, a total of approximately eight treatment units were required in the study.

In order to qualify for participation in the study, each city which showed interest, had to meet a number of selection criteria, which included the availability of a sufficiently large number of addicts who qualify for the study, treatment facilities that would qualify, and willingness to co-finance the study. The criteria to be met by the participating treatment sites included the existence of a methadone maintenance program for at least one year, and the willingness and sufficient equipment, in terms of staff and facilities, to comply to all aspects of the study protocol. Six cities met these selection criteria. The eight treatment sites eventually selected for the study were situated in Amsterdam (two units), Groningen, The Hague, Heerlen, Rotterdam (two units), and Utrecht.

2.4 Stages of the study

The study was conducted in two stages. Following an intensive political debate in September 1997, the parliament of the Netherlands approved the execution of a test period of three months in

two cities (Amsterdam and Rotterdam), involving a total of 185 patients, of whom 50 patients would receive medically prescribed inhalable ($n=25$) or injectable ($n=25$) heroin (see also paragraph 1.1). The main purpose of the test period, which was conducted as an integral part of the total study, was to investigate whether the prescription of heroin was medically safe and would not lead to unacceptable public order problems. For the evaluation of these aspects, two independent committees – the National Safety Committee (LVC), and the National Committee on Public Order and Controllability (LCB) – were installed by the Minister of Health, Welfare and Sports, and the CCBH. Following the installation of the LVC and LCB in June 1998, the first treatment sites opened in Amsterdam and Rotterdam in July and August 1998. Four months later, in November 1998, the LVC and LCB reported to the Minister of Health, Welfare and Sports and to the CCBH that no unacceptable negative side-effects from the study or the treatment with co-prescribed heroin had been observed in either of the areas of interest. In accordance with the decision of the Dutch government and parliament in February 1999, the experimental treatment with co-prescribed heroin was subsequently continued in the already existing treatment sites in Amsterdam and Rotterdam, and extended in the course of the year 2000 to a total of the eight treatment units, situated in the six cities described earlier.

2.5 Ethics, informed consent, and remuneration

The study was conducted under the provisions of the Declaration of Helsinki, as amended in Hong Kong (1989). The study protocols, patient information form, and informed consent form and procedure were approved by the Central Committee on Medical Ethics of the Netherlands, prior to the start of the study. The study was conducted according to the specifications of the Dutch law and the ICH/EU guidelines for Good Clinical Practice (ICH, 1996). In addition, the central laboratory involved in the study was a CKCL-certified laboratory. The liability for study medication induced injury or damage was arranged in accordance with the Dutch law.

All study data were treated confidentially and processed anonymously. The data could only be made available to the treatment staff, police or the justice system after written consent of the patient. Conversely, the research-assistants could only obtain information about the patient from the treatment staff, police or the justice system after written consent of the patient. If utilized, these data were only used for the purpose of this study, and were treated confidentially. Each subject received a unique identification number, which did not contain initials and/or date of birth. These identification numbers were linked with the name and address of the subject on only one location, and were kept in a safe which could only be accessed by authorization from the study coordinator. In the Case Report Forms (CRFs) and other study documents, the subjects could only be identified by their unique identification number. Documents not for submission to the study coordinator (e.g. the patient's completed consent forms) were retained at each local treatment site in strict confidence. The CRFs and the subjects' medical records pertinent to the study were regularly reviewed by the independent monitoring organization. In addition, they could also be subjected to review by the study auditor(s), the medical ethics committee, and by representatives of the Inspectorate of Health Care. Any review was conducted with strict adherence to professional standards of confidentiality.

All potential candidates for the study received – in lay terms – extensive written and oral information about the objectives of the study, the study procedures, and the potential benefits, discomforts, and risks related to the study, prior to the start of the qualification period, and again

prior to the start of the baseline assessment. The subjects were explicitly informed that they could refuse to participate in the study, or withdraw from the study at any time, without consequences for further care and treatment. At the start of the qualification period, all potential candidates provided provisional written informed consent. Prior to the baseline assessment, all participants signed and dated the final informed consent form.

In addition to urinalyses (which took place monthly), the participants in the study were assessed every two months by means of questionnaires and interviews. For their co-operation with the assessments, each patient received a financial compensation of Dfl. 50,- (€23,-) per assessment (i.e. once every two months), but only during the periods that he/she received methadone alone in the study. This remuneration is comparable to the usual compensations given, and provides an incentive for continued participation, while being insufficient to substantially contribute to maintaining the addiction. Although the patients were not paid for the assessments during the periods that they received co-prescribed heroin, the remuneration of less than one Dutch guilder a day was expected to be too low to jeopardize the contrast between the experimental group and control group in the study. The participants were not required to pay for the prescribed heroin. From a medical-ethical perspective, it is not correct to let a patient pay for a yet unproven medication.

2.6 Non-adherence to the protocol

Non-adherence to the study protocol and non-compliance with the treatment procedures were documented on the various parts of the CRF. Reasons for non-adherence and/or non-compliance included refusal to (further) participate in the study and/or the treatment, death, imprisonment, unacceptable behavior (e.g. violence, smuggling heroin out of the treatment site), and moving to another city. All participants were approached by the research-assistants for all assessments, regardless of whether or not they complied to the study treatment schedule, or still participated in the treatment. Hence, only in exceptional cases – i.e. if a participant could definitely not be reached anymore for assessments – the treating physician filled out the study completion form prior to the end of the planned study period of an individual participant.

2.7 Organization and responsibilities

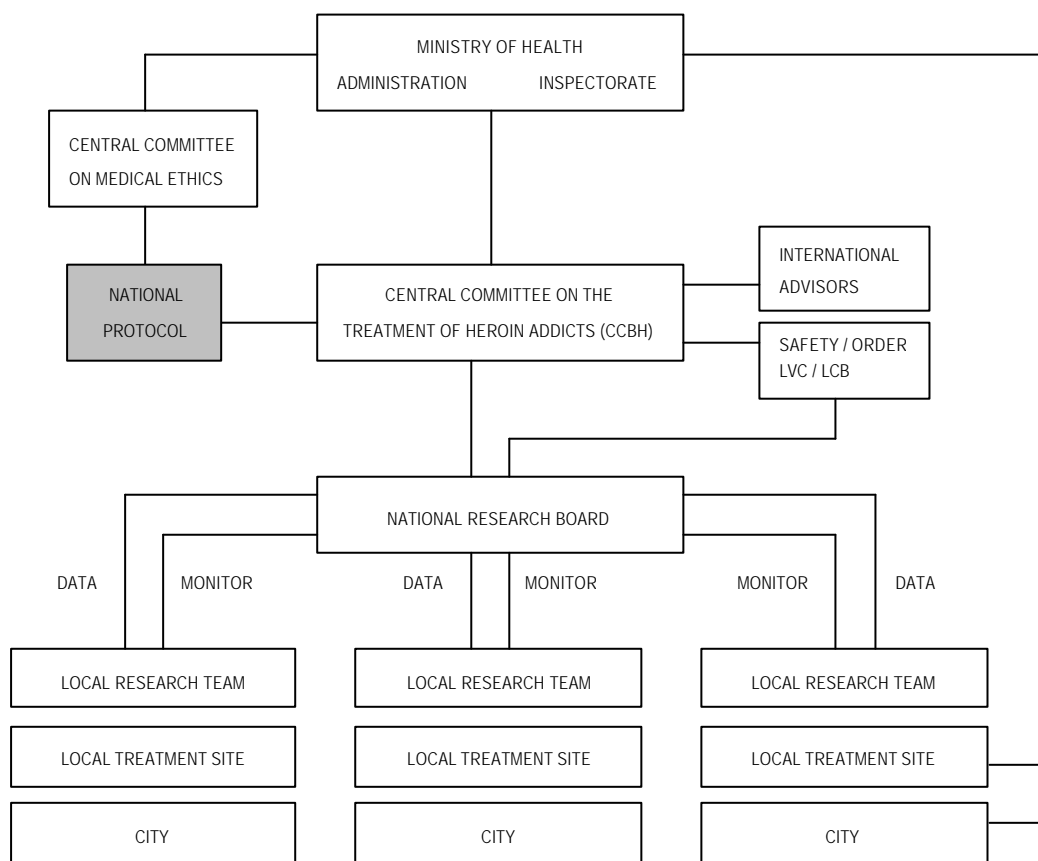
The study was conducted according to an organizational structure which involved participating groups on the national and city level. The responsibilities of the participating groups/participants are outlined below:

- The *Ministry of Health, Welfare, and Sports* commissioned and sponsored the study.
- The *Central Committee on the Treatment of Heroin Addicts (CCBH)*, installed by the Minister of Health, Welfare and Sports to develop and conduct the study, was responsible for the development, conduct and scientific quality of the study. The CCBH reports directly to the Minister of Health, Welfare and Sports. The composition of the CCBH and the expertise represented in the CCBH, are outlined in Appendix 3.
- The *National Research Board*, headed by the *research director*, was responsible for all technical and scientific aspects of the study, including the analysis of the collected data, and for the co-ordination of the treatment sites, monitoring, data collection and reporting of the study

findings (Appendix 4). The National Research Board reports to the CCBH, and – with regard to the medical safety and public order issues – to the LVC and LCB, respectively.

