The German model project for heroin assisted treatment of opioid dependent patients – A multi-centre, randomised, controlled treatment study

Clinical study report of the first study phase
in accordance with study protocol no. ZIS-HV9-0701 of July 23, 2001, and amendments no. ZIS-HA9/1 to ZIS-HA9/10, ZIS-HA9/13 and ZIS-HA9/14

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Introduction

The German model project for heroin assisted treatment of opioid dependent patients was operated and financed jointly by the Federal Ministry of Health (BMG), the federal states of Niedersachsen, Nordrhein-Westfalen and Hessen and the cities of Hamburg, Hanover, Frankfurt, Cologne, Bonn, Karlsruhe and Munich. The cooperating partners are the contractors of the study, based on a cooperation agreement.

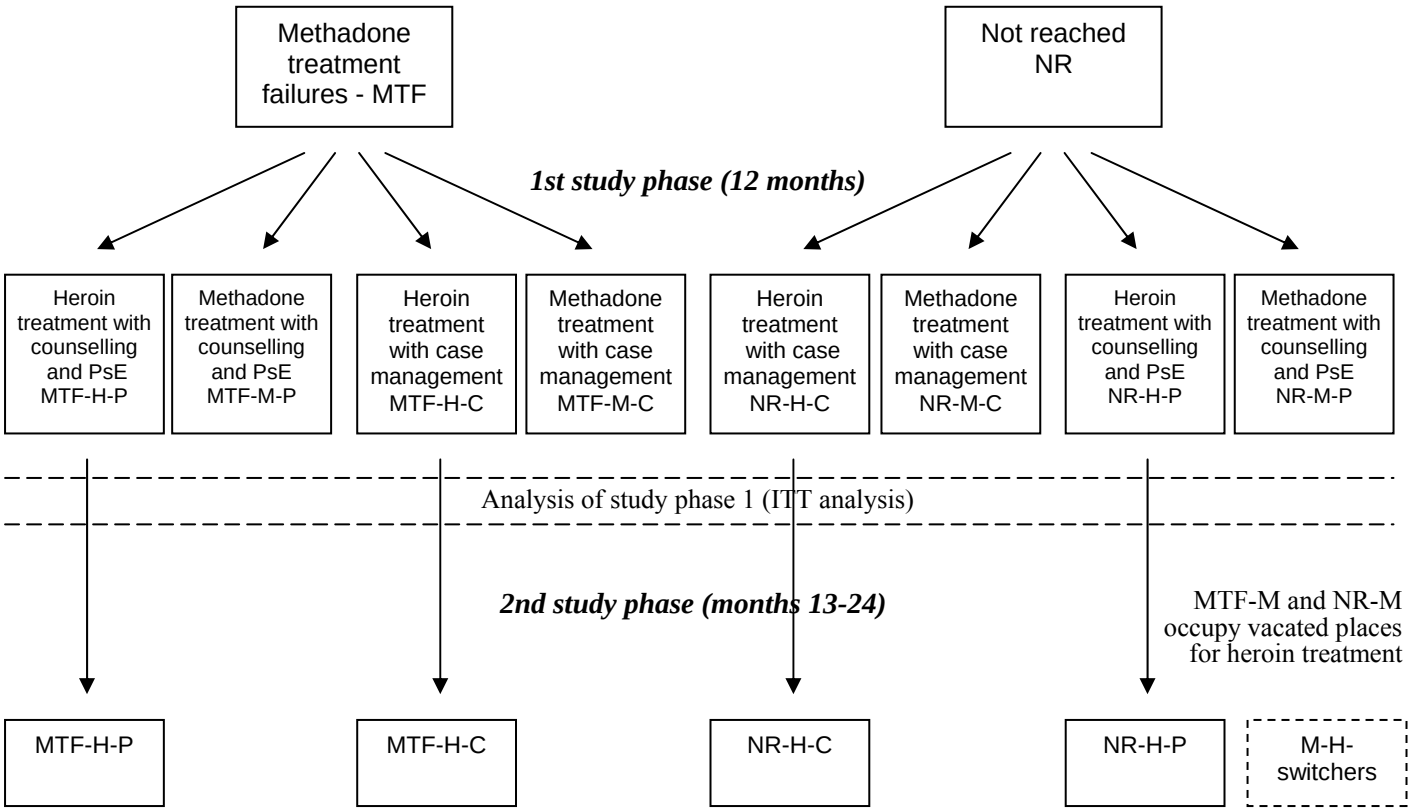
The decision about the principal investigator of the study was taken in late Summer 2000 and the valid study protocol drawn up and approved in 2001. Preparations in the participating centres then started and the treatment units were set up; early in March 2002, the first study patient was treated with heroin in Bonn. The treatment centres in Karlsruhe, Munich, Hanover, Köln and Hamburg followed during the summer. In Frankfurt, study treatment was initiated at the end of February 2003.

The recruitment of patients went on till the end of 2003. 1,032 patients were included in the study; about twice as many had been screened.

The main objective of the heroin trial was to investigate whether, in a structured treatment setting, the prescribing of pharmacologically pure heroin to heroin addicts, who had not responded sufficiently to methadone treatment or were not reached by the therapeutic system, would have greater effects in terms of health stabilisation and decrease of illicit drug use than methadone treatment. Secondary objectives were issues such as abandoning the drug scene context, improved social situation, decline of delinquency, change of quality of life and issues regarding treatment dropouts and follow-up treatment. Concomitant special studies are concerned more in-depth with the development of delinquency, health economic effects, utilisation and specific effects of psychosocial treatment, cognitive and motor functioning and care related issues. These studies are still going on and are not part of the present report.

The study was designed as a 4x2 stratified, randomised, multi-centre study. Two sample strata, the target groups “methadone treatment failures, MTF” (heroin addicts, who had not sufficiently benefited from methadone treatment) and “not reached, NR” (heroin addicts, who were not effectively reached by the drug treatment system) were each randomised to four groups. These four groups differ in terms of medical treatment (experimental group: heroin group vs. control group: methadone) and psychosocial treatment (psychoeducation/drug counselling vs. case management/motivational interviewing). As a result, there were eight groups with a study treatment of 12 months within the first study phase (see figure 0.1 below). At the end of this period, patients could continue with study phase two, also over 12 months. Patients of the experimental group could continue heroin treatment, patients of the control group had the opportunity to switch to vacated heroin treatment places.

Figure 0.1
Strata and groups of the clinical trial of heroin assisted treatment in study phases 1 and 2



The analyses (and the assessment of efficacy) focus on *two primary outcome measures*: A) Improvement of health – a response exists if physical (measured by OTI health scale) or mental health (measured by SCL-90-R) improved by at least 20% between baseline and 12-month examination. B) Decrease of illicit drug use – a response exists if the use of street heroin markedly declined (no more than 2 positive urines out of 5 at 12-month or decrease by 60% based on self-reports) and cocaine use did not increase (measured by hair analyses and self-reports). The study is considered successful if *both* primary outcome measures show a significant superiority of heroin treatment compared to methadone treatment. The primary analysis is carried out as an ITT analysis of all randomised patients; 17 subjects were excluded from the analysis. The ITT sample thus includes n=1,015 patients. Missing data are substituted according to „last observation carried forward“ (LOCF), provided they were collected at the 6-month examination or later. Dropouts are coded asymmetrically according to the conservative worst-case strategy: Patients from the heroin group without valid data are considered as non-responders, patients from the methadone group as responders.

The present study report describes the central results of the first study phase, i.e. the parallel group comparison between heroin treatment and methadone treatment (cf. study protocol part B, Krausz et al. 2001). This phase was terminated for all study patients at the end of 2004.

The central result of the German model project indicates a significant superiority of heroin treatment over methadone treatment for both primary outcome measures. Heroin treatment achieved significantly higher response rates (health: OR=1.41, p=0.023, drug use: OR=1.85, p<0.001) with respect to the state of health (heroin: 80.0%, methadone: 74.0%) as well as the

decrease of illicit drug use (heroin: 69.1%, methadone: 55.2%). Evidence of the higher efficacy of heroin treatment compared to methadone maintenance treatment has thus been provided in terms of the study protocol. Heroin treatment is also clearly superior to methadone treatment (OR=1.67, $p<0.001$) in patients who fulfil both primary outcome measures (heroin: 57.3%, methadone: 44.8%). A significant influence of the factors stratum, kind of psychosocial treatment and study centre cannot be detected in the multivariate analysis model (4-factor logistic regression), with one exception: An effect of the study centre has been found with respect to the POM drug use as there were in general somewhat lower response rates in Hanover and Cologne.

The retention rate of heroin treatment is 67% after 12 months and slightly lower than the rates of the Dutch and Swiss studies. Only 39% of the patients of the methadone group concluded study treatment. This is mainly due to the fact that one third of the patients randomised for the control group did not show up for treatment. However, it must be considered that 39% of the dropouts of heroin treatment and 44% of the dropouts of methadone treatment were in maintenance treatment outside of the study or in some other addiction treatment at T_{12}.

The average daily heroin dose is 442 mg for the whole period of the first study phase (365 days). The mean daily dose of additional methadone prescribed to heroin patients is 39 mg, counting all those who received methadone doses. Methadone patients were treated with an average daily dose of 99 mg.

The study design was successfully implemented according to the specifications of the study protocol. A sufficient number of patients were recruited both for the target group of methadone treatment failures (MTF) and the so-called not reached (NR). The study participants must be counted among the most severely dependent patients because of the great number of physical and mental impairments they suffer from and their heavy, mainly intravenous heroin and cocaine use. One result, however, is that both groups hardly differ with respect to their health and social position at baseline. The only difference consists in a higher degree of intravenous heroin use and a more instable housing situation among the NR. Accordingly, no differences of treatment effects can be detected between the target groups. Heroin treatment is equally effective in methadone non-responders and in opiate addicts not reached by the drug support system.

The setting of psychosocial treatment has no relevant influence on treatment success. Although utilisation behaviour will be analysed in detail in the context of the special study concerning Psychosocial Treatment, the superiority of heroin treatment over methadone treatment for both varieties of psychosocial treatment points to the overall result confirming that the psychosocial setting has no influence on the outcome.

To conclude, it should be noted that heroin treatment involves a somewhat higher safety risk than methadone treatment. This is mainly due to the intravenous mode of administration. Rather frequently occurring respiratory depression and cerebral convulsions are not unexpected and can easily be medically controlled. During the first study phase, the overall mortality rate was 1.2% and rather low considering patients' poor state of health; no death occurred in causal relationship to the study medication. Considering the much higher risk of intravenous application of street heroin, the safety risk of medically controlled heroin application must be assessed as low.

The German model project of heroin-assisted treatment of opioid dependent patients has so far been the largest randomised control group study investigating the effects of heroin treatment. This is enough to lend particular significance the results in the ongoing discussion on the effects and benefits of heroin treatment. For the group of the so-called most severely dependent patients, heroin-assisted treatment proves to be superior to methadone maintenance treatment as far as the objectives of pharmacological maintenance therapies are concerned. This result calls for consequences. In accordance with research results from other countries, it is imperative to examine the possibilities of integrating heroin-assisted treatment into the catalogue of regular treatment options for severely ill intravenous opioid addicts.

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Abbreviations and definition of terms

ADE: Adverse Drug Effect
AE: Adverse Event
Aids: Acquired Immune Deficiency Syndrome
AMG: Arzneimittelgesetz (law on drugs)
AP: Alkaline Phosphatase
ASI: Addiction Severity Index
BAnz.: Bundesanzeiger (federal legal gazette)
BfArM: Bundesinstitut für Arzneimittel und Medizinprodukte (Federal institute for medical drugs and products)
BMG: Bundesministerium für Gesundheit (Federal Ministry of Health)
BtMG: Betäubungsmittelgesetz (Narcotics Law)
CGI: Clinical Global Impression
CI: Confidence interval
CIDI: Composite International Diagnostic Interview
CRF: Case Report Form
CS: Composite Scores
CU: Consumer units
EC: Ethics Committee
ECG: Electrocardiogram
EuropASI: European Addiction Severity Index
GCP: Good Clinical Practice
GSI: Global Severity Index
HA: Hair analysis
HIV: Human Immunodeficiency Virus
ICD: International Classification of Diseases
ICH: International Conference on Harmonization
ITT sample: Intention To Treat sample
LDH: Lactate Dehydrogenase
LOCF: Last Observation Carried Forward
LogReg: Logistic Regression
MTF: Methadone Treatment Failures
MTQ: Methadone daily equivalent dose
NR: Not Reached
OR: Odds Ratio
OTI-HSS: Opiate Treatment Index Health-Symptoms-Scale
POM: Primary Outcome Measure
PPA: Per Protocol Analysis
PST: Psychosocial treatment
SAE: Severe Adverse Event
SCL-90-R: Symptom-Check-List (revised)

SOP: Standard Operating Procedure
SOWS: Short Opiate Withdrawal Scale
TMF: Trial Master File
US: Urine sample
WHO: World Health Organization

1. Ethical and legal aspects

1.1 Ethics committees

The study protocol (No. ZIS-HV9-0701 of July 23, 2001, Krausz et al. 2001) and the amendments to the study plan were examined and positively voted by the Hamburg Ethics Committee (primary vote), responsible for the Principal Investigator (and the study centre in Hamburg), as well as by the ethics committees responsible for the other six study centres. Following ethics committees were involved:

- Ethikkommission der Ärztekammer Hamburg, Heinrich-Hertz-Str. 125, 22083 Hamburg
- Ethikkommission der Medizinischen Hochschule Hannover, Carl-Neuberg-Str. 1, 30623 Hannover
- Ethikkommission der Landesärztekammer Hessen, Im Vogelgesang 3, 60488 Frankfurt/M.
- Ethikkommission der Ärztekammer Nordrhein, Tersteegenstr. 31, 40474 Düsseldorf
- Ethikkommission der Rheinischen Friedrich-Wilhelms-Universität, Reutnerstr. 2b, 53113 Bonn
- Ethikkommission der Landesärztekammer Baden-Württemberg, Jahnstr. 38a, 70597 Stuttgart
- Ethikkommission der Medizinischen Fakultät der Ludwig-Maximilian Universität, Marchioninstr. 15, 81377 München

1.2 Conduct of the study according to ethical principles and the Declaration of Helsinki

The study was conducted in accordance with the valid version of the Declaration of Helsinki (approved by the 18th general assembly of the World Medical Association in Helsinki, Finland, in June 1964, and amended by the 29th general assembly in Tokyo, Japan, in October 1975, the 35th general assembly in Venice, Italy, in October 1983, the 41st general assembly in Hongkong in September 1989, the 48th general assembly in Somerset West, Republic of South Africa, in October 1996 and the 52nd general assembly in Edinburgh on October 7, 2000).

1.3 Patient information and consent

Prior to being included in the study, each patient received comprehensive oral and written information about the aims, method, extent and risks of the study, and each patient gave written consent to participate in the study. This was done the first time prior to the indication examinations (T_{-1}) and a second time shortly before starting treatment (T_0) and before informing the patient about the randomisation results. The date of consent was recorded on the study sheet. With the exception of the screening interview, no study related examinations or actions were performed prior to the first consent.

1.4 BtMG

Heroin is currently not eligible for prescription in Germany. According to the valid § 3 (2) BtMG, heroin may only be used „in exceptional cases for scientific or other purposes of public interest“. In order to use it for medical purposes in the maintenance treatment of opioid addicts, it must be transferred from Annex I of § 1 (1) BtMG (non trafficable narcotics) to Annex III (trafficable and prescribable narcotics). § 5 (1) BtMG infers that medical investigators are responsible for the observance of the regulations of the Law on Narcotics, which guarantee the safety of drug trafficking. The Bundesopiumstelle (federal narcotics bureau) issued (on demand) a BtM number to the leading medical investigators of each centre entitling them to drug trafficking (“dispensing”) within the limits of this study.

1.5 Liabilities and insurance

The principal investigator contracted a proband insurance for all the persons participating in the study. Patients’ obligations under the insurance protection are stated in the patient information brochure.