- The *Inspectorate of Health Care* observed and examined the quality of the care provided and the way and accuracy of registration of the prescribed heroin (drug accountability). The Inspectorate advised the CCBH, and was present as observer during the meetings of the CCBH.
- The *National Safety Committee (LVC)* advised the CCBH, with regard to the evaluation of severe adverse events and other medical safety issues (Appendix 4). This committee could also advise about possible premature termination of the study in case of a medically unacceptable negative balance between effectiveness and harm. The findings of the LVC with regard to the test period of the study were reported to both the CCBH, and the Minister of Health, Welfare and Sports.
- The *National Committee on Public Order and Controllability (LCB)* advised the CCBH, with regard to the evaluation of public order and public safety issues (Appendix 4). The findings of the LCB with regard to the test period of the study were reported to both the CCBH, and the Minister of Health, Welfare and Sports.

Figure 3. Organization of the study



- The draft national study protocol was submitted by the CCBH to independent *international scientific advisors* (Appendix 5).
- The national study protocol was submitted by the Minister of Health, Welfare, and Sports to the *Central Committee on Medical Ethics* of the Netherlands, and was approved by this committee. In addition, amendments to the protocol made in the course of the study were all submitted to, and approved by this committee.

- The *local research teams* were responsible for the collection of data on the local level, in compliance with the national study protocol. In this capacity, they operated independently from the local treatment sites. In each study site, a local study co-ordinator was appointed.
- The *local treatment sites* were responsible for the treatment with heroin and/or methadone, in compliance with the national protocol. The National Research Board monitored, through independent monitors, the execution of the treatment protocol.
- The *independent monitoring organization*, appointed by the CCBH, monitored the data collection and the execution of the treatments. The monitoring in this study was conducted by Kendle. The data management was handled by Imro Tramarko Group. Both the monitoring organization and the data management organization reported to the National Research Board.
- The *cities* involved in the study developed a protocol with respect to aspects of public order and controllability, and made a contract with the Ministry of Health, Welfare and Sports, to conduct the study without impediments.

2.8 Medication and treatment in the study

2.8.1 Objective of the treatment

The medical co-prescription of heroin to heroin addicts is regarded as an extension of the current medical treatment provided to heroin addicts in the Netherlands. The objective of the prescription of heroin is, therefore, connected to one of the main objectives of current care: to improve the health status and psycho-social functioning of addicts who do not sufficiently benefit from the currently available treatments and to prevent further deterioration. For those addicts who – by means of the prescription of heroin and the initiation of medical and social care – become or can be motivated to terminate their drug use, the achievement of abstinence becomes the primary goal of treatment. It should be emphasized that drug users are not "given up" when prescribing heroin, nor that it is accepted that these persons will remain addicted for the rest of their lives. Heroin prescription may be a new hold for heroin addicts for whom there has been no adequate treatment so far. By enabling drug users to return to their original intoxication through medically prescribed heroin, also the use of illicit drugs other than heroin may be reduced (Uchtenhagen et al., 1997; Perneger et al., 1998; Rehm et al., 2001). Most heroin addicts in the Netherlands consume a variety of illicit drugs in addition to heroin. In recent studies, it is estimated that 80-90% of the opiate addicts is also using cocaine, often in the form of crack (Blanken et al., 1996a, 1999; NDM, 2001). In this combination, illicit heroin is sometimes used to reduce the strong stimulating effects resulting from the use of cocaine. Benzodiazepines and alcohol are often used as a relatively cheap substitute for heroin (Benschop et al., 1997). In addition, through the prescription of heroin, medical and social care may be initiated and efforts may be undertaken to help these addicts to structure their lives, and – for some addicts – to achieve abstinence from drugs. For example, 10% of the patients admitted to the Swiss heroin program (22% of all discharges) left the program to start abstinence oriented treatment (Rehm et al., 2001).

2.8.2 Prescribed medications

The medications prescribed in the study were heroin (in injectable hydrochloride and inhalable base form) and oral methadone (hydrochloride). As described in paragraph 2.2.3, methadone was selected as medication in the control condition of the trials, because methadone treatment constitutes the most applied standard reference treatment in the Netherlands. In addition,

methadone was used in combination with heroin in the experimental condition of the trials to prevent withdrawal symptoms during periods that the prescribed heroin is not available to the patient. Hence, subjects in the experimental condition received co-prescribed heroin and methadone, and subjects in the control condition methadone alone. Methadone prescription and dispensing took place in existing treatment locations with an existing treatment-staff, whereas the combined prescription of methadone and heroin took place in newly established locations, with specially recruited staff-members.

Methadone

Similar to the procedures followed in most methadone programs in the Netherlands, methadone was prescribed in the study in oral form once a day (standard methadone treatment). The methadone dose prescribed to an individual patient was determined by the treating physician during the qualification period of the study, using clinical titration procedures. In phase IIa and IIb of the study, an effort was made to maintain the subjects on this initial methadone dosage. A minimum daily methadone dose level of 30-50 mg was recommended. The maximum daily dosage of methadone permitted in the study was 150 mg.

Heroin

Heroin was prescribed in intravenously injectable form (heroin hydrochloride) and inhalable form (heroin base). Given the shorter pharmacological action of heroin compared to that of methadone, the heroin was dispensed three times a day, divided over the day. To avoid the risk of the prescribed heroin being sold "on the street", the heroin had to be taken under supervision at the treatment site. After randomization to the experimental treatment condition, the treating physician – in consultation with the patient – established the initial dosage of prescribed heroin, taking into account the patient's physical health condition, his methadone dosage, his concurrent use of illicit substances, as well as the possible use of additional medications that may affect the pharmacokinetics of the prescribed opioids. This initial dose level was subsequently increased, using a clinical titration procedure. At the end of the titration procedure, the resulting dose level had to be sufficiently high to prevent the subject from seeking additional illicit heroin, while taking into consideration possible adverse effects, such as respiratory depression or overdose, in case the patient would not tolerate the established dosage. The maximum daily dosage of co-prescribed heroin permitted in the study was 1000 mg, and the maximum single dosage 400 mg. Data from the methadone registration system and from several studies have indicated that only a small minority of the Dutch heroin users consume more than 1000 mg of "street heroin" a day (Toet, 1990; Barendregt et al., 1995; Blanken et al., 1996b), while the current purity of the Dutch street heroin is estimated to generally range from 30% to 50%. In Switzerland, the median daily dosage after an initial adjustment phase amounted to approximately 500 mg for injectable heroin (Rehm et al., 2001), and to 1000-1850 mg for smokeable heroin (Uchtenhagen et al., 1997). With regard to these high dose levels of inhalable heroin, it should be noted that the bioavailability of heroin in the applied heroin cigarettes was very low (10-15%), whereas considerable individual variations occurred in both application forms (Uchtenhagen et al., 1997). Based on a pilot study (see below), the bioavailability of the inhaled heroin in the present Dutch trial is estimated to range between 35-45% (Hendriks et al., 2001).

In the course of the qualification period, the treating physician determined whether the subject should receive injectable heroin or inhalable heroin, taking into consideration the patient's physical health condition and his history and current pattern of heroin self-administration. The patients who participated in the injectable heroin trial of the study received the prescribed heroin in the usual (injectable) form. The patient administered the prescribed heroin himself, provided

that this was done in a safe manner. For safety reasons, and to standardize the method of self-injection as much as possible, the patients were instructed by the treatment staff about the method of self-injection at the start of the study. If necessary, the patient could be assisted with the self-injection by a nurse. As described earlier in paragraph 2.2.2, subjects who were assigned to the injectable heroin trial at the start of the study had the possibility to switch to inhalable heroin under certain conditions, but they remained in the injectable heroin trial, and were analyzed as participants in the injectable heroin trial.

The procedures for the patients who were assigned to the inhalable heroin trial of the study were very similar to those for the patients in the injectable heroin trial. For example, the participants in both trials were admitted to the heroin (injection or inhalation) administration rooms in small groups at the same time, for reasons of efficiency and comparability to the social setting in which heroin users often use their heroin. However, given the increased health risks associated with injecting heroin use, no injectable form of heroin was provided to patients who had been assigned to the inhalable heroin trial at the start of the study.

In light of the predominance of heroin inhalation in the Netherlands, the CCBH took the initiative to conduct a pilot study on the development and testing of an inhalable heroin compound, which would yield a sufficient and reproducible amount of heroin smoke after heating and volatilization, did not produce toxic pyrolysis products, would not have toxic effects on the central nervous system, and would be sufficiently stable and easy to manufacture in large quantities (Bronner, 1997). The resulting heroin compound consisted of a mixture of heroin base and caffeine. Caffeine was added to the heroin base, because caffeine has been demonstrated to lower the temperature of volatilization of heroin base, to slightly enhance the recovery of heroin in smoke, and to reduce its pyrolytic decomposition (Huizer, 1987; Cook and Jeffcoat, 1990). In addition, the combination of heroin base and caffeine has been used in illicit street heroin for decades (Grund, 1993; Grund and Blanken, 1993), and has never been observed to produce toxicity.

The developed heroin compound was subsequently investigated in another pilot study (Hendriks et al., 2001) in a sample of 10 heroin addicts, with the objectives to (1) determine the acceptance by the heroin users of the heroin compound and different methods of heroin inhalation (i.e. chasing the dragon from aluminum foil versus inhalation from a heating device), (2) determine the bioavailability of heroin after inhalation, (3) investigate the physiological, behavioral and subjective effects during and following heroin inhalation at various dose levels, and (4) determine the reproducibility of the bioavailability and pharmacodynamic effects of the inhaled heroin. The study findings showed, among others, that the participating heroin addicts strongly preferred the inhalation by means of chasing the dragon, and that an average of 38-47% of the inhaled heroin could be recovered as total morphine in the urine samples of the subjects (Hendriks et al., 2001). Based on the results of this study, a mixture of heroin base and caffeine was chosen as the compound for inhalable heroin trial of the national study, and the – for Dutch heroin addicts usual – method of chasing the dragon was chosen as the route of inhalable heroin self-administration.

2.8.3 Study supplies and drug accountability

The pharmaceutical grade heroin hydrochloride and heroin base for the study was supplied by a pharmaceutical company and delivered to a central pharmacist. In the case of heroin hydrochloride, the central pharmacist further prepared the heroin by diluting the heroin in water, dividing the solution over separate multidose vials, and subsequently freeze-drying the solution. The vials containing heroin powder were then transported to the treatment sites for further

preparation for individual patients. Heroin base was prepared by the central pharmacist by mixing the heroin base with caffeine in a ratio of 3 : 1, and filling the mixture into capsules or sachets, which were then transported to the treatment sites. All procedures in the central pharmacy were conducted in accordance with the guidelines for Good Manufacturing Practice (ICH, 2000).

The central pharmacist was responsible for the drug accountability until the moment of delivery at the local treatment site. The responsibility for the drug accountability was then taken over by the treatment site, which was assisted by a local pharmacist with regard to the documentation of the medication supplies and the dispensing – and if necessary destruction – of the medication. Lastly, the treating physician was responsible for the administration of the medication to the individual patients. The actual amount and route of the medication, as well as any deviation from the prescription regime, were documented in detail on an individual basis for all patients on separate drug accountability forms, and closely monitored by the independent monitoring organization.

2.8.4 Termination of the co-prescription of heroin

Apart from the termination of the heroin treatment at the end of the experimental period for all subjects in the treatment groups B and C, and upon completion of phase III for subjects in group A, the treatment with co-prescribed heroin could be – temporarily or permanently – terminated on an individual basis by the treating physician if a subject clearly evidenced negative effects from the prescription of heroin. In addition, the treatment with heroin was terminated if a patient clearly expressed the wish to stop the treatment with heroin, or if the patient was not able to attend the treatment site anymore (for example, because he had moved to another city, or because he became imprisoned). In female participants, the heroin treatment was terminated in case of pregnancy, confirmed by a positive pregnancy test, in which case the patient was referred to a general practitioner or gynecologist for further prenatal care. Lastly, the heroin treatment was – temporarily or permanently – stopped if a patient was suspended from the treatment program, for example because he had exhibited aggressive behavior or had repeatedly attempted to steal or smuggle heroin out of the treatment unit.

2.8.5 Concurrent treatments

To maximize the comparability of the treatment conditions, the patients in the heroin condition had the same offer – in terms of type and amount – of additional psychosocial care available as patients in the control condition. This treatment offer was comparable to that in a regular methadone program ("treatment as usual"). All patients were medically screened and monitored, and could use the services of a social worker and existing social recovery programs if they wanted to. To investigate if extra places had to be created for additional treatment – if patients in the heroin condition would express an increased need for social care during the course of their heroin treatment – a pilot study was conducted prior to the start of the trials (Van der Lelij and Driessen, 1998). The pilot study indicated, that the amount and diversity of additional psychosocial treatment places was sufficient in all participating treatment programs to handle a possible increase in treatment need, so that waiting lists were not to be expected.

On individual indication and determined by the treating physician, each subject was permitted to receive co-prescribed medications and/or therapies for concurrent medical conditions. Where possible, the physician ensured that the prescribed concurrent medication did not interact negatively with the prescribed methadone or heroin. In addition, as some medications interact pharmacologically with methadone and/or heroin (e.g. medications against HIV or TBC), the

physician could adjust the dose level of the prescribed methadone and heroin, if necessary. As with psychosocial counseling or therapy, all medical interventions and therapeutic prescriptions, including dose levels, reason for administration and outcome, were closely monitored during the two-monthly assessments and recorded in the CRF.

2.8.6 Treatment units and dispensing procedures

Heroin was co-prescribed in newly established treatment units. Each unit consisted of a lobby, a waiting-room, a dispensing-room, separate rooms for injecting and inhaling heroin, and rooms for the physician, nurses, social worker, administrative staff and researchers. In addition, in each unit a specially secured room contained a vault in which the medication was stored. The surface of the treatment units was approximately 300 m².

The dispensing-room was situated in between the two administration rooms and separated from these rooms by safety glass windows, which enabled personnel in the dispensing-room to closely observe the safety and behavior of the patients self-administering the prescribed heroin. In order to prevent passive inhalation of heroin vapors by the treatment staff, negative pressure was created in the heroin inhalation room, by means of ventilation equipment.

The staff of the treatment units consisted of a physician (± 0.6 fte), treatment co-ordinator (± 1.0 fte), nurses (± 7.0 fte), social worker (± 0.6 fte), administrator (± 0.5 fte), supervising pharmacist (± 0.1 fte) and security personnel (± 1.5 fte). Each treatment unit had to be open for patients at least two hours during the morning, afternoon and evening for seven days a week. Common hours for dispensing co-prescribed heroin were from 8.30-10.30/11.30 a.m., from 13.00-15.00/16.00 p.m. and from 18.00-20.00/20.30 p.m.

Each day the necessary amount of medication was taken out of the vault by two nurses. The inhalable heroin was originally available in capsules and later on in sachets, containing 75, 100, 150 or 200 mg of heroine base. The injectable heroin was available in multi-dose vials containing 3,000 mg of freeze-dried heroin HCl. The individual dosages of injectable heroin were prepared in a flow-chamber for each patient separately and checked by a second nurse.

In general, patients received their daily methadone dosage preceding the first heroin prescription. The number of patients allowed to be in the heroin administration rooms ranged from five to six patients simultaneously. Patients were requested by the nurse to enter the heroin administration room. Patients who received co-prescribed injectable heroin entered the injection room and were given a syringe containing the injectable heroin, plus additional attributes through a dispensing window. Patients were allowed sufficient time to self-administer the injectable heroin, following the injection instructions, which for instance precluded injecting in the neck or groin. After injecting the prescribed heroin, the patient had to clean the table and return the used syringe and all the other materials. During the whole process of self-administration the patient was closely observed by the nurse from the dispensing-room.

Patients who received co-prescribed inhalable heroin were requested by the nurse to enter the inhalable administration room and were given their heroin dosage, one sachet at a time, together with a piece of aluminum foil, marked with a CCBH logo, and a small pipe or straw (to inhale the heroine base vapors) through the dispensing window. In order to minimize the possibility that nurses could come into contact with heroin base (and might develop a contact dermatitis, see chapter 10), patients opened the sachets themselves. Since 'chasing the dragon' takes more time than injecting, inhaling patients were allowed approximately 30 minutes to self-administer the inhalable heroin. At the end of the self-administration, patients had to clean the table and return all the remaining materials, including the sachets and aluminum foil. As with injecting patients, inhaling patients were closely observed by the nurse from the dispensing-room.

Finally, a series of additional measures ('house rules') were taken to prevent disturbing effects of the trials and its participants on public order and safety within the treatment center as well as in the surroundings of the treatment center. Among others, these included:

- no lingering in the vicinity of the treatment center during and outside the opening hours;
- no use of other drugs than the prescribed heroin and/or methadone in the treatment center;
- no use of drugs in the vicinity of the treatment center;
- no attempts to take prescribed heroin out of the administration rooms or the treatment units.

Serious or repeated violations of the house rules were followed by temporary or sometimes definite exclusion from the heroin treatment program.

2.9 Assessments

2.9.1 Instruments and outcome measures

Assessments by independent research-assistants

Extensive baseline and follow-up data were collected in the study, both to screen potential study candidates during the qualification phase, to provide an extensive baseline description of the study population, and to investigate pre-treatment to post-treatment changes in the physical, psychiatric, social, and substance use status of the participants. The Addiction Severity Index (ASI; McLellan et al., 1980, 1992; Hendriks et al., 1989) was used as the basic instrument in the study, complemented with various supplements in areas of functioning that required more extensive data. In the present study, the European version of the ASI was used (Blanken et al., 1994; Kokkevi and Hartgers, 1995). The ASI, for which an extensively validated Dutch translation is available, is a semi-structured interview which assesses the status and severity of problems of subjects in the areas of physical health, employment, alcohol and drug use, legal functioning, social functioning, and psychiatric functioning. In previous studies, the ASI has shown sufficiently high inter-rater reliability, test-retest reliability, and concurrent and discriminant validity across a range of alcohol and drug dependent populations (McLellan et al., 1985, 1992; Hendriks et al., 1989; Kokkevi and Hartgers, 1995; Alterman et al., 2000). For the purpose of the present study, the standard items of the ASI in the area of social functioning and social integration were supplemented with detailed questions about current illegal activities, income, and living arrangements of the patient, and an item was added which informed about the number of days the subject had had personal contact with non-drug-using persons in the previous month.

In the present trials, the mean number of days in the previous month the subject had been involved in illegal activities amounted to 10.9 (sd=11.4), and the median to 8. The mean number of days without contact with a non-drug-using person amounted to 14.7 (sd=12.8), with a median of 12.

In the area of physical health, the Maudsley Addiction Profile Health Symptoms Scale (MAP-HSS; Marsden et al., 1998) was used as a supplement to the ASI. The MAP-HSS is a ten-item structured interview, which was adapted from the health scale of the Opiate Treatment Index (Darke et al., 1991, 1992). Each item is scored on a five-point Likert-type scale, ranging from 0 (complaint never present in the previous 30 days) to 4 (complaint always present in the previous 30 days), resulting in a total scale-score ranging from 0 to 40. In previous research among opiate users in opioid substitution, detoxification, and relapse prevention treatment in the United Kingdom, the scores on the MAP-HSS were approximately normally distributed, the internal consistency of

the scale was satisfactory ($\alpha=0.79$), and the test-retest reliability of the scale was high, with an intra-class correlation coefficient amounting to 0.86 (Marsden et al., 1998).