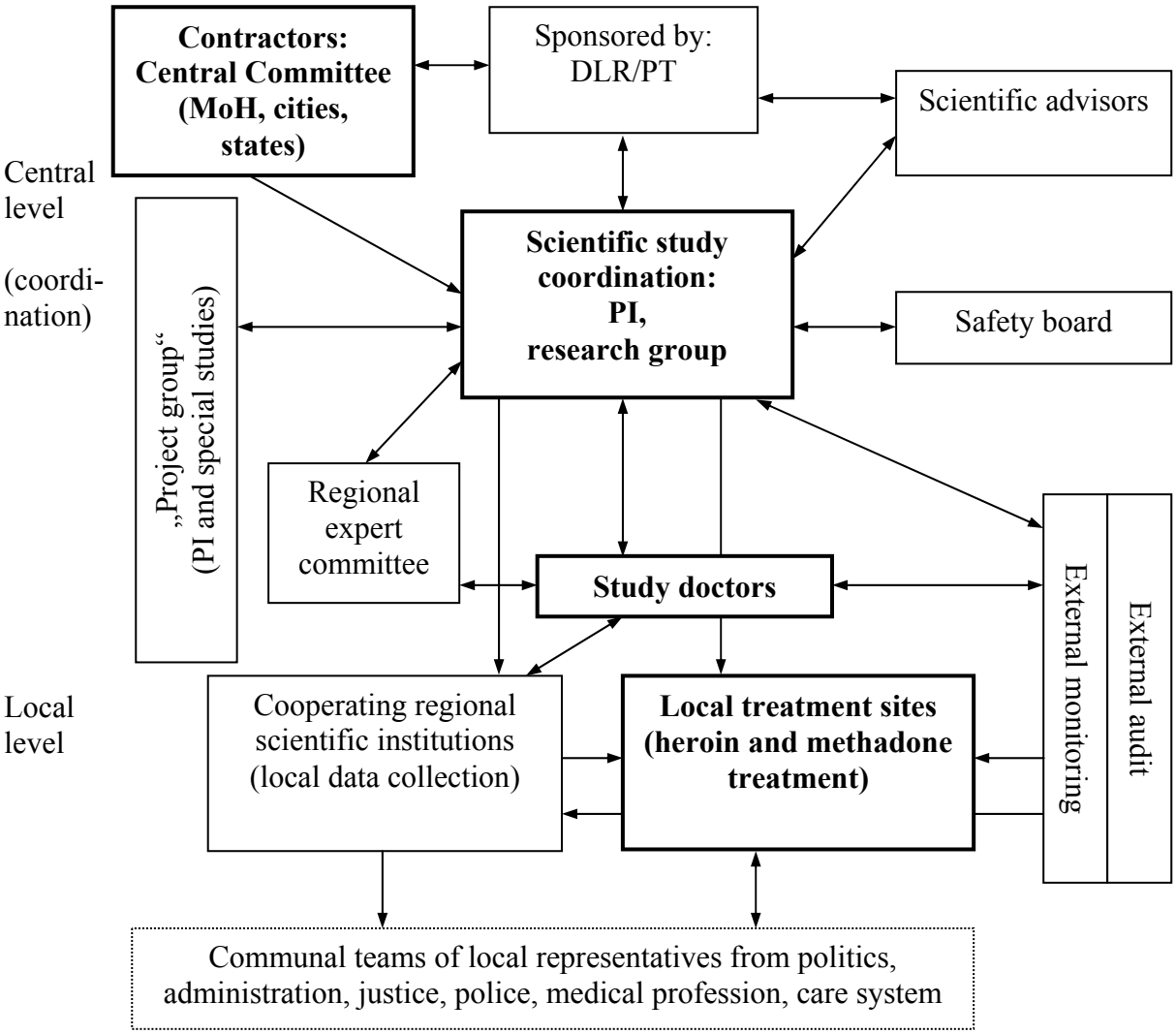
2. Principal investigator and coordination

The model project required a high degree of coordination and cooperation (figure 2.1). As it was conceived as a multi-centre clinical trial with integrated special studies, the scientific evaluation requires a maximum of standardisation. Local conditions and the screening procedure of study participants, treatment settings and treatment practice, local data collection and evaluation had to be adapted to standardised concepts. They involved quality assurance to select appropriate training concepts, as well as independent, close cooperation and coordination between the medical investigators, the persons responsible for case management and psychoeducative interventions and the persons in charge of the treatment sites. These activities were supervised by the principal investigator and coordinated in regular meetings of the project group. Moreover, close cooperation and coordination with local research institutes as well as coordination with external monitoring were necessary. The great scientific significance of the study was expected to attract the interest of a critical (expert) public; therefore, a scientific advisory committee including national and international experts was set up to be consulted throughout the project duration.

The conduction of the study was organised and monitored in line with the binding cooperation agreement with the Ministry of Health and the participating cities and federal states represented in the central committee. On the regional level, local teams with representatives of the relevant local institutions and organisations were engaged in achieving a maximum of acceptance and practical performance.

The persons involved in the study (coordinators and investigators) are listed in Annex I.

Figure 2.1
Cooperation among the parties involved in the clinical trial of heroin-assisted treatment



3. Introduction

In Germany, the introduction of heroin-assisted treatment for most severely dependent heroin addicts had already been discussed in the early nineties. In May 1992, against the background of high drug-related mortality rates (highest rate in 1991: 2,125 deaths) and the spread of HIV infection and Aids among drug users, the city of Hamburg introduced a legislative initiative to the Bundesrat (upper house of the German Parliament) to change the law on narcotics (BtMG) with the objective to create the conditions for medical treatment with heroin. One year later, in February 1993, the city of Frankfurt, in accordance with § 3 (2) of the BtMG, submitted a project of scientifically controlled heroin prescription to the Ministry of Health for approval. Both initiatives were not directly successful but intensified the political and scientific discussion. When the Swiss project (PROVE) started in 1994, the debate on a German model trial of heroin-assisted treatment became livelier. Meanwhile, experiences on the efficacy of methadone maintenance treatment had also been gained in Germany, and its potentials and limitations influenced the debate on the expected benefits of alternative therapies such as heroin-assisted treatment (or the use of LAAM or buprenorphine). When the results of the Swiss Project were published in summer 1997 (Uchtenhagen et al. 1997), with an overall positive assessment of this type of treatment, plans to initiate a model project of heroin-assisted treatment in Germany became more concrete. Against this background, the association of the cities in favour of heroin-assisted treatment and the initiative of the Federal Government led to a call for proposals for a German model project.

The call for proposals of the Federal Ministry of Health of 1999 requested a study design „for a multi-centre, clinical study for outpatient heroin-assisted treatment of opioid dependent patients“. This scientific model project was required to „include clinical testing of medical substances containing heroin (licence study) and provide additional knowledge on the issue if and to what degree opioid addicts, who could be treated only insufficiently or not at all by the existing help offers of the addiction services, might benefit from heroin-assisted treatment in order to be stabilised regarding their health and social integration, be reliably integrated into the help system, retained in the help system and motivated for further treatment.“ The study should „also investigate if and how heroin-assisted treatment could be implemented into the treatment catalogue for opioid dependent patients and contribute to the limitation of safety risks.“

The controlled dispensing of pure heroin occurs in a *structured treatment setting*. The treatment focuses on the target group of heroin addicts in need of treatment, who were not reached by the current addiction services in a *therapeutically effective way* („not reached“, NR) or who *did not sufficiently benefit from previous methadone maintenance treatment* („methadone treatment failures“, MTF). The efficacy trial compares heroin-assisted treatment to the standard treatment with oral methadone, an intervention well studied for the last 30 years (Ward et al. 1998; 1999). Treatment settings for both treatment types are systematically varied regarding psychosocial co-treatment (case management with integrated motivational interviewing or drug counselling with psychoeducation). Study treatment (consisting of medical-pharmacological and psychosocial parts) is therefore conducted in *four different*

settings: i.v. heroin plus case management or i.v. heroin plus drug counselling with psychoeducation *compared to* oral methadone plus case management or oral methadone plus drug counselling with psychoeducation.

The study was conceived as a *clinical drug trial*, conducted according to the guidelines of "good clinical practice" (GCP) (ICH 1996) and should a.o. prepare the grounds for a possible licensing of injectable heroin as medical drug in Germany. It consists of two phases:

- In the first 12 months, a 4x2 stratified randomised control group study investigated the effects of heroin versus methadone treatment under comparable setting conditions (1st study phase, cf. part B of the study protocol ZIS-HV9-0701). The analysis is carried out by a four-factor logistic regression model. This study phase has been completed and is the base of the present study report.
- The second 12-month study phase started immediately after the first phase (cf. part C of the study protocol ZIS-HV9-0701) and investigated long-term effects (stabilisation and connexion to the addiction services) as well as other issues raised in the call for proposals, e.g. integration into the regional care system, regular conclusion of heroin treatment or engaging in further treatment. All patients of the experimental group (heroin) could continue study treatment in phase two. Except for a randomly selected group of control patients, who were offered vacated places of heroin treatment after 12 months, patients of the control group (methadone) were released from study treatment and receive further treatment within the normal treatment system. The second phase was concluded at the end of 2005. Patients could then (based on the amendments ZIS-HA9/11 of 15.1.2004 and ZIS-HA9/12 of 1.3.2004) continue heroin treatment in a follow-up phase, which might continue until a licence decision is taken.

Additional special studies are conducted within the frame of the model project and integrated in the 24-month duration. They investigate criminological and care related issues (health economics, implementation, cooperation), cognitive-motoric and neuropsychological issues as well as issues related to the internal evaluation of psychosocial treatment. The results of these studies will be reported separately.

4. Study objectives, hypotheses

The objective of the study is to investigate whether pharmacologically pure heroin administered to certain groups of heroin dependent patients in a structured and controlled treatment setting, is better able to ensure the goals that are normally associated with standard therapies of addiction treatment: harm reduction, integration into the care system, reduction of illicit drug use and related problems, health, mental and social improvement and stabilisation, controlling and overcoming the dependency.

The study is based on the hypothesis that heroin-assisted treatment is a therapeutically useful addition to the services for the treatment of heroin addicts, who have not been reached in a therapeutically effective way by the addiction services or who did not sufficiently benefit from previous methadone maintenance treatment.

The central hypothesis is:

Heroin-assisted treatment leads to better effects compared to oral methadone maintenance treatment in terms of

- markedly improved physical and/or mental health,
- greater reduction of illicit drug use and accordingly separation from the context of the drug scene,
- markedly improved social situation,
- greater decrease of delinquency,
- higher retention rate and better connection with treatment setting.

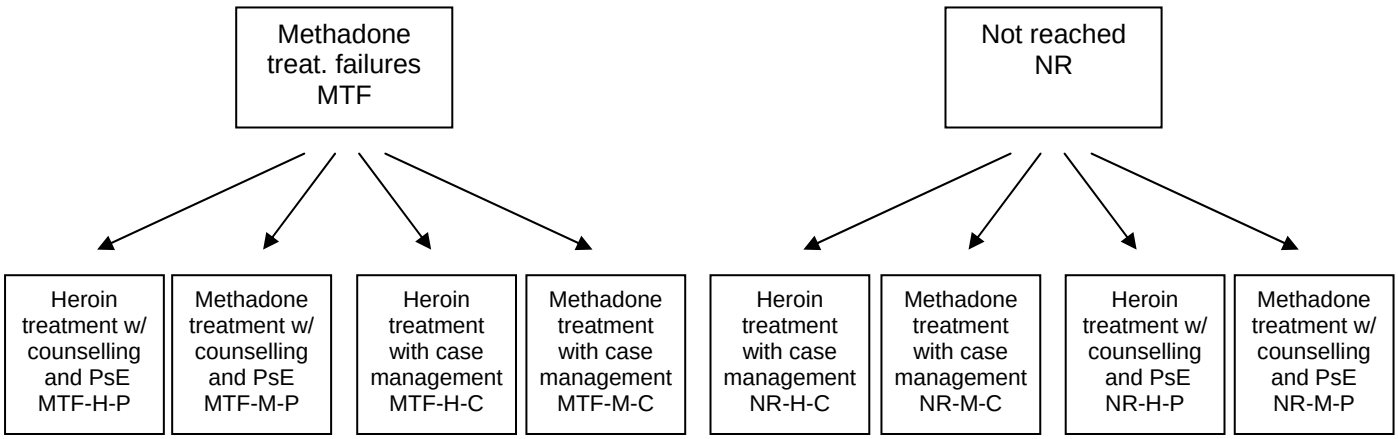
Additional hypotheses state that a tendency of superiority of heroin treatment over methadone treatment can be found in both target groups (MTF and NR) and that the effects of heroin treatment can be reached to a similar degree in both psychosocial settings (case management with integrated motivational interviews vs. drug counselling with psychoeducation).

5. Investigational plan

5.1 Description of study design

In the first phase of the clinical trial, a 4x2 stratified randomised multi-centre study was conducted. The sample consists on the one hand of heroin addicts, who had been in methadone maintenance treatment but did not sufficiently benefit from the treatment (MTF), and on the other hand of heroin addicts, who were presently not in any addiction treatment (NR). Patients from both target groups (or sample strata), who fulfilled the inclusion criteria, were randomised to four branches respectively: *experimental groups (MTF-H-C) and (NR-H-C):* heroin treatment with concomitant case management, *experimental groups (MTF-H-P) and (NR-H-P):* heroin treatment with concomitant psychoeducation/drug counselling and *control groups (MTF-M-C) and (NR-M-C):* methadone treatment with concomitant case management, *control groups (MTF-M-P) and (NR-M-P):* methadone treatment with concomitant psychoeducation/drug counselling (see figure 5.1). The target number of patients to be included in the study was 1,120 patients, each group consisting of 140 study participants.

Figure 5.1
Study groups of the clinical trial of heroin-assisted treatment of opioid-dependent patients after sample stratification in study phase 1



In the experimental group, study treatment includes daily dispensing of intravenously injectable heroin, concomitant examinations by medical staff and regular psychosocial treatment consisting of case management or psychoeducation/drug counselling. Heroin can be dispensed up to three times a day (morning, noon, evening), an additional dose of methadone can be obtained for the night. Due to the complex treatment regimens and the necessity to observe safety regulations and comply with the narcotics law, heroin treatment is carried out only in special outpatient drug units.
The model project of heroin-assisted treatment is conceived as an open study. It is virtually impossible to comply with the requirements of a double-blind design in studies that compare

the efficacy of heroin and other maintenance substances (or even placebos) (Bammer et al. 1999). Experienced users would recognise the study medication, and the different efficacy durations and modes of administration of heroin and methadone could not be masked.

5.1.1 Recruitment of patients

The process of patient recruitment started about 3 months prior to the planned treatment initiation. The model project was publicized in all addiction and local health service sites, among medical practitioners and via the regional press. By letter of information, staffs of institutions were invited to approach and motivate appropriate patients and to inform them about the *registration* procedure. The period of registration is not part of the individual study duration, i.e. patients could register at any time; appointments for the indication examination were issued randomly. At registration, patients were already *screened* for certain inclusion criteria. Patients in maintenance treatment (MTF stratum) were instructed to bring all relevant medical records so that inclusion and exclusion criteria could be verified. Prior to the *indication examination* (T_{-1}) by the medical investigator (or another doctor participating in the study and assigned by the medical investigator) patients received information about the study and were asked to sign the *first consent* of participation. A *regional expert committee* verified inclusion and exclusion criteria. Only then, a final decision regarding the inclusion in the study could be taken. The complete range of *baseline* examinations (T_{-1}) was conducted within the frame of the indication examination, i.e. also the external interview (following the EuropASI, Kokkevi & Hartgers 1995; Gsellhofer et al. 1999), which explored the psychosocial life situation and biographical, criminological and health economical aspects.

5.1.2 Randomisation

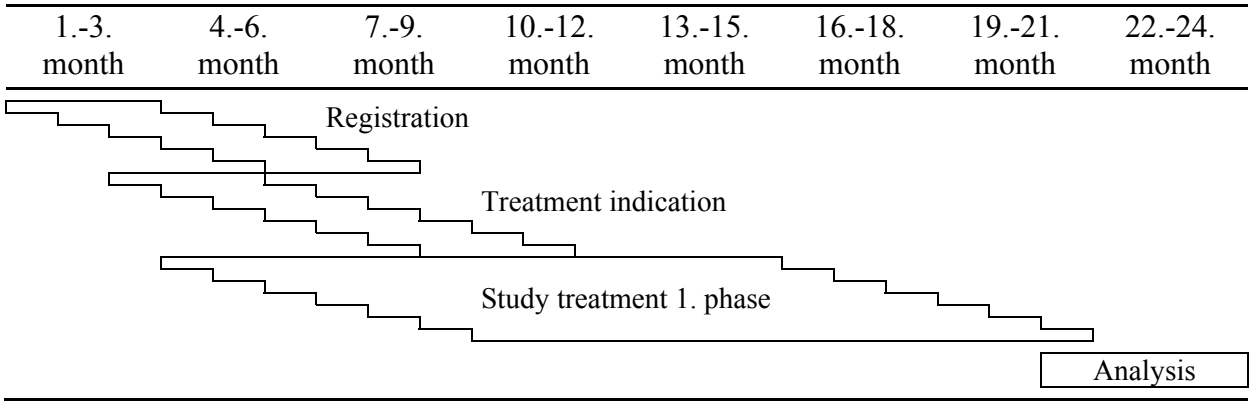
Treatment places of the experimental and control groups were assigned according to a previously determined randomisation code, unknown to persons involved in screening and registration examination. Randomisation was done separately for the two groups (MTF and NR) with permutated blocks of fixed size. The standardised randomisation procedure was meant to guarantee a uniform, completely random assignment of patients and – since it was an open study – to exclude manipulations by persons involved in the inclusion examination and treatment. After evaluation of the indication examination and the first interview (at T_{-1}), persons, who fulfilled the inclusion criteria, were invited to report again at the study site. They were requested to give a *second written consent* of participation and were then informed about the randomisation result. Shortly before the actual start of treatment, patients' current state of health was checked again (T_0).

5.1.3 Duration and course of study

The duration of the 1st study phase was 12 months. It was assumed that the organisation would extend over a period of about 24 months. The project started with the registration phase, when appointments for the indication examination were issued (after positive screening results). This was followed by a preparatory or transitional phase leading to the randomised assignment (and the start of treatment). In the initial planning, a total of 6-9 months were

allowed for the examinations and evaluations of inclusion criteria. The first patient was treated in the 3rd month (see figure 5.2).

Figure 5.2
Organisational course of the 1st study phase of the clinical trial within an overall period of 24 months



5.1.4 Documentation and Examinations

There are three levels of data collection and documentation of the course of treatment: documentation of medical examinations, laboratory results and prescriptions (A, "medical investigator CRF"), internal documentation of psychosocial concomitant treatment (B), which supplies utilisation data for the "medical investigator CRF", and the external scientific evaluation based on interviews and questionnaires (C, "CRF extern"). Schedules of the different examinations are presented in figure 5.3.
All external interviews (CRF extern) were personal interviews assuring confidentiality also vis-à-vis the treatment unit. Self-report questionnaires were filled in during the interview appointments. The sheets were checked for completeness by the interviewer, and the patient could be asked about missing data. Interviewers had been trained in the technique of interviewing and the use of survey instruments. They are not part of the staff of any of the treatment units.
At T_6 and T_{12}, respectively, 5 urine samples were closely analysed by GC/MS in order to determine street heroin use, as required with regard to the POM (see below). These analyses as well as the urinalysis at T_{-1} and the hair analyses were performed at the departments of forensic medicine of the regional universities (or local medical laboratory associations). Elaborate urinalyses at T_6 are necessary in order to complete missing data at the end of the first study phase (T_{12}) (see below) by "last observation carried forward" (LOCF). Weekly urinalyses testing for drug use were based on test strips and carried out at the treatment site, with the exception of quantitative analyses at the indication examination and at T_6 and T_{12}. Local lab associations were involved in the serological analyses of blood and urine samples.

Figure 5.3
Examination and survey schedule of the first phase of the clinical trial. T_{-1} = indication, T_0 = start of treatment, $T_{1,3,6}$ = 1, 3 and 6 months after treatment initiation, T_{12} = end of study phase 1

	T_{-1}	**T_0**	**T_1**	**T_3**	**T_6**	**T_{12}**
Patient information, consent[a)]	X	X				
A. Medical examinations/lab:						
Inclusion and exclusion criteria	X					X
General case history	X			X	X	X
Specific case history	X				X	X
Physical examination	X	X	X	X	X	X
OTI health scale	X	X	X	X	X	X
Mental state	X	X	X	X	X	X
SCL-90-R	X		X	X	X	X
CIDI			X			
SOWS	X	X	X	X	X	X
Swabs in case of skin infections	X	X	X	X	X	X
Blood count	X	X	X	X	X	X
Pregnancy test	X					
Hepatitis B, C, HIV, Syphilis	X					X
Mendel-Mantoux test		X			X[b)]	X[b)]
Thyroid diagnosis	X					
Abdominal sonography	X					
Echocardiography	X					X
ECG	X				X	X
Thorax x-ray	X[c)]					X[c)]
Urinalysis	X	weekly				
Hair analysis	X	X[d)]			X[e)]	X
MSLQ	X				X	X
B. PSB:						
Documentation (activities, contents)		X	concomitant to PST			
Specific course surveys		X	concomitant to PST			
C. External evaluation:						
EuropASI (supplemented)	X				X	X
Social support, SOZU	X				X	X
Readiness to change, VSS-K	X				X	X
Concept of illness, PUK	X					
Treatment satisfaction					X	X
Self-esteem, mental condition	X				X	X
Coping, delay of reward	X				X	X
Abstinence confidence, HEISA					X	X
Survey of economic situation	X				X	X
Delinquency (quantitative interview)	X					X

a) First patient information occurred already at registration.
b) Mendel-Mantoux test at T_6 and T_{12} only in case of negative results of previous examinations.
c) Thorax x-ray only in case of clinical indication.
d) A hair sample was only taken at T_0 if it had not been possible at T_{-1}.
e) Lab analysis of this hair sample only occurred in case of missing 12-month data.

5.2 Background and state of knowledge concerning heroin treatment – recent results and developments

The German study of heroin-assisted treatment is in line with the legal requirements (related to medical drugs) and standards ruling clinical trials as well as with previous surveys investigating the efficacy of this type of treatment. Experiences of heroin prescription to opioid-dependent patients had been gained in the UK, Switzerland and the Netherlands. All trials and observations have in common that the results in general indicate the feasibility and acceptance of heroin-assisted treatment (Krausz et al. 1999; Rehm et al. 2001).
The study protocol includes a summary of experiences of heroin-assisted treatment until 2001 (Krausz et al. 2001). More recent results were meanwhile published and are presented hereafter.
The results of the Dutch study, not yet completed when the study protocol was worked out, are particularly significant. The final report (CCBH 2002) and first publications (van den Brink et al. 2003; Blanken et al. 2005) are now available. The inhalation and the injection trial were both evaluated as successful showing the significant superiority of combined heroin-methadone treatment over methadone treatment alone. A total of 174 patients participated in the injection trial, 375 patients were randomised to the inhalation study.
References hereafter will mostly refer to the injection trial, because the results of intravenously applied heroin treatment are of greater relevance for the German situation.
98 patients were randomised to the control group of methadone treatment (group A), 76 patients were included in the study group of heroin treatment (group B). 85% of the methadone group completed treatment; "only" 72% of the heroin patients stayed in treatment till the end of the 12-month study treatment. 7 patients (9%) did not start heroin treatment. Valid data related to the participation in scientific examinations and interviews were available for almost all heroin patients (97%) at the end of treatment (after 12 months), in the methadone group slightly less with 90%. Treatment response was defined as an improvement of (at least) 40% compared to baseline. The response rate of the heroin group was 56.6% compared to 31.6% among methadone patients.[1] The odds ratio was 2.99 and is significant on the 1‰ level (95%-KI: 1.58-5.56, p=0.0008). The variable "study centre" had no influence on the overall result. On average, the health score HSS of the MAP inventory (Marsden et al. 1998) of heroin patients dropped from 12.1 to 8.6 points, in methadone patients only from 11.1 to 10.5 points. The development of mental symptoms took a parallel course: The SCL-90 score of heroin patients dropped from 76.3 at baseline to 55.1, in methadone patients, the SCL score "only" dropped from 72.7 to 62.1 points. The decrease of cocaine use was not quite so impressive: In both groups, the number of consumption days decreased by almost 3 days on average; in the methadone group, the level of drug use was slightly higher at baseline and at the end of treatment. As the response definition of the Dutch study is a kind of composite score of several target criteria, it was additionally investigated in how many (and which) of the three primary outcome measures – physical health, mental condition, social integration –

[1] Based on the experts' critique regarding the evaluation strategy, response rates changed slightly, but not significantly in the BMJ publication (van den Brink et al. 2003) compared to the final report (CCBH 2002). The original results of the final report are cited here.

patients had a treatment response. The results show that in the heroin group, 30.3% of the patients – nearly half of the responders – had a response rate only in one, 22.4% in two and 4.0% in all three target criteria. The results of the methadone group were quite different: The number of patients fulfilling only one response criterion is, with 31.6%, similar to the heroin group, but this corresponds already to 83.9% of all treatment responders in this group. 5.1% of the methadone patients responded in two target criteria, none of the control group patients responded in all three outcome criteria.

To assess the efficacy of heroin treatment, the results of the so called withdrawal trial are of particular interest: During the 2-month test phase, a marked deterioration of health symptoms or drug use behaviour occurred in more than 80% of the patients of the inhalation trial and in 84% of the patients of the injection trial. Of the 55 participants of the injection trial, who regularly completed heroin treatment, 32 were responders. The state of 27 patients of this group (84.4%) deteriorated by at least 20% in at least one of the outcome categories that had improved in the course of study treatment. The overall deterioration corresponded to a regression to the negative level at baseline. For instance, the health score (MAP-HSS), which had improved from an average of 12.0 to 4.3 points in this group of patients during i.v. heroin treatment, reached again 13.2 points at the end of the withdrawal trial. The development related to mental health was similarly adverse: In month 14, the total SCL-90 score increased to 62.1 points, after having previously dropped from an average of 74.2 to 30.6 points during heroin treatment. The change was particularly dramatic in the field of delinquency. The number of days with criminal behaviour dropped from 13.5 to 0.3 days under study treatment and increased again to 16.0 days during the withdrawal trial. Cocaine use, too, went back to baseline levels with an average of 12.8 days of consumption. This led to the conclusion that the effects of heroin treatment (and of combined heroin-methadone treatment) were directly linked to the maintenance of treatment. Although the majority of positive effects occurred at an early stage of treatment (after 2 months), premature discontinuation of the medication-assisted long-term treatment involves great risks to lose the positive effects already achieved. The authors conclude their report with the recommendation of a long-term follow-up study on heroin treatment, which should a.o. address questions similar to the targets of the German model project.

Long-term effects of heroin-assisted treatment are presented for the first time in the framework of a 6-year follow-up study in Switzerland, now published by Güttinger et al. (2002; 2003). Out of 366 patients, who started treatment between January 1994 and March 1995, 148 patients were still in heroin-assisted treatment after 6 years (40.4%). 175 persons dropped out of treatment (47.8%), 43 patients died during the survey period (11.7%), though only 5 of them participated in the heroin programme at the time of their death. Almost 83% of the patients could be interviewed again after an average of 6.3 years after their (first) start of treatment. It should be noted that a considerable number (24.3%) of the patients, who had discontinued heroin treatment, were now in abstinence orientated treatment and another 21.6% in methadone maintenance treatment. A major result of this long-term study is that patients succeed in stabilising over a longer period the positive changes they achieved after 12 to 18 months of treatment (Rehm et al. 2001). But the most conspicuous result is that positive developments of life situation and illicit drug use are similar in patients, who had dropped out

of treatment (after an average of 2.4 years), to patients, who were still in heroin-assisted treatment after 6 years. Although a significantly higher proportion of persons in the dropout group (18.9%) than in the group still in treatment (3.8%) use (additional) street heroin daily, there had been a drastic decrease from baseline (dropouts: 76.1%, treatment group: 84.7%) in both groups. Regarding regular cocaine use, no significant differences could be detected at follow-up. In both groups, there had been a marked decrease of consumption (dropouts: from 27.5% to 5.3%, treatment group: from 30.8% to 9.8%). The similarities are even more striking when comparing the social situations. Almost all areas – homelessness, unemployment, illicit income, legal proceedings, social contacts – had parallel, mainly positive developments, which show that the life situation was similar for dropouts of heroin treatment and for patients still in heroin-assisted treatment. This shows clearly that many patients can succeed in stabilising their life situation within two or three years and are able to go on without further heroin treatment. On the other hand, patients should have the option to participate in this type of treatment for longer periods of time, in order to benefit in the long run.

Based on the two randomised Dutch studies on heroin-assisted treatment (inhalation and injection study: n=430), Blanken et al. (2005) investigated which baseline characteristics correspond to the treatment response. Of the 44 variables under consideration, just a few interact with the treatment on a significance level of $p<0.25$ in a logistic regression analysis: average/higher education ($p=0.16$), no hospitalisations for somatic problems ($p=0.21$), no medical drugs for psychiatric problems ($p=0.21$), living alone ($p=0.12$), main source of income from employment ($p=0.15$) and almost daily cocaine use ($p=0.21$). Only one interaction effect – previous experiences of abstinence-orientated treatment – is highly significant ($p=0.0003$). For patients with previous treatment experience, the response rate is 60.5% for heroin patients compared to 23.8% for methadone patients. Without previous abstinence treatment, success rates are similar (39.2% for heroin and 37.5% for methadone). The authors assume as an explanation for this effect that patients with repeated experiences of abstinence-orientated therapies are more motivated and can more easily cope with the strict treatment regulations (Blanken et al. 2005).

Regarding secondary target criteria, the Swiss data produced new results. A number of previous studies found, on the one hand, a considerable decrease of delinquency among patients participating in heroin-assisted treatment and, on the other hand, positive developments regarding various indicators of the social situation and of addiction behaviour (Uchtenhagen et al. 2000). However, these results had been analysed on a group level. A more recent study (Ribeaud 2005) investigated the issue of parallel developments of delinquency and other areas of life, based on a sample of n=302 with data available for a 12-month period. Results of previous studies are confirmed showing a marked decrease in all criminological indicators (property offences, drug selling, victim of theft, victim of fraud when buying drugs) (between 59% and 70%). This refers also to the indicators of addiction behaviour (with reservations where cannabis is concerned) and contacts to the scene (decrease between 44% and 51%). The employment situation remains stable with ca. 50% of employed probands; the grey areas of employment (prostitution, delinquency, etc.) decreased by 87%, from 32% of the patients at baseline to 4% after one year of treatment. The development concerning sources of income and housing situation confirms this trend. The specific

objective of this study was whether a decrease of delinquency is related to positive developments in other areas of life on the individual level. The expected parallel developments of procuring delinquency and decreasing risky and unstable income sources could be confirmed. However, procuring delinquency is not substituted by legal sources of income (gainful employment, government support), and there are no indications of parallel developments concerning social integration (employed, own apartment). In summary, the author concludes that the decrease of delinquency in connection with heroin treatment is not a consequence of social integration and that better social integration cannot be expected as a consequence of less delinquency. At least in the initial phase of heroin-assisted treatment, decrease of delinquency and abandoning of risky financial resources are to be considered as a direct consequence of the reduced financial needs to procure heroin (Ribeaud 2005).

Preliminary cost effectiveness analyses comparing heroin-assisted treatment to the standard treatment with methadone are of major importance with respect to its potential implementation into the range of treatment options. A comparison of the costs of combined heroin and methadone treatment (n=193) and of methadone alone (n=237) had been carried out based on the joint evaluation of the two Dutch parallel studies (Dijkgraaf et al. 2005). On the treatment level, the higher costs for heroin treatment are on average 17,634 Euro compared to 1,412 Euro for methadone treatment. On the level of health costs, there is no difference between both groups. Costs for criminal prosecution are to the advantage of heroin treatment. Patients treated with heroin incur costs of 8,656 Euro compared to 12,885 Euro for methadone patients. This difference is even greater in the comparison of direct damages caused by delinquency. Costs for damages amount to 9,617 Euro for patients treated with heroin compared to 34,991 Euro for patients treated with methadone.

The end result thus demonstrates the superiority, i.e. cost effectiveness of heroin treatment of 12,793 Euro a year; costs of 37,767 Euro incurred by heroin patients are contrasted to 50,560 Euro incurred by methadone patients. The higher costs for heroin-assisted treatment are more than compensated by lower costs related to police and justice and damages to victims (Dijkgraaf et al. 2005).

Fischer et al. (2002) presented an overview of current or planned further research projects. Of the randomised and controlled studies they refer to, the preliminary study in Barcelona started in autumn 2004 (research team Casas). The study in Andalusia (research team March), which compared injectable heroin and methadone, was concluded at the end of 2004. The results have not yet been published. The Canadian study (research team Schechter) has been approved, and recruitment of patients started in Spring 2005.

5.3 Discussion of study design

The study design is, on the one hand, the result of a thorough study of the literature, the state of research and the requirements of the call for submissions, and, on the other hand, of numerous discussions with consultants and participating study centres.

The first study phase, presented here, is embedded in an interdisciplinary research project running over two years that fulfils the conditions of a clinical drug trial (licensing study) and is able to answer questions regarding treatment and care research.

The scientific trial project (model project) was carried out as a clinical, controlled, comparative study in the framework of a phase III study according to the guidelines ruling the testing of medical drugs (BAnz. no. 243 of 30.12.1987) and the guidelines of „Good Clinical Practice“ (GCP) (ICH 1996). The object of these studies is usually to verify the therapeutic value of the methods or substances under observation and to compare them to (established) treatment alternatives, weighing up risks and benefits in a large group of patients. The clinical study mainly focuses on the effects of the medical drug (in the framework of an integrated treatment setting), i.e. desired and unwelcome effects related, on the one hand, to the development in the course of time (long-term development) and, on the other hand, in comparison to other therapies.

The study by Hartnoll et al. (1980) and the Swiss study (and its different special studies) (Uchtenhagen et al. 1997; Perneger et al. 1998) can be considered as feasibility studies and pilot treatment studies according to the rules of Good Clinical Practice (though they were not completely followed in these studies). The results, mostly from Switzerland, concerning doses, side effects and pharmacological properties of heroin, as well as the findings on feasibility and safety of the therapeutic setting, justify to conduct a study in a large patient population. The Dutch study, meanwhile concluded, was also conducted as a clinical trial according to phase III (CCBH 2002); however, the partial study investigating intravenously applicable diamorphine was conducted in a markedly smaller number of patients (n=174).

The first phase of the study, presented here, is limited to 12 months of treatment and has the objective – if the results are favourable – to provide the conditions required for transferring i.v. heroin from appendix I to appendix III of the BtMG and its licensing as a medical drug for the treatment of heroin dependence in Germany. Upon conclusion of this section of the study and in case of success, the producer may file a licensing application with the BfArM.

Experiences from the Netherlands show that it is possible to randomise patients that are in methadone maintenance treatment (van den Brink et al. 1999; CCBH 1999). At the time of the conceptual design of the study, it was still open whether patients currently not in treatment („not reached“) are prepared to accept the conditions of the control treatment with methadone for the entire period of investigation. Therefore, a motivational incentive to persevere in treatment was proposed by offering vacated heroin treatment places to patients of the control group (see below).

According to the guidelines of „Good Clinical Practice“, the design of a phase III trial is preferably double-blind in addition to randomisation. However, studies that compare the efficacy of heroin and other maintenance substances (or even placebos) and comply with the requirements of a double-blind design are virtually impossible (Bammer et al. 1999). The study medication would be recognised at once by experienced users eligible for heroin treatment. Moreover, the different durations of efficacy and the related modes of application cannot be masked, in particular if heroin is compared with the so-called standard medication, oral methadone. Therefore, the trial project was conceived as an open study. The clinical drug trial requires, therefore, particular objectivity with respect to the primary outcome measures, which the study design took into account.