As described in paragraph 2.1.2, patients had to have a MAP-HSS score of at least 8 to be included in the present trials in the area of physical health. This inclusion threshold score was based on the instrument's distribution in the study of Marsden et al. (1998), and was determined by subtracting one standard deviation of the MAP-HSS total score ($sd=6.9$) from the mean total score (mean=14.7) found in this sample.

In the context of the present study, the psychometric properties of the MAP-HSS were investigated in a sub-sample ($n=808$) of the Dutch general population, matched on age and gender with the study population of the heroin trials. In the general population, the mean MAP-HSS score amounted to 4.8 ($sd=4.7$), and the median to 4. Utilizing the threshold score of at least 8 on the MAP-HSS, 22% of the males and 25% of the females in the general population in the Netherlands met the threshold. Lastly, the internal consistency of the MAP-HSS in the general population amounted to $\alpha=0.80$.

In the study population of the present trials the mean MAP-HSS score was 11.4 ($sd=7.4$), and the median 11. Cronbach's α of the scale in the study population amounted to 0.82.

In the area of psychiatric status, the ASI was supplemented with the Composite International Diagnostic Interview (CIDI; Robins et al., 1988; WHO, 1996) and the Symptom Checklist (SCL-90; Derogatis, 1983; Arrindell and Ettema, 1986). Like the ASI, the CIDI and SCL-90 are international standards, for which validated Dutch translations are available. In the present study, the computerized version of the CIDI was used to obtain DSM-IV diagnoses (APA, 1994). The SCL-90 is a self-report questionnaire consisting of 90 items, which are scored on a five-point Likert scale, ranging from 0 (symptom absent) to 4 (symptom very often present). Hence, the total score of the SCL-90 could range from 0 to 360. The psychometric properties of the SCL-90 have been established in the general population, and across a wide range of clinical populations, including alcohol and drug dependent patients (Arrindell and Ettema, 1986). In Dutch samples of treatment seeking alcohol and drug addicts, the SCL-90 scales showed high internal consistency, with α coefficients ranging from 0.81-0.89 (Hendriks, 1990a, 1990b), and a clear sensitivity to change from pre- to post-detoxification treatment (Franken and Hendriks, 2001).

As described in paragraph 2.1.2, the cut-off score on the SCL-90 to be included in the trials in the area of mental health was 41 for males and 60 for females. These inclusion threshold scores were based on the distribution of the SCL-90 total score in a general Dutch population norm group (Arrindell and Ettema, 1986). Since the SCL-90 total score showed a skewed distribution in both the male and female norm group (males: mean=27.2; $sd=27.3$; females: mean=38.9; $sd=36.4$), the cut-off score was derived from the minimum value of the total scores falling within the 80th percentile in the norm group (i.e. the percentile in which 20% of the general population scores "high" to "very high" on the SCL-90). For males, this minimum value amounted to 41, and for females to 60.

In the study population of the present trials, the mean SCL-90 score amounted to 67.7 ($sd=56.2$; median=51) for males, and to 95.8 ($sd=76.0$; median=72) for females. The internal consistency of the SCL-90 total scale in the study population amounted to $\alpha=0.98$.

In addition to these standardized instruments, two supplements – both structured questionnaires, which were specifically developed for the present study – were added to the CRF. One supplement was directed at obtaining detailed information about the type and amount of additional (somatic, psychiatric, social, and substance abuse) treatment the patient had received during the study. The other supplement informed about the patient's satisfaction with regard to the treatment provided in the treatment site. Lastly, urine samples were collected and analyzed on various

substances by an independent central laboratory, and registered data in the police records were investigated by an independent research-assistant, to verify the self-report data in the areas of substance use and criminality, respectively (see paragraph 3.2.8).

To minimize information bias, the study assessments were conducted by independent research-assistants, who used standardized instruments and evaluation procedures, and the results of the assessments (including those from the urinalyses and the police records) were not made available to the treatment staff. To obtain standardized and reliable data, all research-assistants received extensive training courses and booster sessions in the administration of the questionnaires and interviews. In addition, comprehensive Dutch manuals for the assessment and scoring procedures were available for each instrument and supplement.

Assessments by the treating physician

The instruments and supplements described above were all intended to collect information, directly related to the eligibility of potential study candidates and the effectiveness of the interventions in the study, and were therefore administered by independent research-assistants. In addition, the CRF contained various supplements which did not directly pertain to the effectiveness of the intervention. These supplements were filled out by the physician to document the findings of medical examinations (including the results of laboratory blood tests and pregnancy tests), the amount and type of prescribed co-medication, the physician's rating on a GAF-scale with regard to the patient's level of psychosocial functioning, and the occurrence of (serious) adverse events (see paragraph 2.10.1). Like the research-assistants, all physicians were extensively informed about the assessment procedures involved in using these supplements. Table 4 provides an overview of the measures collected in the areas of physical and mental health, social functioning and integration, and substance use in the study.

Table 4. Study measures

<i>Outcome domain</i>	<i>Measure</i>	<i>Source</i>	<i>Administrator</i>
Physical health	<ul style="list-style-type: none"> - overall physical condition - medical examination and medical screening (incl. GAF) - co-medication - (serious) adverse events 	<ul style="list-style-type: none"> - ASI / <u>MAP-HSS</u> * - CRF - CRF - CRF 	<ul style="list-style-type: none"> - research assistant - treating physician - treating physician - treating physician
Mental status	<ul style="list-style-type: none"> - psychiatric examination - overall psychiatric status 	<ul style="list-style-type: none"> - CIDI - ASI / <u>SCL-90</u> 	<ul style="list-style-type: none"> - research assistant - research assistant / self report
Social functioning	<ul style="list-style-type: none"> - social functioning (living arrangements, social contacts/problems, contacts outside the drug-scene) - employment situation (financial status, employment/unemployment) - illegal activities (type, frequency, contacts with the police, imprisonment) 	<ul style="list-style-type: none"> - ASI + <u>supplement</u> - ASI - ASI + <u>supplement</u> / police records 	<ul style="list-style-type: none"> - research assistant - research assistant - research assistant
Substance use	<ul style="list-style-type: none"> - heroin (prescribed/illicit; dose, frequency, route of administration) - methadone (prescribed/illicit; dose, frequency, route of administration) - other illicit drugs (cocaine, amphetamines, ecstasy, cannabis; dose, frequency, route of administration) - alcohol and benzodiazepines (dose, frequency) 	<ul style="list-style-type: none"> - ASI + urinalysis - ASI + urinalysis - ASI + urinalysis - ASI + urinalysis 	<ul style="list-style-type: none"> - research assistant / lab - research assistant / lab - research assistant / lab - research assistant / lab

* *The underlined instruments are part of the primary outcome measure in the study (see paragraph 2.9.3)*

2.9.2 Timing of the assessments

The study assessments were conducted every two months during the course of the individual study period of each participant. The full version of the ASI was administered at the initial screening visit (phase I, day 1; see paragraph 2.3), to obtain detailed information on both the lifetime and recent problem status of the patient. At the subsequent two-monthly assessments, including the baseline assessment (phase II, day 1), either the integral follow-up version of the ASI or the alcohol and drug use section of the ASI was used. Each assessment included the MAP-HSS, SCL-90, and the social supplement of the ASI, in addition to either the integral ASI or the alcohol and drug use section of the ASI, since these instruments and supplements contained the components of the primary outcome measure of the study. In addition, each two-monthly assessment included the physician's medical screening, including – if applicable – registration of co-medication, and (serious) adverse events, which were both documented in the patient's medical file on a continuous basis during the study as well.

Various assessments were conducted at less frequent intervals. These included an extensive medical examination by the treating physician (only at study entry), the CIDI (at study entry and at the end of the 12 months experimental study phase), the client satisfaction questionnaire (at study entry, and after six, 12 and 18 months), and the additional treatment supplement (as the client satisfaction questionnaire, with additional assessments at the initial screening visit, and after 10 and 14 months). Lastly, the pregnancy tests among the female participants, and the urine sampling for drug screening were conducted monthly. From these, the collection of urine samples took place both at the regular two-monthly assessment-visits, and on a randomly selected day in the course of the interval between these two-monthly assessments.

2.9.3 Primary outcome measure

Many studies have indicated that addiction is not an "all-or-nothing" phenomenon (Edwards et al., 1981), and that recovery – in terms of abstinence and/or stabilization – constitutes a dynamic process, which includes different dimensions and stages (Prochaska and DiClemente, 1983; Cramer and Schippers, 1994; Driessen et al., 1999; Hser et al., 2001). In the present study population, stabilization or termination of illicit drug use can be expected to encompass corresponding improvements in the patient's physical and mental health condition and his level of psychosocial functioning. The primary effect measure of the study should, therefore, include each of these domains of functioning, and provide a clear operationalization of how these domains are interrelated. Two approaches have been considered. According to the first approach, social integration and rehabilitation is the most important – and possibly the most difficult to achieve – outcome of treatment in the study population. From this viewpoint, improvements in the area of social integration and rehabilitation are preceded by improvements in the patient's health condition and drug use status, and/or reductions in his illegal activities. Improved social integration is, therefore, considered as the primary outcome measure according to this approach, while health and illicit substance use are regarded as intermediate outcome variables. Consequently, since treatment response is likely to occur more frequently on these intermediate variables than on the primary outcome measure, the statistical power analysis should be based on social integration and rehabilitation. In the second approach, treatment outcome is considered to represent a multidimensional process as well, but no assumptions are made as to the hierarchy across the outcome domains. According to this approach, the primary outcome measure should be operationalized in terms of a dichotomous index, which refers to improvements in each of the

relevant domains of functioning. As a consequence, the statistical power analysis in this case should be based on the dichotomous outcome measure.