5.3.1 Target groups

The process of indication for heroin-assisted treatment is an essential part of the study. Through the target group of opioid addicts with previous unsatisfactory methadone maintenance treatment, the German model project systematically included opioid addicts not reached therapeutically. This sample stratification assured that 50% of the heroin treatment places are occupied by this group and it avoids an excessive „chance of participation" of methadone patients. (See experiences of the Swiss trial, where the majority of the sample were recruited directly from methadone maintenance treatment.) The two target groups (MTF and NR) are considered as different groups of opioid addicts. The analysis strategy of the the samplefour-factor logistic regression takes into account the confounding influence resulting from the sample assignment. At the same time, it is possible to work out the importance of the indication (no treatment i.e. not reached vs. unsatisfactory course of methadone maintenance), which is an important clinical and scientific surplus value.
If the treatment study were conducted *solely* among opioid addicts already in methadone treatment, it would contain a conceptual bias with respect to group comparison between heroin and methadone groups. If the effectiveness of heroin treatment is compared to methadone maintenance in patients, whose treatment was not sufficiently effective according to the definition of the inclusion criteria, heroin treatment must be expected from the start to be superior, since part of this group of patient remains in methadone treatment (with partly different setting) and a positive development within the study seems rather improbable. The alternative would be a randomised sample of patients in methadone maintenance treatment *without* the indication of an unsatisfactory course of methadone treatment. However, this would contradict testing the efficacy of heroin treatment as a lower-ranking type of treatment. Moreover, there would be ethical doubts about transferring patients from well running methadone treatment to a more invasive and more complex and restrictive treatment regimen. However, the principle of falsification in group comparisons would be statistically maintained by this trial design: Heroin treatment is not automatically the better alternative in this group of patients (which is to be tested). Moreover, a worsening of the state of the control group patients is not expected due to the structured treatment setting (medical treatment and case management or counselling/PsE); heroin treatment thus has to be proved superior to ongoing methadone treatment. But the comparison between experimental and control groups among the „not reached" is of particular importance, as the above mentioned bias does not exist. Higher efficacy of heroin vs. methadone treatment cannot a priori be admitted for patients of this target group, unless one takes into account that probably some of these patients had (unsuccessfully) tried methadone treatment previously and might, therefore, (subjectively) feel more disinclined to be part of the control group.

5.3.2 Concomitant psychosocial treatment

Modern treatment of drug dependent persons must consider interventions pertaining to pharmacology, psychotherapy, education and social therapy, adjusted to individual needs. The standards e.g. of methadone maintenance treatment (Bühringer et al. 1995; Akzept 1995; APA 1995) as well as the results of treatment research (Woody et al. 1990; McLellan et al.

1993; Lowinson et al. 1997; Crits-Christoph et al. 1999) show the necessity of offering qualified psychosocial treatment as integrated part of addiction treatment in its various settings.
Many therapeutic interventions have not been sufficiently investigated. There are hardly any high-standard studies on psychotherapeutic interventions in addiction treatment (Grawe et al. 1993; Strain 1999). The state of treatment research with respect to disorder-specific interventions is unsatisfactory despite their clinical relevance and dissemination. In the German language area, hardly any studies of high methodological standards and based on randomisation and with a control group design were published during the last years (Ladewig 1997). The comments by the WHO review board (WHO 1996; 1999) on the Swiss heroin trial also point to the necessity of a more thorough investigation of the effects of psychosocial therapies compared to substance specific effects in the framework of a multidimensional treatment approach, in order to better evaluate the usefulness and effectiveness of medical heroin prescription.
Research on methadone maintenance treatment showed the positive influence of concomitant psychosocial treatment (e.g. Ball & Ross 1991; Joe et al. 1991; McLellan et al. 1993; Verthein 1995) and thus justifies the assumption that favourable effects can also be expected in heroin treatment. However, the issue of standards of psychosocial treatment for different target groups is as yet unsettled. To define the added value of heroin treatment compared to previous treatment offers and the significance of psychosocial and substance related effects, it was necessary to chose standardised (i.e. manualised) types of interventions that could be compared under controlled conditions and include a large study sample. Therefore, two different intervention strategies are integrated into the study and compared: case management with integrated motivational interviews (Oliva et al. 2001; Miller & Rollnick 1999) vs. manualised psychoeducation in addition to drug counselling (Hornung 1998).

5.3.3 Filling vacated heroin treatment places

The concept of the design attaches great importance to the stability of the control group. An increased dropout rate has to be expected in particular from patients of the target group who were not reached therapeutically (NR), who were randomly assigned to the control group and thus enter methadone maintenance treatment, which is possibly associated with negative experiences in the past. For the patients coming from methadone treatment, whose treatment will be continued with added case management or the combination of counselling and psychoeducation, this aspect is probably less important, since they essentially continue their treatment except for more structuring and a new form of concomitant treatment.
In order to prevent patients from the control group to prematurely drop out, those who followed treatment according to the study protocol were informed that, on request, they could fill vacated places of heroin treatment at the conclusion of the first study phase (after 12 months), though not every patient could be promised a vacated place. This was explained to the patients prior to the start of the study. The probability of change is limited by the number of vacated heroin treatment places. After 12 months, a rate of about 20% to 25% of dropouts (or concluders) of heroin treatment was expected. Therefore, a substantial percentage of control group patients, who were still in methadone treatment after one year and expressed the

wish to change, could start heroin treatment. The vacant heroin places were assigned randomly to those who wished to change (re-randomisation).

5.3.4 Optimised methadone maintenance treatment for the control group

Although heroin treatment targets certain groups of opioid addicts in accordance with the indication criteria and positive effects are expected mainly in accordance with the Swiss results, it can be ethically justified to randomise patients to methadone maintenance treatment (control groups), a type of treatment that many of them had already passed through with none or only moderate success. In the framework of the study, methadone treatment occurs in a structured setting with concomitant case management and integrated motivational interviewing or with drug counselling and psychoeducative group therapy, which, in most cases, is probably different from the treatment received so far. According to (international) experiences, positive effects in terms of individual improvements in patients are to be expected from this kind of comprehensive structured treatment setting (Ball & Ross 1991; McLellan et al. 1993).

5.4 Selection of study sample

Heroin-assisted treatment targets opioid addicts, who used heroin intravenously for many years, who were not reached by the addiction services or did not sufficiently benefit from previous treatment and who are in a poor state of health.

5.4.1 Inclusion criteria

According to the overall question whether heroin treatment is an effective, though lower-ranking addition to the catalogue of existing addiction services for heroin addicts, persons, who fulfilled following criteria, were included in the study:

- Minimum age 23 years
- Opioid dependency for at least 5 years
- Current main diagnosis of opioid dependency according to ICD-10
- Current daily, mainly i.v. heroin use or continued heroin use under maintenance treatment
- Symptoms of physical illness indicating a poor state of health as measured by the OTI health scale with at least 13 current symptoms
  OR
  Current mental symptoms or impairments, i.e. a standardised GSI score on the SCL-90-R (Franke 1995) of at least 60 points
- No addiction treatment (in particular no maintenance treatment, outpatient or inpatient treatment) for at least 6 months, but documented previous experience with drug treatment
  OR
  Negative course of maintenance treatment conducted according to the guidelines of the federal medical council (Bundesärztekammer 1997), due to continued co-use of heroin (50% positive urinalyses during the last 6 months) or cocaine (harmful use of cocaine/crack according to ICD-10) with at least 6 months of documented maintenance

treatment and a current maintenance dose of at least 60 mg d,l methadone (or 30 mg levomethadone) daily[2]
- Residence or registration in the city (or city state) or region, where heroin treatment is delivered, for at least 12 months
- Voluntariness and ability to comply with the treatment conditions (readiness to change treatment centre; compliance; treatment control/documentation; evaluation)
- Written consent to follow the treatment conditions.

The previously performed screening explored, in addition to personal data, the inclusion criteria age, length of opioid dependency, current i.v. heroin use, state of health, treatment state and residence as well as the exclusion criterion pregnancy. This allowed the stratification into methadone patients (MTF) and patients not reached (NR). Moreover, the screening instrument included checklists for obtaining information relevant for study inclusion from drug counselling centres or doctors involved in maintenance treatment.

5.4.2 Exclusion criteria

Persons with at least one of the following criteria could *not* be included in the study:
- Persons in custody or serving a prison sentence or who could be expected to be imprisoned within 3 months at the time of registration
- Persons with voluntary phases of abstinence of at least 2 months during the last 12 months
- Known epilepsy or generalised convulsions within the last 12 months
- Sensitiveness to study medication and additives
- Regular intake of MAO inhibitors
- Severe asthma bronchiale, COPD, cor pulmonale
- Severe cardiac arrhythmia
- Prostatic hypertrophy (with urinary retention)
- Urethral stricture
- Life-threatening liver disease (exogenous hepatic coma)
- Severe renal disorders
- Insulin-dependent diabetes mellitus
- Diagnosed malignancy during the last 6 months
- Pregnant women or nursing mothers
- Patients, who, according to the medical investigators, are unable to comply with the conditions of the model project, i.e. to participate in the therapeutic and scientific programme, due to severe physical or mental disorders
- Patients who, at the time of registration, participated in other clinical trials focusing on the evaluation of addiction treatment.

In each case, inclusion and exclusion criteria were verified by an outside regional expert committee (see paragraph 5.1.1). In ambiguous cases, medical investigators' decision to

[2] This alternative, which describes the assignment to one of the two target groups, makes clear that patients, who dropped out of maintenance treatment or some other treatment because of unsuccessful results only recently (less than 6 months), could not be included in the study. This differentiation was necessary to prevent deliberate discontinuations in the hope that it might count as an indication for study participation.

include patients in the study could thus be covered, weighing the individual risks and benefits of participation.

5.4.3 Exclusion of patients from study treatment

Patients' participation in the study is voluntary, i.e. they can withdraw their consent to treatment (and further participation in the study) at any time. Patients with at least one of the following criteria were excluded from study treatment:

- Patients with severe somatic complications in connection with the heroin or methadone treatment, when treatment continuation would be irresponsible according to medical investigators and safety board
- Patients with abnormal changes of laboratory values, whose treatment continuation would involve too great health risks according to the decision of the safety board
- Patients, who stayed away from the treatment unit for more than 14 days (or longer) for reasons caused by themselves or without giving a reason and who interrupted the intake of study medication
- Patients taken into custody or who go to prison for 1 month or longer
- Heroin patients whose treatment is interrupted for more than 3 months due to hospitalisations or other specific treatments
- Patients, who, according to medical investigators, are no longer able or willing to comply with the conditions of the model project, i.e. to participate in the therapeutic and scientific programme
- In case of violence or threats of violence against staff members or other patients
- In case of drug dealing on the premises of the project
- In case of theft, passing on or sale of prescribed/dispensed substances.

Patients, who dropped out of heroin or methadone treatment during the trial period, are included in the statistical ITT analysis after 12 months. On request, they were offered or mediated to alternative treatment (e.g. methadone maintenance (for the heroin group), buprenorphine treatment, mediation to outpatient or inpatient detoxification treatment with the option of subsequent outpatient or inpatient abstinence treatment).

5.5 Study treatment

During the study phase, heroin treatment must be delivered in outpatient wards (or similar institutions such as local health offices, dispensaries and the like or in specialised medical practices – though not in the practices of individual GPs). This is due to the necessity to assure comprehensive care according to the study design and the requirements of a clinical trial, the safekeeping of the drug storage and the cost effectiveness of the units. The units should be able to assure a minimal number of treatment places; i.e. in terms of practicability, economic efficiency and general conditions for the evaluation (finances), they must be of an appropriate size to accommodate a relevant number of patients. Equipment and training of the (responsible) staff members must correspond to the requirements formulated in §§ 5 and 6 of the BtMG. The treatment centres must provide space for the concomitant case management and the psychoeducative treatment/drug counselling. Psychosocial treatment is provided by

trained staff members of the treatment unit or in some other institution experienced in outpatient drug treatment.

5.5.1 Description of medical treatment

The medical treatment setting for patient groups included in the study was based on a minimum of one weekly contact with the treating doctor, to coordinate the course of treatment and to react without delay to consequences of potential complications during the treatment process. Extensive physical examinations and blood count (10 ml per sampling) took place at baseline and after 1, 3, 6 and 12 months (see paragraph 5.1.4). The course of treatment was additionally controlled by weekly urinalyses (qualitative evidence). Urine sampling occurred under supervision, if necessary with temperature controls. In addition, hair samples were taken at inconspicuous places at the back of the head at the beginning of treatment (at the time of inclusion), after 6 months and at the examination at T_{12}.
Problematic (co-)use, e.g. of benzodiazepines, should be reduced under heroin treatment (and if possible changed previously) with the aim to completely withdraw these substances. Heroin or methadone doses can be refused to patients, who are under the influence of alcohol, barbiturates or benzodiazepines. If excessive alcohol use was suspected (smell of alcohol), a breath control was performed. Denial of the study medication must be recorded on the test sheet. § 5 (1) BtMG infers that medical investigators are responsible for assuring that the rules of the law on narcotics are kept.
The settings of medical treatment included four alternatives:

- *Experimental group MTF-H: heroin treatment:*

Patients switched directly from methadone treatment to an *outpatient heroin treatment unit* with an interdisciplinary treatment team and were treated there.

- *Experimental group NR-H: heroin treatment:*

Patients were newly admitted and treated in an *outpatient heroin treatment unit* with an interdisciplinary treatment team.

- *Control group MTF-M: methadone treatment:*

Patients were treated in an *outpatient methadone treatment unit* with an interdisciplinary treatment team, i.e. upon inclusion into the control group, patients had to leave their former doctor, where they received maintenance treatment, and switch to a centre involved in the study. The regional outpatient methadone treatment centre can also be a specialised medical practice operated by free sponsorship or by medical practitioners complying with the requirements of clinical drug trials. Patients, who had received maintenance treatment in an outpatient treatment centre, might continue treatment there (under study conditions).

- *Control group NR-M: methadone treatment:*

Patients were newly admitted and treated in an *outpatient methadone treatment unit* with an interdisciplinary treatment team.
The treatment setting thus created allowed structural comparisons between the experimental and the control groups. In principle, it is not unreasonable to switch patients of the control group MTF-M, who had been treated by a medical practitioner, to an outpatient unit, although they will not (at first) receive heroin as hoped for. Due to the unsatisfactory course of

methadone maintenance treatment, it can be assumed that both parties were not satisfied and that it is justifiable to offer a new, probably more successful, integrative treatment setting.

5.5.2 Description of psychosocial treatment

The setting of psychosocial treatment (PST) for study patients was based upon regular contacts of varying intensity with the responsible case manager/drug counsellor with the aim to coordinate psychosocial treatment steps and to react to possible treatment complications at an early stage. The general psychosocial situation and perception of the treatment were documented at the beginning of treatment and then at regular intervals.
There were two alternatives of psychosocial treatment:

- *Case management with integrated motivational interviewing*. Case management is a structured, person-centred, follow-up care concept with a flexible design orientated towards the patient's needs and including the counselling method of "motivational interviewing".
- *Drug counselling with psychoeducation*. Continuation of established drug counselling with additional psychoeducational programme consisting of 12 weekly group sessions and subsequent refreshing sessions based on a manualised treatment programme.

The PST alternatives are two distinct settings that are compared under similar medical treatment conditions. Intensity and utilisation of case management and counselling/ psychoeducation might differ, which was considered in the secondary analyses. The concept of case management is expected to result in an overall higher degree of care intensity.
When selecting these two care varieties, it became obvious that definitions of PST related to maintenance treatment differ a great deal regionally. In some cities, it consists of rather elaborate care for individual cases in specialised addiction centres combining psychotherapy with counselling in case of social problems; in other regions, it is based e.g. on the "come structure" with often only sporadic contacts to drug counselling. In Germany, there are no established standards for PST so far. The combination of drug counselling and psychoeducation is a care variety more or less equivalent to case management and adequately adapted to the needs of patients in maintenance treatment.

Case Management with integrated motivational interviewing
For half of the study patients, concomitant care, as required by the integrative treatment concept, consisted in *case management* as previously tested in the German model project on case management (Oliva et al. 2001). In this concept, a staff member (most often a social (educational) worker) of the addiction centre establishes contact with the patient and keeps it up over the entire period of treatment. Moreover, the concept of case management integrates the method of *motivational interviewing* (Miller & Rollnick 1991; 1999). Two elaborate and tested concepts of addiction care are thus used. While case management describes the organisational frame of activities, motivational interviewing is the counselling method used. The diversity of problems and the related help requirements of drug addicts as well as the different motivational phases preclude the standardisation of concomitant psychosocial treatment. Frequency of care is at least one personal contact per week. The case manager disposes of adequate space at the treatment centre during opening hours.

Case Management is based on the principle of bringing together the clients with their individual needs of help (demand part) and the available help resources (offer part) (Wendt 1997). The course of care is ruled by following processes: 1. agreement of cooperation, 2. assessment, 3. target agreement and help plan, 4. execution (incl. mediation, organisation, coordination), 5. monitoring and reassessment, 6. evaluation of results. All processes are documented. Staff members involved in drug care were trained in case management and motivational interviewing prior to the beginning of the study.
The experiences of the cooperation model of follow-up social work for addictive patients with multiple chronic impairments (Oliva et al. 2001) indicated that, for the target group of heroin treatment, case management cannot be just limited to coordinative performances. Case managers must be care providers themselves and follow up individual cases. The care ratio of case management is 1 : 25.