In clinical studies in the field of psychiatry, patients are usually selected on the basis of a clinical diagnosis, whereas the effects of treatment are evaluated on the basis of a severity scale. When using a severity scale, treatment outcome is often operationalized in terms of mean improvements since the baseline assessment, or in terms of percentage treatment responders. Both approaches have advantages and disadvantages. An outcome measure in terms of mean improvements can be used relatively easily in statistical analyses, and is quite sensitive. A statistically significant difference can, therefore, be demonstrated with a relatively small number of subjects. The clinical relevance of pre-treatment to post-treatment changes on a scale, however, is often difficult to interpret, particularly if the results are compared with those in a placebo or active comparison group, or if various scales are used, which diverge with respect to the observed level or direction of change. When using a dichotomous outcome measure, on the other hand, the degree of improvement, considered to be clinically relevant, is defined before the start of a study. The clinical relevance of a difference in percentage of patients who meet this definition – for example 60% responders in the experimental condition and 35% in the control condition – is evident. However, when using a dichotomous outcome measure, more patients are generally needed to demonstrate statistical significance.

With regard to these approaches, the European College of Neuropsychopharmacology (1995) concluded in a consensus meeting, that " (...) *a statistically significant difference between drug and placebo treatment with respect to the percentage responders defined as a pre-established degree of reduction on a pivotal severity scale may provide the most objective information about clinical relevance yet available*" (pp. 533). If carefully selected, the use of a composite measure, in which the relevant outcome domains are integrated, offers the advantage of clear clinical relevance. In addition, it is important to note, that all information can still be retrieved if a dichotomous measure is used.

Based on these considerations, treatment response was defined in the present study as a dichotomous, multi-domain outcome index. In general terms, patients were considered as responders if they showed at least 40% improvement at the month 12 outcome assessment, compared to the situation at baseline, in at least one of the areas in which they functioned poorly at the start of the study (i.e. on the basis of which they were included at baseline), while these improvements should not have gone at the expense of similar deterioration in functioning in any of the other outcome domains. The operational definition of response is given in Table 5.

In addition to these criteria, the person should not have been in a controlled environment (e.g. detention, hospital, residential addiction treatment) for more than seven days in the month prior to the outcome assessment, in order to qualify as responder.

2.10 Documentation of safety and public order aspects

2.10.1 Adverse events, and serious/unexpected adverse events

Definitions

In accordance with the ICH/EU Guideline for Clinical Safety Data Management (ICH, 1994), an adverse event (AE) was defined as any untoward medical occurrence in a patient who received medically prescribed heroin and/or methadone during the study, regardless of whether the occurrence was causally related to the treatment. A Serious Adverse Event (SAE) was defined as

Table 5. Response definition

<i>Outcome domain</i>	<i>Response criterion</i>
Physical health	- at study entrance a MAP-HSS score of at least 8, and - at least 40% improvement on the MAP-HSS
	<i>and / or</i>
Mental status	- at study entrance a SCL-90 total score of at least 41 (males) or 60 (females), and - at least 40% improvement on the SCL-90 total score
	<i>and / or</i>
Social functioning	- at study entrance at least six days in the previous month of drug-related illegal activities, and/or - at study entrance at least six days in the previous month without personal contact with a non drug-using person, and - at least 40% improvement on the social item (or items) on which the person was included at study entrance
	<i>and</i>
Substance use	- no increase of more than six days in the previous month that cocaine and/or amphetamines were used
	<i>and</i>
General	- no deterioration of 40% or more in the physical health condition, and/or mental status, and/or social functioning since the baseline assessment *

* *For all areas, the deterioration should result in poor functioning, as defined by the inclusion-thresholds. For the social area, additional criteria include, that there should be (a) no deterioration of 40% or more on both social items, and (b) no deterioration of 40% or more on one of the social items, if the person remains functioning poorly – according to the inclusion-thresholds – on the other social item.*

an AE, which resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability or incapacity, or was a congenital anomaly or birth defect. Lastly, an unexpected adverse event was defined as an AE of which the nature, severity or frequency was not consistent with the currently available published literature or with the information described in Martindale (1997). In addition to these various types of AEs, drug overdoses, psychoses and epileptic attacks were registered separately throughout the study.

The severity of an AE was defined as mild, in case the AE was transient and easily tolerated, moderate, if the AE caused the patient discomfort and interrupted his usual activities, and severe, if the AE caused considerable interferences with the patient's usual activities and was potentially incapacitating or life-threatening. In addition, whereas there is currently no accepted standard international nomenclature to describe the degree of causality between a medication and an event (ICH, 1994), the causal relationship with the experimental medication was defined according to a widely used scale, consisting of the categories "certainly", "likely", "possibly", "certainly not" and "unknown".

Registration and reporting

As described before, all clinically significant adverse events and all serious and/or unexpected adverse events were documented by the treating physician in the patient's medical file on a continuous basis when they occurred, and in the CRF at the two-monthly assessments. All

clinically significant AEs had to be subjected to follow-up investigation, and documented until the adverse event had disappeared or stabilized. In case of any serious and/or unexpected adverse event, the event was immediately reported by the local study co-ordinator to the monitoring organization, both by telephone and by sending an SAE-report by telefax. Within 24 hours after receipt of the SAE-report, the monitoring organization sent a written confirmation of the receipt back to the local study co-ordinator, and within 48 hours to the National Research Board of the CCBH. Reports of adverse events which were both serious and unexpected, and which were considered to be at least possibly related to the experimental medication, were forwarded to the National Safety Committee (LVC) (see paragraph 2.7), and to the Central Committee on Medical Ethics within 48 hours of receipt, and within 15 calendar days to the Inspectorate of Health Care of the Netherlands. This report had to be accompanied by information about the involved treatment site, the patient's identifier code, and a detailed description of the adverse event, in terms of its background and circumstances, possible cause, and causal relationship with the experimental medication. In case of a fatal adverse event, the SAE-report was sent to the National Safety Committee within 48 hours of receipt, regardless of a (possible) causal relationship with the experimental medication.

2.10.2 Public order and controllability

Definitions

Undesirable events in the area of public order, criminality, and controllability were defined in similar terms as those in the area of medical safety. A public order event was considered to be relevant if it represented an untoward and/or serious event, which was at least possibly causally related to the execution of the study. Analogous to the scale used in the area of medical safety, the degree of causality between the event and the conduct of the study was rated as "certainly", "likely", "possibly", "certainly not" and "unknown". In addition, the severity of the event was defined as mild, in case the event caused a small and short disturbance in the treatment site or in the surroundings of the treatment site, moderate, if the disturbance was moderate, and severe, if the event resulted in a considerable and/or long-lasting disturbance of the public order and controllability. In case of a (failed or succeeded) attempt to take prescribed heroin out of the treatment site, the severity of the event was rated as mild to moderate, if it concerned an amount of heroin smaller than, or equal to the participant's total dose of that day, and severe, if a larger amount of prescribed heroin was involved.

Registration and reporting

To assure that events and complaints, related to public order, controllability, and public safety, were correctly registered and handled, a local complaints office was installed in each participating city, where citizens could report an event or complaint, related to the conduct of the study. In some cities, the complaints office was installed especially for the present trials, whereas in other cities, an existing police station in the surroundings of the treatment site served as the complaints office. Residents who lived in the direct environment of the treatment site could report their complaint directly to the treatment site. Lastly, events that occurred within the treatment site (e.g. aggressive behavior, attempts to take heroin out of the treatment site) were registered directly by the treatment staff as well.

In all cities, the staff working at the complaints office were instructed about the procedures used to register and evaluate the complaints. Events and complaints that were judged to be severe by the staff of the complaints office had to be reported to the treatment site within 24 hours. In addition, severe and/or untoward events and complaints had to be reported to the monitoring

organization. The monitoring organization subsequently sent a written confirmation of the receipt back to the complaints office, and within 48 hours to the National Research Board of the CCBH. All severe events and complaints that were judged to be at least possibly causally related to the execution of the study, were reported within 48 hours to the National Committee on Public Order and Controllability (LCB) (see paragraph 2.7). This report had to be accompanied by information about the involved treatment site, and a detailed description of the event or complaint, in terms of its nature and background, and – where possible – its causal relation with the execution of the study. Lastly, routine overviews of all events and complaints were sent on a monthly basis to the LCB.

2.11 Data quality assurance

A broad range of measures was taken to maximize the quality of the study data. As described earlier, the study was conducted in accordance with the ICH/EU guidelines for Good Clinical Practice (ICH, 1996), and the study protocols, patient information form, and informed consent form and procedure were submitted to and approved by the Central Committee on Medical Ethics of the Netherlands, prior to the start of the study.

Data collection and training

In each participating study site, the data were collected by independent research teams. The study data were treated confidentially and processed anonymously, and were not made available to the treatment staff. In addition, the data were collected by means of standardized instruments and assessment procedures, and were documented in a standardized paper Case Report Form.