Drug counselling with psychoeducation
According to the integrative treatment approach, the second half of study patients must be affiliated to a counselling centre, which provides psychoeducative group therapy in addition to counselling. It consists in 12 manualised and standardised sessions. Psychoeducative group therapy starts in the third month of treatment.
In connection with the treatment of other chronic diseases, psychoeducative therapy proved to be an effective intervention improving mental symptoms, social competency and integration, quality of life, subjective coping and illness related problem solving and treatment compliance (e.g. Goldman & Quinn 1988; Hornung et al. 1993; Atkinson et al. 1996). The advantages consist in a high degree of standardisation and problem and practice orientation requiring patients' active involvement and learning of appropriate coping strategies. Moreover, the manualised psychoeducative treatment can be easily implemented in a short time and does not require lengthy (and costly) psychotherapeutic basic training.
Treatment intensity consists in one weekly session over a period of about 3 months. In a framework of psychoeducative behavioural therapy (following e.g. Kieserg & Hornung 1996), the programme addresses topics relevant for persons who have been drug dependent for many years, such as facing the issue of addiction and dependency, understanding subjective concepts of disorder, relapse management and risks, coping with comorbidity, encouraging healthy behaviour, social contact and communication training, problem solving strategies and self-help potentials as well as the structure of regional support systems. Local facilities and institutions (or treatment associations) may be used. But the treatment centres should also provide suitable space for psychoeducation during opening hours in order to warrant the integration of group therapy into the overall treatment. Content and structure follow the manualised criteria. The training occurred parallel to the regional project preparation and recruitment phase.
Contacts with the drug counsellor should occur at least once a week. Care ratio of combined drug counselling (1 : 50) and psychoeducation (1 : 50) is also 1 : 25.

5.5.3 Identity of investigational product

Experimental study medication is the DIAPHIN injectable solution of the drug company DiaMo GmbH & Co KG with their headquarters in D-72793 Pfullingen. One ampoule contains 10 g of diacetylmorphine hydrochloride and H_2O (corresponding to 8.71 g anhydrous base) as lyophilised powder. The injectable solution is prepared by mixing the active ingredient under aseptical conditions with 93 ml or 93 g respectively of sterile water using a syringe. The content has to be well agitated to obtain a homogenous solution (100 mg/ml). The date of production of the solution is noted on the label. Individual doses are prepared immediately before dispensing them to the patient. This is done by filling the solution under sterile conditions from the container into the syringes.
The dried substance is stored at room temperature (15-25 °C), the reconstituted solution in the refrigerator (2-8 °C, protected from light). The solution can be kept in the refrigerator for 2 weeks. During the first study phase, batches no. 101-107 were used (see table 5.1).

Table 5.1
Batches of diacetylmorphine used at each study centre

Study centre	**Batch**	**from**	**to**	**Number of bottles**
Hamburg	101	4.9.2002	11.1.2003	151
	102	11.1.2003	10.7.2003	599
	103	10.7.2003	4.12.2003	674
	104	4.12.2003	13.3.2004	525
	105	13.3.2004	26.8.2004	763
	106	26.8.2004	11.12.2004	438
	107	11.12.2004		
Hanover	101	12.8.2002	7.12.2002	152
	102	8.12.2002	26.7.2003	750
	103	27.7.2003	9.11.2003	985
	104	10.11.2003	10.1.2004	1,125
	105	11.1.2004	10.6.2004	1,484
	106	11.6.2004	17.12.2004	1,874
	107	18.12.2004		
Frankfurt	102	7.3.2003	22.7.2003	214
	103	22.7.2003	12.10.2003	450
	104	13.10.2003	29.1.2004	825
	105	30.1.2004	8.7.2004	1,419
	106	9.7.2004	4.11.2004	1,875
	107	4.11.2004		
Cologne	101	22.8.2002	25.1.2003	150
	102	26.1.2003	14.4.2003	150
	103	15.4.2003	4.10.2003	375

	104	4.10.2003	25.1.2004	225
	105	25.1.2004	1.9.2004	460
	106	2.9.2004	17.12.204	225
	107	18.12.2004		
Bonn	101	4.3.2002	10.12.2002	300
	102	10.12.2002	31.5.2003	416
	103	1.6.2003	4.10.2003	300
	104	5.10.2003	23.5.2004	525
	106	23.5.2004	29.1.2005	525
Karlsruhe	101	13.5.2002	17.7.2003	225
	103	17.7.2003	2.2.2004	150
	104	2.2.2004	7.8.2004	150
	105	7.8.2004	28.9.2004	38
	106	28.9.2004	13.1.2005	75
Munich	101	9.7.2002	[a)]	75
	102	29.8.2002		75
	103	27.11.2002		150
	104	5.6.2003		225
	105	17.12.2003		253
	106	15.7.2004		148
	107	6.10.2004		75

[a)] Data from Munich refer to the delivery date of the batches.

The other study medication is racemic d,l-methadone, which is obtained as 1% d,l-methadone-HCL solution formulas from pharmacies. The substance is dispensed for oral taking in a non-injectable potable solution. The solution can be kept at room temperature (in a safe) for 3 months.

5.5.4 Assigning patients to treatment groups

Patients assessed as eligible for study participation after verification of the inclusion and exclusion criteria by the regional expert committee were asked to give again their consent. The final assignment to a stratum occurred after the baseline examination (T_{-1}). Then, the next envelope of the respective stratum (MTF or NR) was retrieved and the patient was informed of the randomisation result. After a brief re-examination (T_0) to check the current state of health (in individual cases some days or weeks had elapsed since the T_{-1} examination), study treatment could be initiated.

Randomisation envelopes for each study centre (see also paragraph 5.1.2) had been prepared by the institute for medical biometrics and epidemiology of the University Medical Centre Hamburg-Eppendorf (Institut für Medizinische Biometrie und Epidemiologie des Universitätsklinikums Hamburg-Eppendorf (IMBE)). The programmes, which produced the randomisation lists as well as the codes (random seed, within the programme syntax) at the base of the chance calculation, are deposited at the TMF.

5.5.5 Dosage

Patients should be stabilised to a maintenance dose of i.v. heroin over the entire study phase within an initiation phase of one to two weeks. Right from the start, i.e. *at the earliest on the second day of treatment*, additional d-l methadone medication is offered for the night. Heroin is dispensed up to 3 times a day during the opening hours of outpatient units, in the morning, at noon and in the evening. Similar to the Swiss and Dutch trials, the maximum daily dose of i.v. heroin is 1,000 mg, the individual maximum dose 400 mg, assuming that 600 mg i.v. heroin per day produces the maximum heroin effect in heroin addicts (Seidenberg and Honegger 1998). If methadone is claimed for the night, it can be taken on the premises during the evening opening hours, or else it can be taken away as a potable individual dose, not applicable intravenously (most often diluted in fruit juice). The maximal daily dose of additionally prescribed d-1 methadone should not exceed 60 mg. The amount of methadone taken was controlled by regular urinalyses.
Oral methadone was dispensed once a day at the outpatient unit. It was dispensed as a potable individual dose in non-injectable form (normally diluted in fruit juice) and was taken under observation. Take-home doses were handled according to the specifications of the BtMVV and based on a "patient permit". A maximum daily dose had not been specified; according to experience, daily prescriptions between 40 and 160 mg methadone (in individual cases up to 250 mg) are realistic.

5.5.6 Dosage and schedule of drug dispensing

Following dosage regimens – divided according to stratum and group – are guidelines for the process of switching or stabilising to i.v. heroin. The various dosage regimens (initial upgrading at the beginning of treatment or after disruptions at various points, downgrading at the conclusion of treatment) are based upon a methadone daily equivalence dose (MTQ)[3]. The basic rule for all dosage regimens states that the heroin dose for one day, alone or in combination with oral methadone, must not exceed the MTQ of the previous day by more than 50% (Seidenberg and Honegger 1998; Bundesamt für Gesundheit 2000).

Experimental groups (heroin treatment), MTF stratum:
Switching from oral methadone to i.v. heroin is orientated towards the methadone dose of the previous day. A daily dose of methadone corresponds to about 3 times the amount of heroin, distributed over the day (methadone equivalence dose). Figure 5.4 represents the transition

[3] When (partly) switching from methadone to heroin (and vice versa), the so-called equivalence tables proved to be useful (Seidenberg and Honegger 1998; experiences from the Dutch study); in addition to the equivalent (subjective) lasting effect, they also take into account the differing half-times. One methadone equivalent (MQ) corresponds to an opioid dose whose single dose is equivalent to the effect (subjective opioid effect, degradation of effect) of 1 mg oral methadone. A methadone daily equivalent (MTQ) corresponds to an opioid dose, which, evenly distributed over one day, has an effect equivalent of 1 mg oral methadone.
Based upon this definition, following equivalences are assumed (evenly distributed heroin intake three times a day): 1 mg iv-heroin once = 1 MQ; 3 mg iv-heroin over the day = 1 MTQ. In case of upgrading, of (occasional) switching from one opioid to an other and of downgrading, is it useful to recur to MTQ units.

from a low dose of methadone to i.v. heroin based on the rule that the total dose of the subsequent day must not exceed the dose of the previous day by more than 50%.

Figure 5.4
Increase of i.v. heroin dosing starting from a low dose of methadone

	Methadone oral	Heroin i.v.	MTQ (Heroin i.v.)	MTQ total	Subsequent daily dose
Day1	30 mg	15 mg + 30 mg + 2 x 30 mg	15 MTQ 20 MTQ	65 MTQ	(65:2) x 3 = 97.5
Day 2	20 mg	100 mg + 2 x 100 mg	33 MTQ 66 MTQ	120 MTQ	(120:2) x 3 = 180
Day 3	10 mg	3 x 180 mg	180 MTQ	190 MTQ	(190:2) x 3 = 285
Day 4	5 mg	3 x 285 mg	285 MTQ	290 MTQ	(290:2) x 3 = 435
Day 5	0 mg	1,000 mg (max)	333 MTQ	333 MTQ	--

If the patient receives *d,l methadone p.o. for the night* right from the start, Seidenberg and Honegger (1998) advise, in case of immediate increase of heroin dosing, to dispense half of the amount of methadone on the first day, i.e. 50 mg and 2x150 mg i.v. heroin. The heroin dose can be further increased on demand. However, the individual dose may not exceed 50% of the total consumption of the previous day (including all opioids).

Experimental groups (heroin treatment), NR stratum:
On the first day, the initial dosing starts from the assumption of *non*-tolerance. If street methadone or other opioids are used, it is possible to dose according to the pattern of "quick upgrading of dosage" (see below). For patients, who had not been in drug treatment prior to the study, the initial dose should not exceed 15 to 20 mg i.v. heroin. Due to the short half-live period of heroin, doses can be increased the same day. Standard procedure is an initial dose of 15 mg i.v. heroin on the first day. After waiting for at least 30 minutes, another dose of 30 mg can be dispensed. During the first day, two more doses of 30 mg are given. The total dose on the first day is thus 105 mg i.v. heroin (15 + 30 +30 +30), i.e. 35 MTQ. On the second day, the patient can start with a dose of 50% of the MTQ of the previous day (i.e. 17.5 MTQ, i.e. a total of 52.5 mg i.v. heroin).

Standard pattern of quick upgrading of dosage (7 days):

1. day: 15 mg i.v. heroin + after 30 minutes 30 mg i.v. heroin, followed by 2 x 30 mg i.v. heroin during the day
2. day: 50 mg i.v. heroin + 2 x 50 mg i.v. heroin
3. day: 3 x 75 mg i.v. heroin
4. day: 3 x 125 mg i.v. heroin
5. day: 3 x 175 mg i.v. heroin
6. day: 3 x 250 mg i.v. heroin
7. day: maximal dose.

Upgrading may only occur if no complications are expected during the process.

Standard pattern of a slow upgrading of dosage (maximum 2-4 increases per week):

1. day: 15 mg i.v. heroin + 3 x 30 mg i.v. heroin during the day
2. day: 50 mg i.v. heroin + 2 x 50 mg i.v. heroin
3. day: 3 x 75 mg i.v. heroin
5. day: 3 x 125 mg i.v. heroin
8. day: 3 x 175 mg i.v. heroin
11. day: 3 x 250 mg i.v. heroin
14. day: maximal dose.

Of course, not all patients require the maximal dose of this pattern.

If *d,l oral methadone for the night* is prescribed, it is advisable to give an initial dose of 15-30 mg of methadone in addition to 15-20 mg of i.v. heroin per day (Seidenberg und Honegger 1998). On the second day, the heroin dose can be augmented to 30-45 mg and, on the third day, to 60-90 mg.

5.5.7 Blinding

Blinding of the study medication was not done as it cannot be realised effectively for the reasons mentioned above (cf. paragraph 5.3).

5.5.8 Previous and concomitant treatment

Patients of the MTF stratum switched directly from methadone treatment conducted according to the guidelines of the federal medical council to the study treatment. The decisive factors for being (potentially) included in the study were unsatisfactory results of the previous treatment mainly with respect to co-use. The previous maintenance treatment had normally been conducted in medical practices or outpatient drug centres. The minimum dose was 60 mg d,l-methadone daily (corresponding to 30 mg of levomethadone).

For the NR stratum, the inclusion criteria required that patients had not participated in any addiction treatment for at least 6 months prior to the study treatment. However, they should have had previous experience of addiction treatment.

Concomitant psychosocial therapies are described in paragraph 5.5.2. They are offered during the entire duration of the study treatment.

The study does not impose any restrictions on the treatment of concomitant diseases such as infections or abscesses. One exception is the treatment with antiretroviral substances, which exercise an influence on the metabolic activity and might require a readjustment of the dosage (if necessary after determination of plasma level).

5.5.9 Compliance

The compliance of study participants is recorded on the one hand by documenting the daily drug doses and medical visits, on the other hand by participation in psychosocial treatment. The medical investigators document the regular termination of the first study phase on the

CRF, which is also decisive for the per-protocol analysis. Moreover, regular termination of the first study phase is prerequisite for the continuation of study treatment in the second phase. In addition, weekly urinalyses are performed.
In the external interviews (ext-CRF) it is investigated whether patients were in any addiction treatment at the time of the interview (or in the last 6 months).

5.6 Variables

Efficacy and safety variables are continuously documented in the course of the study. In addition, general and more specific patient data such as gender, age, length of opioid dependency, number of former treatments, current social situation (housing, employment, family status/partnership) are documented by appropriate statistical categories.

5.6.1 Efficacy and safety variables

In the course of the study, all adverse events (AEs and SAEs) and side effects are consistently recorded in terms of safety variables. Side effects – similar to main effects – are measured quantitatively. At every scheduled examination, following effects and side effects occurring during the last 24 hours, were recorded as a matter of routine:
Effects of intoxication:

- "Flash", "kick" (expression, duration)
- Feeling high, euphoria (expression, duration)

Undesired effects:

- Histaminergic effects (expression/intensity):
  Itching, burning, feeling of heat, fit of perspiration, prickling, pains like pinpricking, nettles, edema, headache, bronchospasm
- Cholinergic effects (expression/intensity):
  Miosis, obstipation, abdominal pains, bradycardia
- Signs of intoxication/incidents (occurrence):
  Bradypnea, apnea, cyanosis, muscular spasms, convulsion, pulmonary edema, loss of conciousness, hypotension.

Blood counts, performed in the context of the study, are checked for deviations from the norm (safety lab). Such deviations are recorded on the CRF and counted to the adverse events (AE) and, if applicable, to the adverse effects of the medical drugs (ADE). Moreover, the examinations described in figure 5.5 include the collection of safety-relevant data, which, as the case may be, are recorded as adverse events, but are also analysed separately. The degree of severity of AEs and SAEs and their relationship with the study medication were evaluated by the medical investigators. Moreover, severe adverse events were discussed with the safety board.

Figure 5.5
Schedule of safety-relevant examinations within the first study phase

	T_{-1}	T_0	T_1	T_3	T_6	T_{12}
Anamnesis	X				X	X
Physical examination	X	X	X	X	X	X
OTI health scale	X	X	X	X	X	X
Swabs in case of skin infections	X	X	X	X	X	X
Diff. blood count	X	X	X	X	X	X
Clin. chemistry	X	X	X	X	X	X
ECG	X				X	X
Echocardiography	X					X
Effects of intoxication	X				X	X

Data collection of efficacy variables, mainly focusing on health and consumption parameters, is presented in figure 5.6. Retention rates of heroin and methadone treatment are also compared. The retention rate is defined on the basis of the proportion of patients still in treatment after 12 months, i.e. patients who complied with the treatment conditions in the 12th month of treatment, in relation to the total number of all patients included in the study.

Figure 5.6
Schedule of examinations and data collection of efficacy variables in the first study phase

	T_{-1}	T_0	T_1	T_3	T_6	T_{12}
Health: OTI-HSS	X	X	X	X	X	X
Health: SCL-90-R	X		X	X	X	X
Withdrawal symptoms: SOWS	X	X	X	X	X	X
Drug use: urinalyses	X	weekly				
Drug use: hair analysis	X	(X)			(X)	X
Quality of life: MSLQ	X				X	X
Life situation: EuropASI (completed)	X				X	X
Drug use: EuropASI	X				X	X
Readiness to change: VSS-K	X				X	X
Treatment satisfaction: TPQ					X	X
Economic situation	X				X	X
Delinquency: quantitative interview.	X					X

The sum score of the OTI-HSS (health scale) and the GSI score (Global Severity Index) of the SCL-90-R are calculated by the respective medical investigator and recorded on the CRF. The urinalyses are assessed as positive or negative based on qualitative or semi-quantitative evidence on site; hair samples are analysed at regional institutes of forensic medicine or local laboratories. All other scales (e.g. SOWS), instruments (e.g. MSLQ) or questionnaire scores (e.g. ASI-Composite Scores) are analysed centrally under the responsibility of the principal investigator.

5.6.2 Appropriateness and selection of criteria

The majority of the ascertained safety and efficacy variables have already been used in evaluation studies concerning addiction treatment and generally in clinical trials. With the exception of the method used for recording the effects of intoxication, which had previously been used only in safety-related follow-up surveys required for the licensing procedure of heroin in Switzerland, all other recording instruments are standardised or at least structured procedures, which are evaluated either according to standardised patterns or – in case of categorical, qualitative data – as individual information. The research interest of the specific studies, whose objectives were predominantly integrated in the regular surveys, also account for the abundance of investigations and instruments used in this study.

5.6.3 Primary outcome measures

Efficacy is tested *primarily* on *two primary outcome measures*, the improvement of health (A) and the reduction of illicit drug use (B). They are evaluated independently by the statistical comparative analysis. The success of one treatment compared to the other one is proved, if both analyses have significant results pointing to one direction.

State of health (A)

A1. Physical health:

Number of symptoms according to the health scale of the *Opiate Treatment Index OTI* at T_{-1} and T_{12} (Darke et al. 1991; 1992).

$VA1_n$ = *OTI* Health Scale $(0 \leq VA1_n \leq 50)$.

A2. Mental health:

Global Severity Index GSI of the *SCL-90-R* at T_{-1} and T_{12} (Franke 1995).

$VA2_n$ = GSI score $(0 \leq VA2_n \leq 4)$.

Treatment response with respect to health improvement is assumed if one of the two criteria (VA1 *or* VA2) indicates improvement *and* the other one does not indicate worsening. Improvement and worsening are defined as follows:

- For physical health (VA1): Improvement is assumed if the score of the OTI scale decreased by at least 20% and, additionally, by at least 4 points, worsening is assumed if the score increased by at least 20%, when comparing between T_{12} and T_{-1}.
- For mental health (VA2): An improvement is a decrease of the GSI value by at least 20%, worsening is an increase by at least 20%, when comparing T_{12} to T_{-1}.

If the patient dropped out of treatment and no results of the medical examinations at T_{12} are available, the results of the OTI health scale and SCL-90-R of the external interview can be used. With respect to LOCF procedure, this applies also to T_6.

Illicit drug use (B)

B1. Use of street heroin:

Number of urinalyses (USs) positive to street heroin in the 12th month of treatment, i.e. among the last 5 USs prior to T_{12}.

$VB1_n$ = number of positive USs $(0 \leq VB1 \leq 5)$.

If the patient dropped out of treatment and no results are available for T_{12} and if LOCF is not possible due to missing urinalyses in the 6th month of treatment, but if at least one follow-up occurred in line with the ITT approach, then the patient's self-report as documented on the CRF of the medical investigator may be used (Med-CRF). If these data are missing, too, patients' self-reports in the external interview are used. The number of days with street heroin use within the last 30 days (VB1‘) prior to the respective investigation are considered.

$VB1'_n$ = number of days of street heroin use $(0 \leq VB1' \leq 30)$.

B2. Use of cocaine:

Cocaine concentration found in hair analyses (HAs) at T_{-1} and T_{12} within following proof limits:

$VB2_n$ = cocaine concentration $(VB2_n \geq 1\ \mu g/g)$.

If the patient dropped out of treatment and no results are available for T_{12} and if LOCF is not possible due to missing HA at T_6, but if at least one follow-up occurred in line with the ITT approach, then it is allowed to resort to the patient's self-report as documented on the CRF of the medical investigator. If these data are missing, too, the patient's self-report of the external interview is considered. The number of days with cocaine use within the last 30 days (VB1‘) prior to the respective survey are considered.

$VB2'_n$ = number of days of cocaine use $(0 \leq VB2' \leq 30)$.

For the hair analyses, 1μg/g is assumed as lowest proof limit. Increase of cocaine use is definitely proved, if the value increased by 30% between T_{-1} and T_{12}.

A treatment response with respect to the reduction of illicit drug use is assumed if there is a decrease of street heroin use (VB1) *and* no increase of cocaine use (VB2) between baseline (T_{-1}) and the end of study phase one after 12 months (T_{12}). Decrease of use and non-increase are defined as follows:

- Decrease of street heroin use is considered as proved, if *not more* than 2 of the 5 urinalyses tested by GC/MS are positive in the 12th month of treatment. If only 4 urinalyses are available in the 12th month of treatment, only one urinalysis may be positive for street heroin. If only 3 urinalyses are available, none may be positive for street heroin for the result to be considered as a response. If there are fewer urinalyses in the 12th month of treatment, the analyses of the 6th month were considered (LOCF) using the same evaluation plan. Only if no urinalyses are available for the 6th month of treatment (because the patient dropped out of study treatment prematurely), it may be resorted to the patient's self-report (VB1‘). A response is assumed if the *use of street heroin decreased by at least 60%* between T_{-1} and T_{12} as measured by the number of consumption days within the last 30 days.

Hierarchical procedure of defining treatment response with respect to street heroin use (VB1, VB1‘)

1.	5 urinalyses at T_{12} available	At most 2 positive	
2.	4 urinalyses at T_{12} available	At most 1 positive	
3.	3 urinalyses at T_{12} available	None positive	
4.	5 urinalyses at T_6 available	At most 2 positive	LOCF
5.	4 urinalyses at T_6 available	At most 1 positive	LOCF
6.	3 urinalyses at T_6 available	None positive	LOCF
7.	Self-report at T_{12} 1. Med-CRF, 2. Ext-CRF	60% decrease compared to T_{-1}	
8.	Self-report at T_6 1. Med-CRF, 2. Ext-CRF	60% decrease compared to T_{-1}	LOCF
9.	No information at T_6, T_{12}		Worst Case[a)]

a) In terms of „worst-case“, patients of the heroin group with no valid data are rated as non-responders, patients of the methadone group as responders (see paragraph 7.4.1).

- Non-increase of cocaine use is proved by the (traceable) cocaine concentration in the hair (see above). If HA is not possible at T_{12}, the hair sample at T_6 is used (LOCF). Only if no HA is available for T_6 (because of premature dropout of study treatment), it may be resorted to the patient’s self-report from the Med-CRF or to the ext-CRF in case of missing data (VB2‘). A response is assumed if the number of consumption days *decreased or did not change (with a tolerance of ± 2 days)* within the last 30 days between T_{-1} and T_{12}. That is, an increase of the days with cocaine use within the last month by no more than 2 days compared to the value at T_{-1} is still regarded as a response; only if the value at T_{12} increased by more than 2 days, non-response is assumed.

  Hierarchical procedure of defining treatment response with respect to cocaine use (VB2, VB2‘)

1.	HA at T_{12} available	No increase compared to T_{-1}	
2.	HA at T_6 available	No increase compared to T_{-1}	LOCF
3.	Self report at T_{12} 1. Med-CRF, 2. Extern. CRF	Decrease/no change compared to T_{-1}	
4.	Self report at T_6 1. Med-CRF, 2. Extern. CRF	Decrease/no change compared to T_{-1}	LOCF
5.	No information		Worst Case

5.6.4 Measurements of medication concentration

In the context of the study, methadone and heroin takings (evidence of opioid) were controlled qualitatively by urine samples. The concentration of the blood plasma level was measured if specific SAE occurred and if interactions of medication were suspected. No other examinations on pharmacokinetics and bioavailability were performed.

5.7 Quality assurance of data

The quality of data and documentation is assured by a number of quality assurance systems and by routine procedures of data processing. All interviewers had previously been trained to conduct the external interviews (ext-CRF). Moreover, the manual describes in detail the process of data collection. A comprehensive CRF manual is also available for the examinations by medical investigators; each individual examination and the related patient questionnaires are explained and commented in detail. In addition, the psychosocial treatment staff (case manager, group leader, drug counsellor) was repeatedly trained in the documentation of the concomitant treatment.
Independent monitoring was performed by the company *monitornet*. The implementation and handling of CRF controlling (matching of source data, checking for completeness) are described in the monitoring conventions attached to this report.
Data processing is subject to complex controls. For instance, based on the list of so called *crucial variables* (see monitoring conventions), plausibility controls were performed and missing values checked. Implausible or missing data of the crucial variables were checked with the study centres (queries). If necessary, data were corrected by a programme syntax, the primary data are not affected. Thus, the entire process of data processing is reproducible, all changes are recorded. Data clearing processes and logical compensations (self-evident corrections) were described in a self-evident correction guideline (attached) and also recorded in a programme syntax. Data, which are not counted among the "crucial variables" such as lab data and data regarding examinations by medical apparatus, were checked for missing or implausible values ("outliers") and matched with the CRF data, but no queries were initiated. Any corrections were performed according to the self-evident correction guideline. Data processing, data assurance and documentation were carried out according to the SOP No. 26/04 „EDV" of the ZIS of the University of Hamburg.
All analysis laboratories and forensic institutes involved in the study presented valid ring test certificates. All study centres as well as the principal investigator (ZIS) in Hamburg were audited by the company Verdandi in the period 2002 to 2003. Audit findings were adequately attended to and corrected in accord with the auditor as soon as possible. Data management by the principal investigator was audited separately in Spring 2004, deficiencies were corrected within a short time. Both audit reports certified a good management quality to the principal investigator
Severe adverse events (SAE) were reported according to lawful regulations (see also SOP 25/03 of the ZIS). All SAEs were discussed with the safety board at regular intervals.
The principal investigator operates in accordance with the standard operating procedures (SOPs) of the Centre of Interdisciplinary Addiction Research of the University of Hamburg.

5.8 Plan of statistical analyses and determination of sample size

In addition to the study protocol no. ZIS-HV9-0701, the analyses are based upon the statistical analyses plan, version 3 of March 2005 (Verthein et al. 2005).

5.8.1 Statistical and analytical plan

In line with the study protocol no. ZIS-HV9-0701 of the German model project for heroin-assisted treatment of opioid dependent patients (Krausz et al. 2001), following conditions apply a.o. to the statistical analysis of efficacy:

Proof of efficacy is based upon separate analyses of the *two primary outcome measures* "Improvement of physical and mental health" and "Decrease of street heroin and cocaine use". Proof of successful heroin treatment is assumed if both analyses yield significant results pointing to the same direction. The *null hypothesis* of the effects to be proved in the primary analysis with respect to the primary outcome measures "state of health" (A) and "illicit drug use" (B) consists in the response rate of the experimental group (heroin) being lower or equal to the response rate of the control group (methadone).

The primary analysis is carried out according to the *"Intention to treat" principle (ITT)*, according to which all patients, who have been randomised, i.e. assigned to a treatment group after twice giving written consent to be treated, are included in the analysis.

According to the *4 x 2 branched study design*, a four-factor logistic regression model is used for the primary analysis. It investigates first of all whether the principal effect of heroin vs. methadone is significantly different from 0 on the 5% level (Likelihood-Ratio Test), after having considered the three other factors (target group: MTF vs. NR, concomitant treatment: case management/MI vs. counselling/PsE and centres as indicator variable). In this case, an additional test is performed to explore potential interactions between main effect and affiliation to the target group (MTF or NR) to check whether heroin or methadone effects are independent of previous treatment experience.

In order to obtain an estimate of the influence that dropouts have on the study results, a *Per-Protocol Analysis,* based on the patients who remained in the respective treatment, is conducted in addition to the ITT analysis. In contrast to the ITT analysis, the PP analysis is able to produce results that are closer related to the treatment setting, especially if retention rates are different. The per protocol sample includes all patients of the respective branch, who have completely concluded the first study phase. That is, the PP sample consists of all patients, who were reported in the CRF on page A1 "Patient data – study conclusion/end of treatment" to have regularly concluded the study phase, and of those patients, who were admitted to the second study phase.

In 9 patients, the external interview (ext-CRF) at T_{-1} (study initiation) was not or only partly conducted so that it is not possible to analyse the course of their treatment based on externally collected data. Due to this serious breach of the protocol, these patients are excluded from the statistical analysis. Patients, who revoked their consent to take part in the study and *did not* start the study treatment, are also excluded from the analysis, since their conscious decision to recede from participation cannot be related to the treatment.

The analysis strategy as presented in the statistical analysis plan is an interim analysis in the context of model project for heroin-assisted treatment and is based on the controlled efficiency comparison of heroin and methadone treatment (first study phase). The final report of the heroin trial will be presented after the evaluation of the second study phase, i.e. after a total of 2 years' study treatment.

As part of the patients, who had previously been treated with methadone (MTF stratum), received less than the required 60 mg of methadone (or 30 mg of levomethadone) (their inclusion in the study had been recommended by the regional expert committee), this group is presented descriptively compared to the other patients and evaluated separately with respect to the primary outcome measures (cf. paragraph 6.2).

5.8.2 Determination of sample size

The determination of the sample size was based on following expected efficacy:

- Primary outcome measure (A) – health improvement:
  Expected efficacy in control groups: ≤ 30% of responders,
  Expected efficacy in experimental groups: > 50% of responders.
- Primary outcome measure (B) – reduction of illicit dug use:
  Expected efficacy in control groups: ≤ 30% of responders,
  Expected efficacy in experimental groups: > 50% of responders.

With respect to the 4 x 2 branch study design, a four-factor logistic regression analysis is conducted for each POM. Starting from the (conservative) assumption that the two primary outcome measures are stochastically independent, a power of 90% for each POM ensures a (multiple) overall power of 80% [$(1-\beta)^2 \approx 0.80$ for $\beta = 0.10$]. As an overall success of the trial is only assumed if treatment effect has been proved for both primary outcome measures, a correction of the first order error is not necessary.

A certain proportion of the patients will (prematurely) drop out of the study and will not be included in the analysis via LOCF, as they cannot be reached again for examinations and interviews. These are patients, who dropped out prior to T_6 or did not show up for treatment, or who had refused their consent to explorations related to the two target variables. These patients are treated as "worst case" according to the conservative analysis strategy, that is, methadone patients not reached are counted as success (responders) and heroin patients not reached as failure (non-responders). This reduces the magnitude of the assumed effect in relation to the proportion of not reached dropouts of the heroin and the methadone group respectively. A realistic estimate of the respective proportions are 10% losses in the methadone group and 5% in the heroin group. The rest of the patients were expected to be reached again at T_6 or T_{12}. According to these expected percentages, the assumed effect value, which determines the sample size, is reduced from 0.3 vs. 0.5 to 0.370 vs. 0.475 (difference = 0.105).

Under these considerations, a minimum of n=482 persons are required in each treatment group in order to reach a multiple total power of 80%, (based upon Chi^2 test for odds ratio, approximation of case numbers according to Nam 1992). Related to the individual strata, this means that four heroin and four methadone strata with a minimum of 121 patients each are necessary to prove the expected effect with a statistical power of 80%. For practical reasons, (appropriate distribution among study centres, better measuring accuracy) this figure is rounded up to n = 140 so that eight strata result in a total number of n = 1,120 patients. This number of cases assures that, under the described conditions, a significant difference between methadone and heroin treatment can be proved in both tests with a power of at least 80%.

5.9 Changes in the conduct of the study or planned analyses

Changes of the study protocol related to the conduction and analyses of the study, and group assignments deviant from the randomisation are specified hereafter. These changes are described in detail and justified in the corresponding amendments to the study plan and in the plan of analyses.

5.9.1 Deviance in sample assignment

Incorrect stratum assignments:
The patients with the randomisation numbers 10104, 40035, 40099 and 80003 are "not reached" (NR), but were wrongly assigned to the MTF stratum ("methadone treatment failures"). In the analysis, these patients were assigned to the correct target group NR. Recruitment proceeded in accordance with the randomisation list, which led to deviant numbers of patients per stratum in the study centres Hamburg (10), Frankfurt (40) and Munich (80).

Incorrect assignments to the mode of psychosocial treatment:
The patient with the randomisation number 40047 – a person, who should receive drug counselling/psychoeducation according to the randomisation plan – was wrongly assigned to case management. Similarly, the patient with the randomisation number 40056 – assigned to case management by the randomisation plan – was wrongly assigned to drug counselling/psychoeducation. For the analysis, these patients were counted to the treatment group, whose kind of PST they received; recruitment proceeded according to the randomisation list.

5.9.2 Changes in the study protocol

Following changes are described in the amendments no. ZIS-HA9/1 to no. ZIS-HA9/7, no. ZIS-HA9/9, no. ZIS-HA9/10 and no. ZIS-HA9/13 and nr. ZIS-HA9/14 of the study plan. The amendment no. ZIS-HA8/1 (additional blood samples for research related to molecular genetics) was not realised, as the Hamburg ethics committee did not sanction this project. This amendment is not specified hereafter (and not included as annex). The amendments no. ZIS-HA9/11 and no. ZIS-HA9/12 concern the follow-up phase of the study and are also not considered here.

Modification and specification of the accessory substance required to detect street heroin:
Instead of acetyl-codeine, evidence of street heroin is obtained via accessory substances and metabolites such as papaverine, noscapine or codeine (Amendment 2, amendment ZIS-HA9/1 of 8.1.2002, voted by the Hamburg EC on 21.1.2002).

The inflammation parameter erythrocyte sedimentation rate *ESR* is replaced with *CRP*:
The C-reactive protein (CRP) as classical acute-phase protein is particularly sensitive and can be measured easily and quickly in the laboratory. An elevated CRP serum concentration is

always indicator of an inflammation and thus more reliable than ESR (Amendment 3, amendment ZIS-HA9/1 of 8.1.2002, voted by the Hamburg EC on 21.1.2002).