All members of the local treatment and research teams received extensive training in GCP by the independent monitoring organization. The research teams were trained in the administration of the questionnaires and interviews, and received booster training sessions throughout the course of the study. In addition, comprehensive Dutch manuals were available for the assessment and scoring procedures of each instrument and supplement.

All study procedures relevant to either the research teams, the treatment staff or both, were outlined in a comprehensive manual, which contained Standard Operating Procedures (SOPs) for a broad range of topics, including the general study design, the tasks and responsibilities of all parties involved, the selection and randomization procedure, the treatment aspects (e.g. the requirements for the treatment unit, dose-schedules for injectable heroin, inhalable heroin, and methadone, drug accountability), and the assessment aspects (e.g. time-frames and planning of the assessments, maximizing the co-operation of participants, collection of urine samples).

Co-ordination

Regular meetings were held between the CCBH and all local study co-ordinators, local treatment co-ordinators, and local treating physicians, each in separate group meetings. These meetings focused on general aspects (e.g. explanation of the study design, treatment regimen, drug accountability procedures), as well as on specific topics which became relevant in the course of the execution of the study (e.g. termination of the experimental treatment for individual patients at the end of the experimental study phase), and were meant to provide a platform to instruct and co-ordinate the local teams on a central level – in order to enhance the quality and consistency of the treatment and assessment procedures across the study sites and throughout the study-period – and to discuss the rationale and consequences of the procedures – in order to improve the acceptance of all study and treatment procedures. In addition, the local treatment sites were visited monthly

by the study co-ordinator of the CCBH, both to check whether the procedures were conducted in accordance with the study protocol and SOPs, to discuss possible difficulties, and to give directions for solutions.

Monitoring

The study was monitored by a GCP-certified external independent monitoring organization. The monitor visited each treatment site and local research team every two weeks, during which the treatment and data collection procedures were checked. These checks included verification of the presence and correctness of all informed consent forms, 100% verification of the information in the first CRF (phase I, day 1) with that in the existing medical files and other source documents, 100% verification of the inclusion and exclusion criteria at baseline, and of the primary outcome data at each following assessment-point, and 20% verification of the other information recorded in the CRFs. In case of an incomplete, inconsistent or incorrect CRF, the monitor consulted the responsible person – i.e. the treating physician or the local study co-ordinator – and attempted to resolve the problem. In addition, the monitor observed and checked the drug accountability procedures at each study site, and the registration and reporting of serious (medical and public order) adverse events.

Data management

The information recorded in the CRFs was entered into a computerized database and validated by an external data management organization. Data entry was conducted independently by two data entry typists, using the Clintrial software program. The information entered into the database was subsequently checked according to a pre-established validation plan on the occurrence of missing values, incorrect values, and inconsistencies, with regard to the inclusion and exclusion criteria, the time frames of the assessments, and the primary outcome variables. In addition, all text fields pertaining to concomitant medication, medical history and adverse events data were checked on spelling errors and unclearness. In case of error messages, the CRF was checked manually by the data manager. Remaining errors were sent as queries to the external monitoring organization, and after resolution corrected in the database according to the answers to the queries. After having resolved all queries in a particular dataset (e.g. the patients' baseline values on the SCL-90), the data management organization sent the dataset to the CCBH as a SAS datafile.

Audits and inspections

Throughout the study, several Clinical Quality Assurance (CQA) audits were conducted by the CQA auditor of the independent monitoring organization to assess the study conduct compliance with the protocol, regulations and guidelines for the conduct of clinical trials. These included the ICH/EU guidelines for Good Clinical Practice (ICH, 1996), Good Manufacturing Practices (GMP), the Declaration of Helsinki (1989), and the Dutch Law on medical-scientific research in humans (WMO; Ministry of Health, Welfare, and Sports, 1998). The audits included a visit to the study facility, interviews with the study site personnel (both treatment and research staff), a 100% review of the regulatory documentation and informed consent forms, and a 100% review from a 20% random sample of the total number of patients enrolled in the study on the study site. Upon completion of the audit, the audit findings and recommended corrective actions were communicated to both the National Research Board of the CCBH and the external monitoring organization.

In addition, the Inspectorate of Health Care of the Netherlands conducted inspections at all study sites to assess the compliance of the study conduct and procedures with the protocol, manual, and regulations.

Lastly, a study audit was conducted by an external CQA auditor, independent from the external monitoring organization. This audit consisted of both a system audit, to assess and to evaluate whether the study and its procedures were conducted in accordance with the protocol, regulations and GCP-guidelines, and a late study audit, to evaluate the quality of the collected data.

Chapter 3

Data analysis

3.1 Calculation of sample size

As described in paragraph 2.9.3, treatment response was defined in the present study in terms of a dichotomous, multi-domain outcome index (responders versus non-responders), based on the difference in patient status after 12 months compared to the baseline measurement. To determine the sample size needed to demonstrate effect, a comparison of two groups, two-tailed testing, $\alpha=0.05$, a power of $(1-\beta) 0.80$, and – based on the most often required minimum difference in effectiveness in trials on depression and schizophrenia – a difference in percentage responders between the treatment conditions of at least 20% were used as starting points. On the basis of these parameters, and the procedures and formulas described in Armitage and Berry (1987, 1990) and Fleiss (1981), the number of subjects needed was estimated to be 108 subjects per treatment group (CCBH, 1997, 1999a).

Furthermore, based on a recent study in Amsterdam into the stability of attending methadone maintenance treatment of patients with similar characteristics as those projected for the target population of the current clinical study (Buster and Van Brussel, 1996), it was estimated that the drop-out rate during the experimental study-phase could amount to 20% in the control condition (group A), 6% in the experimental condition (group B), and 14% in group C (inhalable heroin trial only). Taking these anticipated drop-out rates into account, the number of subjects required at the start of the study amounted to $n=135$ in group A, $n=115$ in group B, and $n=125$ in group C.

3.2 Statistical analysis of the primary study question

The primary statistical analysis concerned the primary research question in the study – to evaluate the effectiveness of 12 months of maintenance treatment with oral methadone and co-prescribed heroin, compared with that of standard maintenance treatment with oral methadone alone – and was conducted for the trial on injectable and inhalable heroin separately. The primary analysis plan was developed without knowledge of the results of the study, and was approved before first indications of effectiveness, in terms of percentage responders in the various study conditions, were revealed. The draft Statistical Analysis Plan was approved at the meeting of the CCBH on September 2, 1999, and the final plan was approved on September 30, 1999 (CCBH, 1999b). Some technical amendments were made to the Statistical Analysis Plan on November 2, 2001, i.e. before any analyses were conducted (CCBH, 2001).

3.2.1 Null hypothesis

The null hypothesis for the primary analysis was, that there would be no statistically significant difference after 12 months between the proportion responders in the experimental condition (group B) and that in the control condition (group A). As described before, the sample size was determined on the basis of a 20% difference in percentage responders between the conditions, and a two-tailed test with α set at $p=0.05$.

3.2.2 Primary assessment-points

As has been outlined in paragraph 2.2.1, the study subjects were randomized to one of two (injectable heroin trial) or three (inhalable heroin trial) treatment conditions. The conditions and primary assessment-points in the study are schematically displayed in Figure 3.

Figure 4. Treatment conditions and primary assessment-points

Group	Qualification	Phase IIa		Phase IIb		Phase III			
		baseline	month 6	month 12	month 14	month 18			
A	[1] M *	[2] M	[3] M	[4] M + H	[5]	[6]			
B	[7] M	[8] M + H	[9] M + H	[10] M	[11] M **	[12]			
C	[13] M	[14] M	[15] M + H	[16] M	[17] M **	[18]			

* M = treatment with methadone alone; M + H = combined treatment with methadone and heroin.

** After two months in phase III, the treating physician had the possibility to reinstate the treatment with heroin on individual, medical indication for responders who had deteriorated considerably after termination of the experimental treatment. Deterioration was assessed at month 14 for groups B [11] and C [17], and at month 20 for group A [6].

The primary analysis of the effectiveness of treatment with heroin and/or methadone during 12 months was conducted on the comparison between the assessment on day 1 of phase III in group A (assessment [4]) and that in group B (assessment [10]), with as baseline the assessment on day 1 of phase IIa (assessment [2] and [8], respectively).

3.2.3 Study population in the primary analysis

The present study is primarily focused on the pragmatic value of a treatment strategy. Therefore, the analysis of effectiveness is primarily concerned with the treatment offer, regardless of possible deviations from the protocol. Since all participants after randomization have the opportunity to make use of the treatment offer, the intention-to-treat population in the study consists of all patients who have been notified about the result of their randomization (ICH, 1998). Consequently, the month 12 data (Figure 3: assessments [10] and [4]) of every subject in the intention-to-treat population are used for the primary research question on effectiveness, regardless of whether the patient has adhered to the protocol. Although the choice for this intention-to-treat population was considered to be strict, it was anticipated that it would yield estimates of treatment effects most similar to those in subsequent treatment practice, as well as produce the most undisputed results.

3.2.4 Missing endpoint-assessments

In the present study, it could not be ruled out that the probability of response would systematically and considerably differ between patients with and without endpoint-assessments. However, since the primary analysis of effectiveness concerned the total treatment-offer, regardless of possible deviations from the protocol, statistical methods to correct for bias in the findings caused by missing endpoint-assessments, like multiple imputation or propensity score estimation, were only of limited applicability. It was therefore considered crucial to minimize the occurrence of missing endpoint-assessments as much as possible, by conducting intensive field work and by providing

additional financial compensation for participating in the endpoint-assessments. Nevertheless it could not be excluded that some missing endpoint-assessments would occur in the study population. In case of such missing endpoint-assessments, and because of lack of satisfactory alternatives, the "last observation carried forward" (LOCF) method was used in the primary analysis.