The determination of hepatitis A serology (Anti-HAV-IgM, Anti-HAV-IgG) is dropped:
Unlike infections with hepatitis B or C virus, an infection with the hepatits A virus had no further clinical or therapeutic consequences for the patient (Amendment 4, amendment ZIS-HA9/1 of 8.1.2002, voted by the Hamburg EC on 21.1.2002).

Modification of testing for tuberculin reaction:
Instead of the *Tine-Tests* indicated in the study protocol, which had been removed from the market for insufficient specifity, the *Mendel-Mantoux-Test* is used to detect tuberculin reaction (Amendment 5, amendment ZIS-HA9/1 of 8.1.2002, voted by the Hamburg EC on 21.1.2002).

Definition of the maximum permissible value in breath controls after alcohol consumption:
When measuring patients' degree of alcoholisation by breath controls, a limit of 0.1 millilitre is specified; if this limit is exceeded the current heroin or methadone dose must be refused for safety reasons (Amendment 6, amendment ZIS-HA9/1 of 8.1.2002, voted by the Hamburg EC on 21.1.2002).

Change from DM to Euro:
Patients' remunerations are stated in Euro. The amount is rounded up to full Euros. Patients' information sheets were corrected accordingly prior to the study (baseline examination T_{-1}) (Amendment 8, amendment ZIS-HA9/1 of 8.1.2002, voted by the Hamburg EC on 21.1.2002).

Justification for thorax x-rays:
As the study design does not require serial x-rays, they should only be performed in case of clinical indication (Amendment 11, amendment ZIS-HA9/3 of 22.2.2002, voted by the Hamburg EC on 8.3.2002).

Only one treatment centre in Hamburg:
Instead of two centres as stated in the study protocol (no. 10 and 20), only one study centre provides study treatment with heroin in Hamburg (Nr. 10) (Amendment 12, amendment ZIS-HA9/4 of 4.6.2002, voted by the Hamburg EC on 13.6.2002).

Redistribution of strata (target groups MTF and NR) between Cologne and Frankfurt:
The study centre Cologne (Nr. 50) takes 10 patients of the target group "not reached" (NR) from the study centre Frankfurt (Nr. 40). In return, Frankfurt takes 10 patients of the target group "methadone treatment failures" (MTF) from Cologne. All patients concerned receive case management. The total number of the sample strata remains unchanged (Amendment 15, amendment ZIS-HA9/5 of 20.2.2003, voted by the Hamburg EC on 1.4.2003).

Extension of the overall study period:
Due to the long delayed and time-consuming implementation of the seven study centres as well as the patient recruitment exceeding the estimated time of the study protocol, the overall period of the study is extended by about 10 months (Amendment 16, amendment ZIS-HA9/5 of 20.2.2003, voted by the Hamburg EC on 1.4.2003).

Modification of strategy when switching methadone patients to heroin treatment places:
The switching of patients from methadone to heroin treatment occurs in terms of randomised blocks of a determined size instead of 4-week blocks (Amendment 17, amendment ZIS-HA9/5 of 20.2.2003, voted by the Hamburg EC on 1.4.2003).

Redistribution of strata (target groups MTF and NR) between Cologne and Hamburg:
The study centre Cologne (no. 50) takes 10 patients of the target group "not reached" (NR) from the study centre Hamburg (no. 10). In return, Hamburg takes 10 patients of the target group "methadone treatment failures" (MTF) from Cologne. The exchange concerns only patients with case management. The overall sample size of the strata remains unchanged (Amendment 19, amendment ZIS-HA9/6 of 5.3.2003, voted by the Hamburg EC on 13.3.2003).

Determination of the laboratory parameter HbA1c:
Determination of the laboratory parameter HbA1c can be dropped in individual cases for logistic or financial reasons. In the study centre Munich for instance, the laboratory parameters are analysed by various institutes. The analysis of HbA1c would require an additional blood sampling tube and the services of an additional chemical laboratory; time and effort as well as the cost incurred in each case bear no relation to the clinical relevance of this parameter (Amendment 20, amendment ZIS-HA9/7 of 28.4.2003, voted by the Hamburg EC on 22.5.2003).

Specification of inclusion criteria:
The inclusion criteria "participation in addiction treatment" (no. 6A in CRF), "negative course of maintenance treatment" (no. 6B) and "residence in the city where heroin treatment is dispensed for at least 12 months" (no. 7) are explained in more detail, as in particular the concepts of previous addiction treatment differ due to regional differences of the care system. If patients of the MTF group did not reach the limit of 50% positive urinalyses (during the last 6 months) as specified by the criterion 6B, but urinalyses have obviously been faked to avoid being dismissed from methadone treatment, the medical investigator may submit a comprehensive explanation to the regional expert committee to justify why the patient still qualifies for participation in the heroin trial. The same applies to those cases, where the methadone dose has been consciously kept below the specified limit of 60 mg, in order to avoid risks because of continued co-use and to retain patients in methadone treatment. Also in these cases, the expert committee should receive a detailed statement justifying the study inclusion. For the inclusion criterion 7 "residence in the city where heroin treatment is

dispensed for at least 12 months", the required proof is specified (Amendment 21, amendment ZIS-HA9/7 of 28.4.2003, voted by the Hamburg EC on 22.5.2003).
Moreover, the exclusion criterion "voluntary phases of abstinence" (no. 2) is specified designating persons, who, voluntary, independently and outside therapeutic measures, had been abstinent during the last 12 months (Amendment 22, amendment ZIS-HA9/7 of 28.4.2003, voted by the Hamburg EC on 22.5.2003).

Specification of the definition of severe adverse events (SAE):
Due to the great number of previously existing (chronic) diseases among heroin addicts, it is possible that the individual treatment concept of some study patients requires a *planned* hospitalisation, which does not meet the criteria of a severe adverse event (SAE) (Amendment 23, amendment ZIS-HA9/7 of 28.4.2003, voted by the Hamburg EC on 22.5.2003).

Explanation of the difference between end of treatment and end of the study:
For patients, who do not wish or cannot continue taking the study medication, this is the *end of treatment*, but not necessarily the *end of the study* (Amendment 24, amendment ZIS-HA9/7 of 28.4.2003, voted by the Hamburg EC on 22.5.2003).

Remuneration for patients:
At the examination 12 months after study initiation (T_{12}), patients receive a remuneration of 15.- Euro also for the examination by the medical investigator (not only for the external interview) (Amendment 26, amendment ZIS-HA9/9 of 25.8.2003, voted by the Hamburg EC on 15.9.2003).

Specification of the exclusion criterion "imprisonment" (during treatment):
If patients are taken into custody in the course of the study treatment, but are in maintenance treatment during the prison term, the study treatment can be resumed after an interruption of up to 3 months (similar to the procedure in case of hospitalisation) (Amendment 27, amendment ZIS-HA9/9 of 25.8.2003, voted by the Hamburg EC on 15.9.2003).

OTI health scale and SCL-90-R at T_6 and T_{12} in treatment dropouts:
In patients who discontinued treatment, physical and mental health (POM A) are also explored by the external interviewers using the OTI health scale and SCL-90-R at the examination times T_6 and T_{12}. The results of these examinations can be used to complete missing information for the primary analysis in terms of LOCF (Amendment 31, amendment ZIS-HA9/13 of 29.3.2004, voted by the Hamburg EC on 29.6.2004).

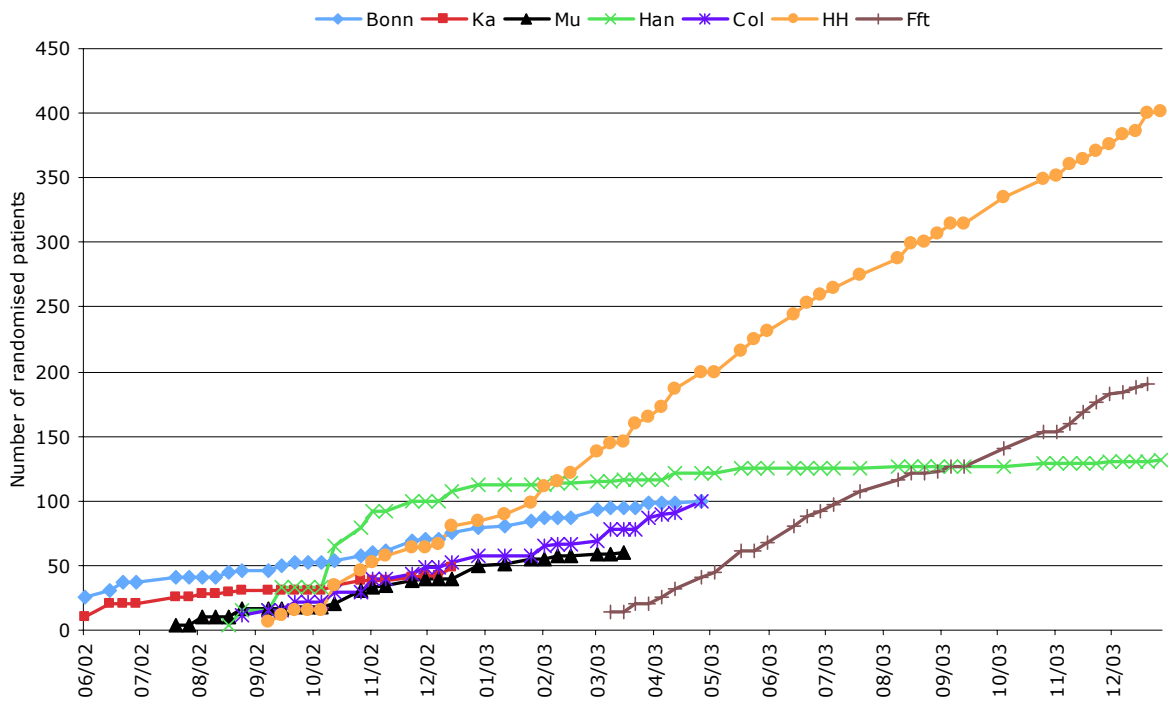
Specification of the LOCF procedure for the POM B "drug use":
In case of missing laboratory data (urinalyses and hair analyses), self-reported data on drug use during the last 30 days, to be analysed by LOCF, can be collected either by the medical investigators or by the external interviewers (Amendment 31, amendment ZIS-HA9/13 of 29.3.2004, voted by the Hamburg EC on 29.6.2004).

Exclusion of patients from the statistical analysis:
Patients, who revoke their consent to participate in the study and did not start the study treatment, are excluded from the statistical analysis, since these patients did not undergo any therapeutic interventions in the context of the study and their conscious decision to recede from participation can, therefore, not be related to the treatment and its potential effects (Amendment 33, amendment ZIS-HA9/14 of 23.3.2005, voted by the Hamburg EC on 25.4.2005).

6. Study patients

Heroin-assisted treatment focuses on opioid addicts with many years of intravenous heroin use, who have not been reached by the addiction services or did not sufficiently benefit from previous therapies, and who are in a poor health condition. The inclusion and exclusion criteria are described in the study protocol no. ZIS-HV9-0701. Patients can also be excluded from study treatment if complications arise (in connection with the study treatment) or in case of safety-related doubts. Exclusion could also occur for disciplinary reasons (see study protocol no. ZIS-HV9-0701). Study participation is basically voluntary and the patient is entitled to revoke his consent to treatment (and further participation in the study) at any time.
Recruitment occurred according to a stratified procedure, i.e. it was planned to include opioid dependent persons for each target group (MTF or NR), until the target sample size was reached. For organisational reasons, patients' recruitment was concluded on 31.12.2003. This concerned mainly the study centres Hamburg and Hanover; in the other centres, recruitment had been completed earlier. A total of 1,032 heroin dependent patients were included in the study. Progression of the recruitment process is presented in figure 6.1. It shows that the larger centres of Hamburg and Frankfurt could recruit comparatively many patients per time unit (steeper curve). The speediness of recruitment was kept up until the end of 2003. In Bonn and Karlsruhe, screening started already in February 2002. The first patient of the model project was included in Bonn, and heroin-assisted treatment was initiated on 4.3.2002. In Karlsruhe, study treatment was initiated on 10.5.2002. Munich (30.6.2002), Hanover (5.8.2002), Cologne (22.8.2002) and Hamburg (28.8.2002) followed shortly. The study centre in Frankfurt was the last to initiate study treatment on 28.2.2003, one year later than Bonn. Karlsruhe concluded the recruitment phase already in December 2002, although only 48 of the targeted 60 patients could be included. In the centres of Munich, Bonn and Cologne, the target numbers of 60 and 100 patients resp. were reached in spring 2003. The larger study centres of Hanover, Hamburg and Frankfurt concluded the recruitment phase in December 2003 (figure 6.1). In Hanover, 132 patients were reached, which is slightly below the target number of 140; in Frankfurt, 191 patients were reached, also slightly below the target number of 200. Hamburg reached a total of 401 patients and thus fell short of the targeted 460 patients. However, the total number of recruited patients (n=1,032) is clearly higher than the calculated minimum of required case numbers of n=964 (see paragraph 5.8.2) so that the divergence from the initially targeted figure of n=1,120 patients is not expected to have negative effects on the statistical analyses.

Figure 6.1
Patients' recruitment phase for each study centre (n=1,032) [a)]



a) The representation of recruitment figures starts only in June 2002. The centres of Bonn and Karlsruhe started including patients in the study already early in 2002.

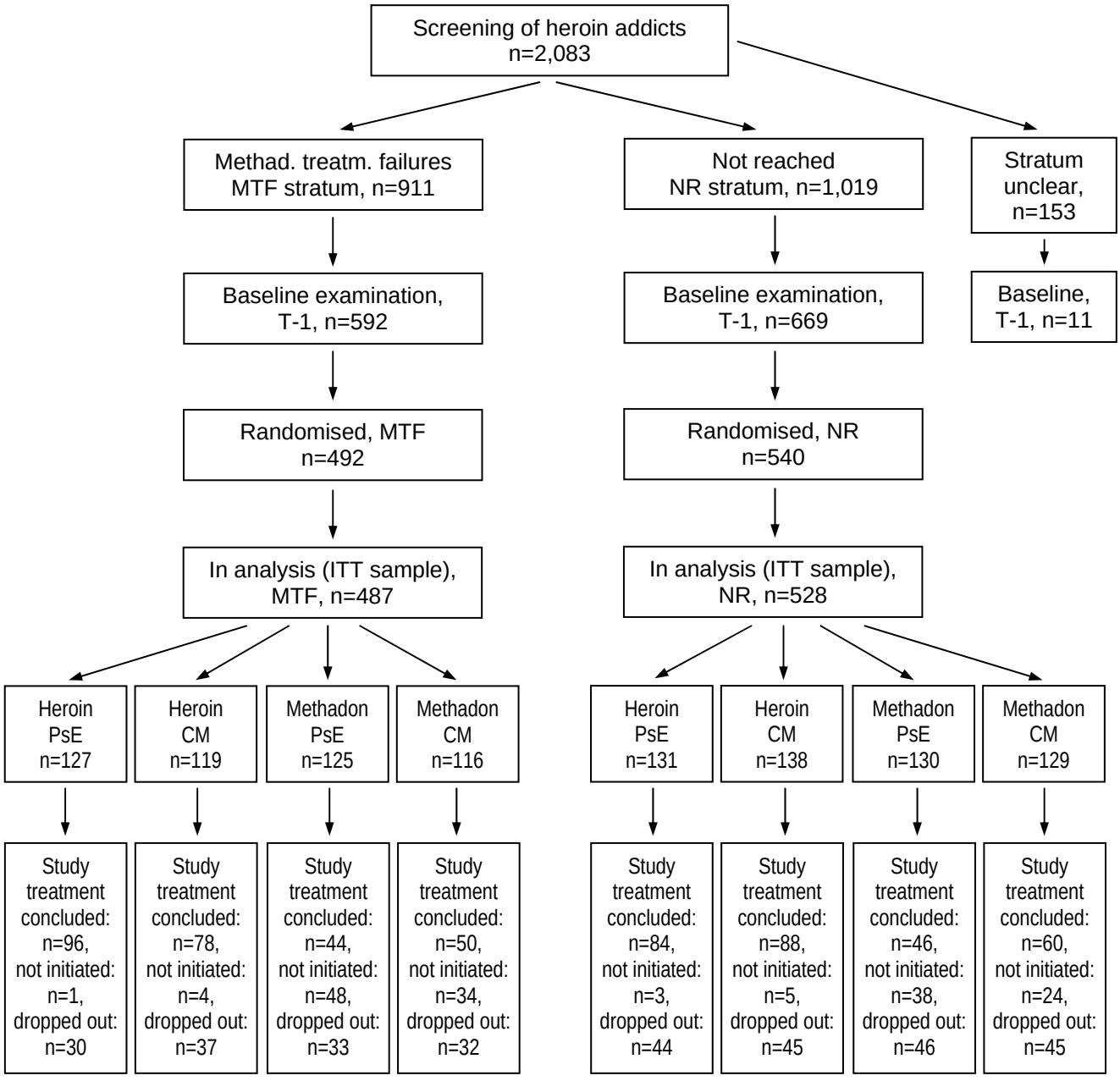
6.1 Distribution of study patients

The inclusion of a total of 1,032 study patients required that a far greater number of heroin addicts were contacted and screened. n=2,083 patients, that is twice as many, were screened. The number of opioid addicts examined at T_{-1} – 240 did not fulfil the inclusion criteria or did not show up for randomisation –, is still higher (n=1,272) than the final number of patients. There were only slight differences between the target strata MTF and NR; of the heroin addicts examined at baseline, 83% of the MTF stratum and 81% of the NR stratum were randomised for the study (see figure 6.2).[4]
Nine patients were excluded from the statistical analysis, because the external interview (ext-CRF) at baseline T_{-1} (see paragraph 6.2) was not available. Nine patients revoked their consent before even starting treatment (according to amendment ZIS-HA9/14 of 23.3.2005, see paragraph 5.9.2). All these patients had been randomised to the control group (methadone). Three of them were in Hamburg, three in Frankfurt, one in Cologne and two in Munich. These patients were excluded from the analysis, too. As one patient from Munich fulfilled both conditions, the statistical analysis is finally based on a total of n=1,015 patients (ITT sample: MTF: n=487, NR: n=528) (see paragraph 7, table 7.1). The distribution

4 It must be considered that, for many patients who took part in the T_{-1} examination and were not included in the study, only incomplete data sets were available. The detailed analysis of the recruitment process and the sample description of candidates excluded in the course of recruitment is part of the special study on treatment research.

according to the kind of psychosocial treatment resulted in eight subgroups of approximately equal size.