Regarding LOCF within the framework of the study, it is important to emphasize that this technique does not provide an estimate of the patient's status at the time of the month 12 assessment, but rather of his status at the time of his last available assessment. Assuming a progressively effective treatment intervention as a patient participates longer in the treatment program, LOCF will underestimate the effectiveness of the treatment of patients with a missing endpoint-assessment, who still participated in the treatment after their last available assessment. In addition, it is not unlikely that participation in a study is more frequently discontinued at times when a patient is performing poorly, which may once again result in an underestimation of the treatment-effect of that particular participant when using LOCF. The influence of these factors on the outcome of the study depends upon the extent to which these factors occur differentially in the two treatment conditions, and result in a diverging likelihood of response among participants with and without an endpoint-assessment between the two treatment conditions. These issues will be explored in secondary analyses, testing the robustness of the findings.

3.2.5 Robustness of the findings

To obtain more information about the treatment effects in different scenario's for the missing endpoint-assessments, the robustness of the results was analyzed. The purpose of this analysis was to investigate whether the – possibly – observed difference in effectiveness between the treatment conditions would hold if the missing endpoint-assessments would be dealt with using an even more conservative scenario than LOCF, which would reduce the contrast between the experimental and control condition. To this end, the robustness of the findings was investigated in a worst-case scenario, in which the patients with missing endpoint-assessments were considered as non-responders in the co-prescribed heroin condition, and as responders in the methadone alone condition.

3.2.6 Exploratory analyses of the validity of the findings

Anticipation effects

Since the participants in the study were well aware of the fact, that the treating physician had the possibility to reinstate the experimental treatment with heroin on individual, medical indication for responders who deteriorated considerably after the termination of the experimental treatment at month 12, it could not be excluded that the data of the month 12 outcome assessment would be biased to some extent by anticipation effects, in particular because the outcome measure in the study consisted of self-report data, which could only partly be verified with objective data. To gain insight into such possible bias due to anticipation effects, the findings were investigated in relation to the course of the changes in the patient during the last months of the experimental study-phase. A sudden and considerable increase in self-reported improvements in the months preceding the outcome assessment would be indicative of anticipation bias. Therefore, the effectiveness of the treatments, if significantly different between the experimental and the control condition (incorporating LOCF) at the month 12 assessment, was similarly investigated on the basis of the data collected at the month 10 assessment. If the observed difference in effectiveness between the conditions at month 12 would also occur at month 10, it would be sufficiently

demonstrated that anticipation effects could not be held responsible for the observed effect after twelve months of treatment.

Treatment completers analysis

An additional treatment completers analysis was conducted into the efficacy (as opposed to effectiveness) of the treatments among those patients who had completed the planned treatment with methadone alone and/or co-prescribed heroin. To this end, "treatment completers " were defined as patients who still participated in treatment (i.e. received methadone in the control condition, and co-prescribed heroin in the experimental condition) in month 12. The percentage responders and the difference in response between the treatment conditions among the treatment completers were subsequently similarly investigated as in the intention-to-treat analyses.

In the Statistical Analysis Plan (CCBH, 1999b), an additional per-protocol analysis of treatment compliant patients was described, but since the definitions for treatment compliance were based on different criteria for both treatment groups, this type of per-protocol analysis was omitted.

3.2.7 Analysis model and statistical program

The primary study question into the 12 months effectiveness was analyzed by means of a logistic regression model, with treatment condition (co-prescribed methadone and heroin versus methadone alone) as independent variable and treatment site as the only covariate (six treatment sites). To investigate whether or not the treatment effect was homogeneous across the treatment sites, a treatment-by-site interaction term was subsequently incorporated in the logistic regression model, and its significance tested. The adequacy of the statistical model was determined by means of a goodness-of-fit test, and the difference in effectiveness between the two treatment conditions was subsequently presented as percentage responders in both treatment conditions and as Odds-Ratio, utilizing a 95% confidence interval. The difference in effectiveness between the treatment conditions was tested by means of a two-tailed test of significance, with alpha at $p=0.05$. The statistical analysis was conducted on the Statistical Analysis System (SAS-version 8; SAS Institute, Inc., Cary, NC).

3.2.8 Verification of self-report data

As described in paragraph 2.9.3, the primary outcome measure in the study was based on self-report data in the areas of physical and mental health, social functioning, and substance use. In accordance with the study protocol, the self-report data pertaining to the patient's substance use and criminality were verified by analysis of urine samples and by investigation of registered data in the police records, respectively. Urine samples were collected both at the regular two-monthly assessment-visits, and on a randomly selected day during the interval between these two-monthly assessments, and were analyzed by a central laboratory. The registered data in the police records were investigated by an independent research-assistant.

Substance use

From the data collected in the areas of substance use, the use of cocaine and/or amphetamines was part of the primary outcome measure. Verification of self-reported substance use focussed, therefore, on these two substances. In the self-report questionnaire, related to the urinalysis, the subjects were asked about their cocaine and amphetamine use in the 48 hours prior to the assessment. Due to the low prevalence of amphetamine use, the analyses were restricted to the use of cocaine.

A first investigation pertained to the degree of underreporting at the time of the month 12 outcome assessment in treatment conditions A and B combined. To this end, the level of agreement was determined between the use of substances (i.e. cocaine) according to self-report and according to urinalysis, in the intention-to-treat population in conditions A and B combined, using Kappa as measure of concordance, and regarding the results of the urinalyses as "golden standard". Additionally, a possible difference in degree of underreporting between the month 12 and month 10 assessment was analyzed by means of the McNemar test. In this case, the analysis set consisted of all patients with a positive urine sample on month 12 and month 10, in conditions A and B combined.

The second type of investigation pertained to the occurrence of differential underreporting in conditions A and B. Differential underreporting was investigated for the month 12 and month 10 assessment separately, among patients with a positive urine sample, using a logistic regression model, with underreporting (yes/no) as dependent variable, treatment condition (A or B) as predictor, and treatment site as covariate.

The third type of investigation focussed on possible differences in level of underreporting between the regular month 12 assessment and the random – hence unpredictable – assessment between month 10 and 12 ("month 11 assessment"). As in the first investigation, differences in level of underreporting were analyzed by means of the McNemar test, among patients with a positive urine sample on month 12 and month 11, in conditions A and B combined.

At month 12, 76.8% of the urine samples were positive for cocaine, whereas 64.4% of the patients reported the use of cocaine in the previous 48 hours. At month 10, 76.5% of the subjects had positive urines for cocaine, whereas 62.6% reported cocaine use. Results for the random assessment at month 11 were similar: 78.7% positive urine samples; 69.4% self-reported cocaine use.

Agreement between the two assessment procedures was generally good. At the month 12 assessment, overall agreement between self-report and the results of urinalysis amounted to 85.8%, with a Kappa of 0.66 (95%-CI: 0.58-0.75). At month 10, overall agreement amounted to 84.6%, with a Kappa of 0.64 (95%-CI: 0.55-0.73). Similar results were obtained at the random assessment at month 11 (overall agreement: 88.5%; Kappa=0.70; 95%-CI: 0.59-0.82). Between the two trials, no differences in level of agreement were detected (injectable heroin trial: overall agreement at month 12: 84%; Kappa=0.64; 95%-CI: 0.51-0.78; inhalable heroin trial: overall agreement at month 12: 87%; Kappa=0.68; 95%-CI: 0.57-0.78).

Of all patients with a positive urine sample on cocaine at month 12, 82.6% also reported cocaine use, indicating 17.4% underreporting. A similar result was obtained at month 11: 13.2% underreporting. In the trial on injectable heroin, underreporting at month 12 amounted to 20.2%, and in the trial on inhalable heroin to 15.5%.

In the trial on injectable heroin, no significant differences between the treatment groups A and B in underreporting were observed at month 12: group A: 17.2% underreporting; group B: 23.9% underreporting. However, in the trial on inhalable heroin, underreporting in group B (24.3%) was significantly higher than in group A (8.8%). A similar difference in underreporting occurred at the month 10 assessment (group B: 25.7%; group A: 12.1%). In the logistic regression model with underreporting as the dependent variable, and treatment site as covariate, a group effect remained significant for both the month 12 (adjusted OR=3.31; 95%-CI: 1.32-8.26; p=0.01) and month 10 assessment (adjusted OR=2.57; 95%-CI: 1.07-6.17; p=0.03). In summary, the data indicate acceptable agreement between the two assessment procedures, with some differential underreporting in the inhalable heroin trial.

Criminality

Whereas the primary outcome data could be verified directly with regard to the self-reported use of substances, the self-reported data in the criminality domain of the primary outcome measure (i.e. number of days in the previous month of illegal activities) did not allow for such direct verification, because no external verification-source was available. Therefore, verification took place with regard to the variable whether the person had been charged by the police for possession and dealing of drugs, crimes against property, crimes of violence, and other crimes, a variable which was available in the CRF and could be retrieved from the police records. Analogous to the types of investigations described for self-reported substance use, the self-reported charges by the police were verified by analyzing (1) the degree of underreporting at the time of the month 12 outcome assessment in treatment conditions A and B combined, (2) the difference in degree of underreporting between the month 12 and month 10 assessment, and (3) the difference in degree of underreporting between conditions A and B at the month 12 assessment, and separately at the month 10 assessment.

Given that the data in the police records are routinely registered with some delay, the analyses were limited for the present report to the patients in conditions A and B in the cities of Amsterdam and Rotterdam ($n=137$), who entered the study during the first study stage (see paragraph 2.4). In the four months prior to the month 12 assessment, these patients reported 20 charges, whereas in the police records, 18 charges were registered. Overall agreement amounted to 89.6%, with a Kappa of 0.62 (95%-CI: 0.43-0.82). These preliminary data suggest acceptable agreement and no systematic underreporting by the patients. A more comprehensive analysis will be provided in future reports.

3.3 Statistical analyses of the secondary study questions

The two secondary objectives of the study, which are the subject of the present report, concerned a comparison of the effects of co-prescribed heroin given for six months and 12 months duration, and an evaluation of the effects of the discontinuation of co-prescribed heroin after six and 12 months of treatment. The statistical analyses of these secondary study questions are described in the following sections. The relevant assessment-points for the secondary study questions are outlined in Figure 5.

Figure 5. Primary and secondary assessment-points

Group	Qualification	Phase IIa		Phase IIb		Phase III			
		baseline	month 6	month 12	month 14	month 18			
A	[1] M*	[2] M	[3] M	[4] M + H	[5]	[6]			
B	[7] M	[8] M + H	[9] M + H	[10] M	[11] M**	[12]			
C	[13] M	[14] M	[15] M + H	[16] M	[17] M**	[18]			

* M = treatment with methadone alone; M + H = combined treatment with methadone and heroin.

** After two months in phase III, the treating physician had the possibility to reinstate the treatment with heroin on individual, medical indication for responders who had deteriorated considerably after termination of the experimental treatment. Deterioration was assessed at month 14 for groups B [11] and C [17], and at month 20 for group A [6].

Treatment effects after six months

The effectiveness of treatment with co-prescribed heroin after six months was analyzed in two ways. The first type of investigation pertained to the question whether the 12 months effects could

already be achieved after six months. To this end, the percentage responders was compared between the treatment conditions B and C at the time of the month 12 assessment (in Figure 5: [10] vs. [16]). Response was defined in a similar manner in condition C as in condition B (i.e. based on the degree of change in the status of the patient between the baseline and month 12 assessment). Since condition C was absent in the injectable heroin trial, this investigation was conducted in the inhalable heroin trial only. Analogous to the primary analysis described in the previous paragraph, the difference in percentage responders between conditions B and C was analyzed on an intention-to-treat basis, by means of a logistic regression model, with treatment site as the only covariate, and by applying LOCF for the missing month 12 outcome assessments. As in the analysis of the 12 months effects, the homogeneity of the treatment effect across the treatment sites was investigated by incorporating a treatment-by-site interaction term in the regression model.

An additional analysis focussed on the six months effects ([10] vs. [16]) among the treatment completers in groups B and C, utilizing the same definition for treatment completers as in the analysis of the primary study question.

The second type of investigation of the six months effects consisted of a comparison of the percentage responders between conditions A and B at the time of the month 6 assessment (in Figure 5: [3] vs. [9]). In this case, the underlying study question pertained to the six months effectiveness of ongoing treatment with co-prescribed heroin, compared to that of ongoing methadone treatment. This investigation – utilizing a similar analysis model as in the first type of investigation – was conducted for both trials in the study.

Effects of discontinuation

The effects of discontinuing the experimental treatment with co-prescribed heroin after 12 months were investigated descriptively, by determining the percentage responders in condition B who had subsequently deteriorated considerably – i.e. at least 20% of the baseline value – on at least one of the outcome domains on which the patient had responded, two months after termination of the heroin treatment (assessment [11]). This analysis was conducted only for treatment completers who were responders at the 12 months assessment. In the inhalable heroin trial, the percentage responders who had subsequently deteriorated was compared between subjects in conditions B and C ([11] vs. [17]), to gain insight into differential effects of discontinuing the heroin treatment after six and 12 months.

3.4 Supplementary analyses

To gain a better understanding of the meaning of the primary outcome data of the trials, various supplementary analyses were conducted, using additional outcome parameters.

The first supplementary analysis focussed on the question whether or not the improvements in some patients in the experimental and control group occurred at the expense of deteriorations in other patients. To this end, the group of non-responders was divided into (1) subjects who had improved 40% or more on at least one of the outcome domains, but had concurrently deteriorated on at least one of the other outcome domains, (2) subjects who had neither improved, nor deteriorated according to the criteria, and (3) subjects who had not shown improvement (of 40% or more) on any of the outcome domains, but who had deteriorated on at least one of the outcome domains.

The second supplementary analysis concerned the percentage of response at subsequent assessments in the course of the trials. To investigate this topic, the percentage responders in the intention-to-treat population was calculated for each assessment-point, using LOCF for each missing assessment during the trial.

The third analysis looked at the relative contribution of the outcome domains to response. To this end, the type(s) of outcome domains on which the patients responded in the course of the trial ("response profiles") were investigated. In addition, the number of response domains were investigated, distinguishing single-domain responders and multi-domain responders.

The fourth and fifth supplementary analyses focussed on two very conservative approaches of response. The fourth analysis pertained to the issue of stable or sustained response. Sustained responders were defined as patients who (1) became responder prior to the month 12 assessment, and (2) remained a responder during the course of the trial, once they became responder for the first time. The fifth analysis focussed on a definition of response in which patients were not allowed to meet any of the inclusion thresholds.

The sixth supplementary analysis concerned an investigation of the potential effect of differential underreporting of illegal drug use between the treatment groups in the inhalable heroin trial on the occurrence of response (see paragraph 3.2.8). To this end, illegal drug use (i.e. cocaine and amphetamines) was removed as component of the primary outcome measure. Thus, the percentage responders was calculated, regardless the occurrence of deterioration in the area of illegal drug use.

Chapter 4

Protocol amendments

In the course of the study, several changes were made in the original study protocol (CCBH, 1997). These changes have been integrated in the second, revised edition of the protocol (CCBH, 1999a), and are described in detail in a separate addendum of this second protocol edition (CCBH, 1999c). All amendments were submitted to and approved by the Central Committee on Medical Ethics, prior to implementation of the proposed adaptations. In addition, all adaptations were made prior to the availability – and without knowledge – of outcome results. Most protocol amendments represented more explicit formulations, further operationalizations, or minor adaptations of certain specific study procedures. Two major changes were made in the original protocol – one concerning dropping a treatment condition in the injectable heroin trial, and one with regard to a change in the definition of the study population for the primary outcome analysis. The protocol amendments are summarized in this section.

Omission of treatment condition C in the injectable heroin trial

Against the background of declining prevalence rates of injecting heroin use among heroin addicts in the Netherlands, it became apparent during the recruitment and selection phase of the first study stage in the cities of Amsterdam and Rotterdam, that the number of eligible subjects for the injectable heroin trial would be insufficient to achieve at the – according to the power analysis – necessary total of 375 subjects. To cope with this problem, the CCBH decided to omit the treatment condition in the injectable heroin trial in which patients were treated with methadone alone during the first six months of the experimental study phase, and subsequently treated with co-prescribed heroin and methadone during the following six months (treatment condition C). This omission – which reduced the required number of participants in the injectable heroin trial from $n=375$ to $n=250$, and hence the total number of required participants in both trials from $n=750$ to $n=625$ – did not affect the primary analysis of effectiveness of 12 months treatment with oral methadone and co-prescribed heroin, compared with that of standard methadone maintenance treatment, since this analysis involved only the treatment conditions A and B. However, in the absence of condition C, the secondary study question into the treatment effects after six months, which involved a comparison between the treatment conditions B and C at the time of the month 12 assessment, could consequently be answered only for the trial on inhalable heroin (where treatment condition C was maintained).

Definition of the intention-to-treat population in the primary analysis

In the original study protocol, the intention-to-treat population in the primary analysis of 12 months effectiveness was defined as all patients who were randomized and who had received at least one post-baseline assessment. Since this definition would implicate exclusion from the primary outcome analysis of all patients with only a baseline assessment – an approach that would be inconsistent with the basic meaning of the intention-to-treat principle – the definition of the intention-to-treat population was changed to all patients who had been randomized in the study and had been notified about the result of their randomization. In addition, a final choice was made in the second version of the study protocol to deal with missing endpoint-assessments by means of the Last Observation Carried Forward approach.

Response definition

In the original protocol, response was defined in global terms, as percentage of change from the baseline assessment in medical condition, social functioning and substance use of the patients. In the second edition of the protocol, the response definition was further operationalized by referring to specific instruments, scales and items, and by including explicit inclusion thresholds and required degree of change on each of the primary outcome domains. As part of this operationalization, the original requirement for response of at least 20% change on any of the outcome domains was adapted to at least 40% change.

Randomization

According to the first edition of the protocol, patients would be randomized in blocks of 12 subjects, with gender and ethnicity as stratification variables. Given the total maximum of 80-90 participants in each study site for both trials combined, the use of two stratification variables, and the allocation of subjects to five treatment conditions, the randomization block length was adapted to three subjects in the inhalable heroin trial, and to two subjects in the injectable heroin trial.

Partners

During the execution of the first stage of the trials, it became apparent that some study subjects had partners who were also eligible for the study. In those cases where the partners were randomized to different treatment conditions (i.e. one partner receiving co-prescribed heroin and the other partner receiving methadone alone), this tended to cause considerable stress in their relationship. In these cases, and provided that both partners met the inclusion criteria of the trial, the CCBH decided to randomize both partners to the same treatment condition, and to designate one partner (with the lowest patient identifier number) as the index partner to be included in the primary outcome analysis. Hence, the other partner had the possibility to receive the same type of treatment, but was excluded from the primary analysis.