Figure 6.2
Screening and inclusion of study patients per stratum

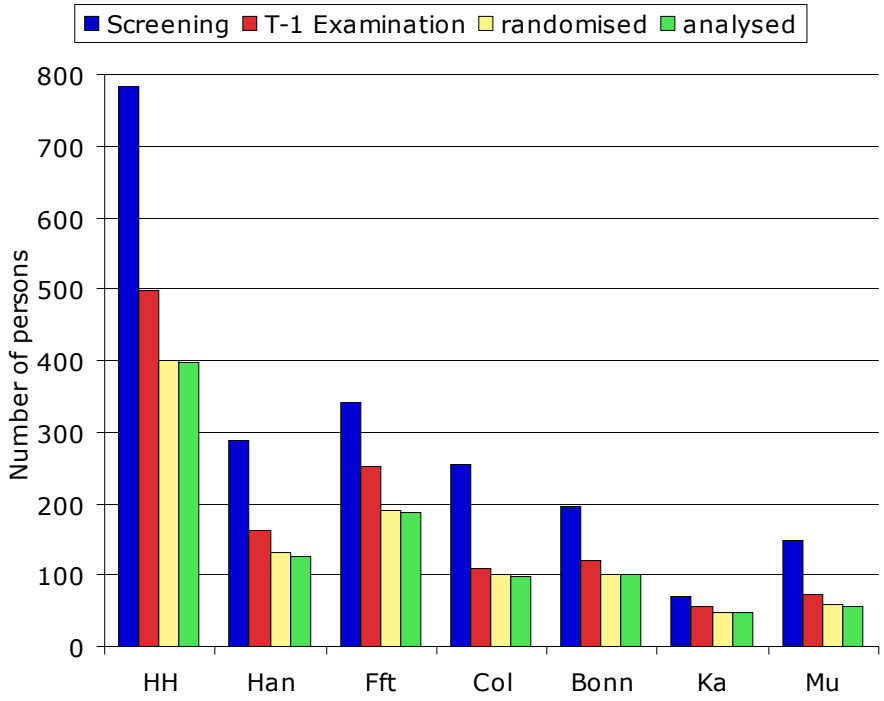


A total of 546 patients regularly concluded the study treatment of phase one. 434 of them continued with phase 2 of the study treatment. 90 of these patients switched from methadone treatment to vacated places of heroin treatment (21%). The other 344 patients continued heroin treatment.

The relationship between the number of screened and randomised patients is similar in all the study centres except Karlsruhe, the smallest of the study centres (see figure 6.3). In Hamburg, 784 heroin addicts were screened, which corresponds to 1.96 times the number of randomised

patients, in Karlsruhe, only 71 patients were screened (1.48 times). In the larger centres of Hamburg and Frankfurt, comparatively more patients dropped out of the recruiting process after the baseline examination (T_{-1}).

Figure 6.3
Screening and randomisation of patients in each study centre



Deviant from the distribution based on the initially calculated number of patients of n=1,120, following groups are formed in each centre (see table 6.1), counting only patients included in the analysis:

Table 6.1
Number of patients and groups included in the analysis of study phase one (ITT sample) in the seven study centres

	Heroin (experimental groups)				Methadone (control groups)				Total
	Case Management/ MI		Counselling/ PsE		Case Management/ MI		Counselling/ PsE		
	MTF	NR	MTF	NR	MTF	NR	MTF	NR	
Hamburg	62	49	41	48	62	47	40	48	397
Hanover	-	19	25	21	-	14	24	23	126
Frankfurt	27	20	22	27	26	20	22	24	188
Cologne	15	35	-	-	15	34	-	-	99
Bonn	-	-	25	25	-	-	25	25	100
Karlsruhe	-	-	14	10	-	-	14	10	48
Munich	15	15	-	-	13	14	-	-	57
Total	119	138	127	131	116	129	125	130	1,015

The total number consists of n=515 heroin patients (experimental group, 50.7%) and n=500 methadone patients (control group, 49.3%). The strata distribution is slightly less even – MTF: n=487 (48.0%), NR: n=528 (52.0%) –, as it was apparently easier (in particular in Cologne) to recruit individuals "not reached" than patients in unsatisfactory methadone maintenance treatment. Randomisation according to psychosocial treatment was even again: counselling/PsE: n=513 (50.5%), case management/MI: n=502 (49.5%).

6.1.1 Retention rate

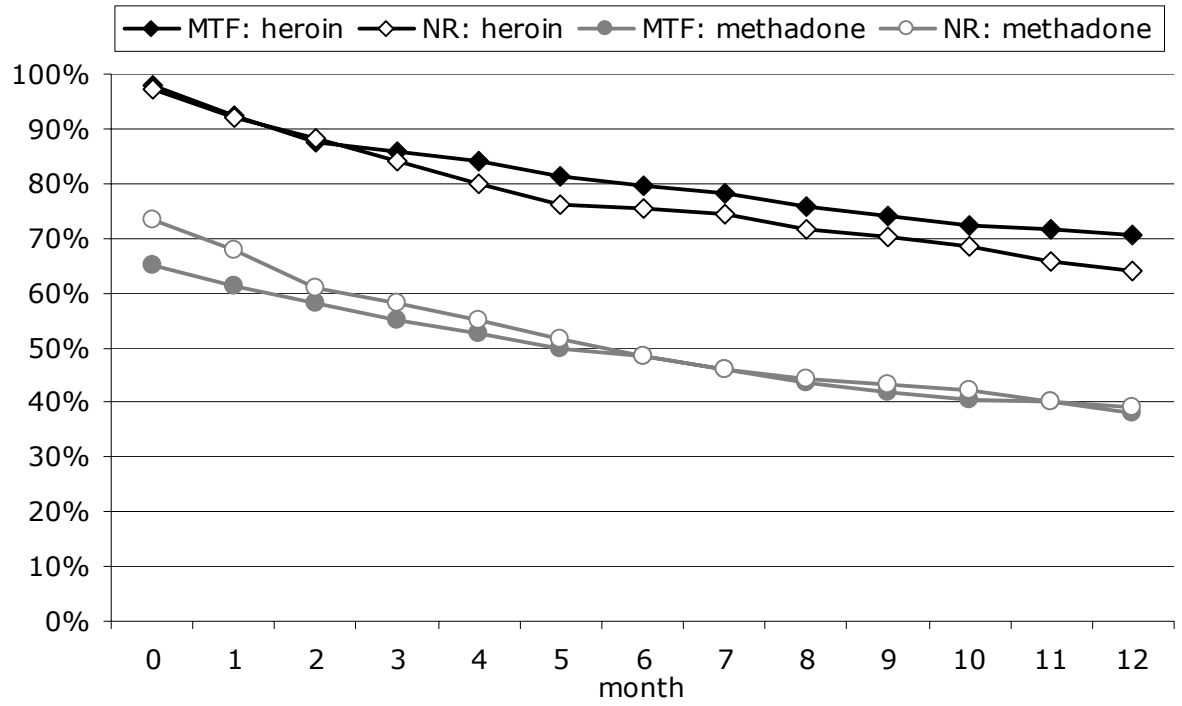
The treatment retention rate for the first study phase is calculated based on all 1,032 randomised patients. 158 methadone patients, i.e. 31%, and only 12 heroin patients (2%) had not shown up for treatment. After 6 months, more than three quarters (77%) of the heroin patients were still in treatment, with only minor differences between the sample strata – as in the further course of the study (MTF: 80%, NR: 75%, see figure 6.4).[5] The expected better compliance of MTF patients, who had directly switched from methadone treatment, is confirmed in tendency in the heroin group in the course of treatment. This is not the case in the methadone group, where the retention rate is lower, as was expected: After 6 months, slightly less than half of the patients were still in the study treatment (48%), after 12 months, the retention rate had even dropped to 39%. Compared to the experimental group, where 67% of the patients were still treated with heroin after one year, the dropout rate of the control group is therefore extremely high.

The course of retention rates emphasises the low impact of methadone treatment conducted under clinical trial conditions; on the other hand, the attachment to treatment is almost identical in heroin and methadone patients, as shown by the mostly parallel curves. The fact that many patients did not even take up treatment, is probably mainly due to their disappointment at the "wrong" result of randomisation. Moreover, many methadone patients of the MTF group apparently do not see any reason why they should comply with the numerous conditions and rules of the new study treatment instead of returning to their former maintenance setting. NR patients apparently wait a few weeks longer before dropping out of the (for them novel) control treatment.

A total of 486 patients prematurely dropped out of the study treatment (47.1%).

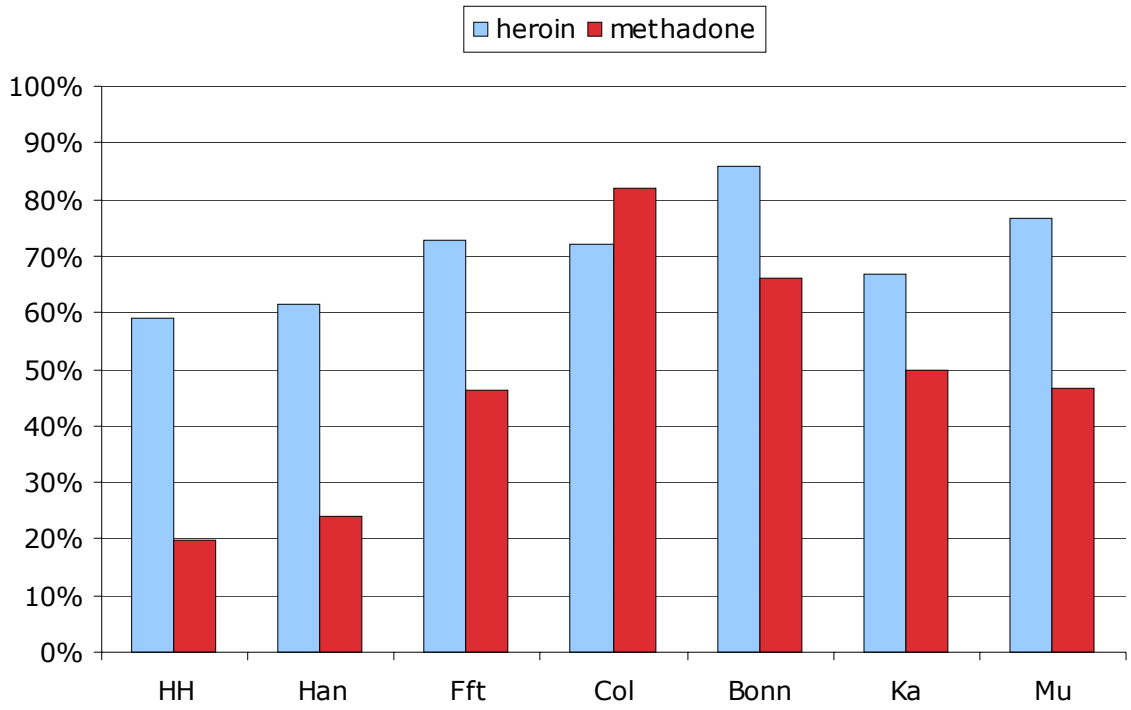
[5] For the calculation of the retention rate, the date of randomisation was taken as starting date. (4 days were added to the treatment duration.) The maximum rate for patients, who regularly concluded the first study phase, was taken to be 365 days, although in some cases – e.g. switchers – the first study phase was actually a little longer.

Figure 6.4
Retention rates of heroin and methadone treatment over 12 months for each stratum (n=1,032)



During the first study phase, the average treatment duration of all randomised heroin patients was 290 days (MTF: 295 days, NR: 285 days), i.e. slightly less than 10 months. Methadone patients participated in the study treatment on average only 189 days, slightly less than 6 months (MTF: 186 days, NR: 192 days).
Marked differences with respect to the 12-month retention rates exist between the study centres. Readiness to participate was lowest in Hamburg and Hanover. This concerns mainly control group treatment; only just above one fifth of the sample remained in treatment for 12 months (figure 6.5). In the other centres, the rate of concluders of methadone treatment is 20%-30% lower than that of heroin treatment. There is one exception: In Cologne, more patients of the control group than of the experimental group concluded the first phase of study treatment. Apparently, the study centre in Cologne succeeded in maintaining the attractiveness of methadone maintenance treatment compared to heroin treatment (also under study conditions) so that patients had no reason to leave the treatment. However, the proportion of patients "not reached" is comparatively high in Cologne, so that the methadone study treatment was a new start of addiction treatment for many patients.

Figure 6.5
Retention rates of heroin and methadone treatment after 12 months for each study centre (n=1,032)



The experimental and the control group have different reasons for dropping out of study treatment. Among methadone patients, reasons for dropping out were mainly their staying away from treatment or other reasons, most often the wrong randomisation result; heroin patients drop out most often because they switch to another medical addiction treatment (methadone maintenance as a rule) (see table 6.2). More than one tenth of each group had to leave the study treatment because of imprisonment.

Table 6.2
Reasons for premature discontinuation of study treatment

Reason for discontinuation	**Heroin**	**Methadone**	**Total**
Exclusion criterion 3: absence from treatment	11.8%	24.0%	19.8%
Exclusion criterion 4: imprisonment	14.2%	11.0%	12.1%
Exclusion criterion 6: patient cannot/does not want to participate	2.4%	12.0%	8.6%
Exclusion criterion 7: violence, threat of violence	4.7%	0.9%	2.3%
Exclusion criterion 9: theft/passing on medication	6.5%	1.6%	3.3%
Other exclusion criterion	3.6%	-	1.2%
Participation refused	3.6%	7.6	6.2%
Abstinence treatment	5.9%	4.7%	5.1%
Other medical addiction treatment	27.2%	6.6%	13.8%
Side effects/SAEs	0.6%	1.6%	1.2%
Patient died	2.4%	1.3%	1.6%
Other reasons	16.6%	26.5%	23.0%
Not known	0.6%	2.2%	1.6%
N	**169**	**317**	**486**

The retention rate presented refers exclusively to the conclusion of study treatment. If no equivalent alternative to heroin treatment was available outside the study, patients of the control group apparently found it easier to prematurely switch to a methadone treatment not conducted under study conditions. As already mentioned, this concerns mainly MTF patients, who could, in principle, return to their former maintenance treatment. Table 6.3, which presents the treatment status of the study patients at T_{12}, shows that a major part of the control patients are (again) in outpatient maintenance treatment (35%). Almost one third of the heroin patients, however, also take up maintenance treatment after leaving the study prematurely (31%). In percentage, this difference is small related to all dropouts. The number of dropouts being much higher among methadone patients than heroin patients (n=52), twice as many of them (n=104) switched to regional maintenance treatment. Another 8% of the heroin dropouts and 9% of the methadone dropouts are in some other addiction treatment at T_{12}.
If, based on this information, the retention rate is "readjusted" and participation in other treatments at T_{12} is welcomed and rated as treatment continuation rather than dropout, the overall picture is more positive. The 12-month retention rate in the heroin group would be raised to 79.8% (MTF: 85.8%, NR: 74.3%), in the methadone group to 64.0% (MTF: 69.9%, NR: 58.7%). Mainly patients from the MTF stratum take up some other addiction treatment after having dropped out of the study treatment; it is easier for them because of their previous treatment experience.

Table 6.3
Treatment status of dropped out patients at T_{12} (n=469 based on the ITT sample n=1,015)

	Heroin	**Methadone**	**Total**
Maintenance treatment	30.8%	34.7%	33.3%
Inpatient long-term treatment	3.6%	4.0%	3.8%
Detoxification	2.4%	2.3%	2.3%
Other addiction treatment	1.8%	2.7%	2.3%
Other clinic/hospital	3.0%	1.0%	1.7%
No treatment	24.9%	26.0%	25.6%
In prison	17.2%	9.7%	12.4%
Not known[a)]	16.6%	19.7%	18.6%
N	**169**	**300**	**469**

a) The category "not known" includes also patients, who stated at the external interview at T_{12} that their current treatment status was "study treatment methadone/heroin". This partly included wrong statements (patients actually dropped out) but also statements that were due to different investigation times (the external interview was conducted while study treatment was still ongoing, prior to the medical investigator's examination). In the heroin group, this concerned 9 patients (5.3%), in the methadone group 37 patients (12.3%).

6.1.2 Participation in examinations and interviews

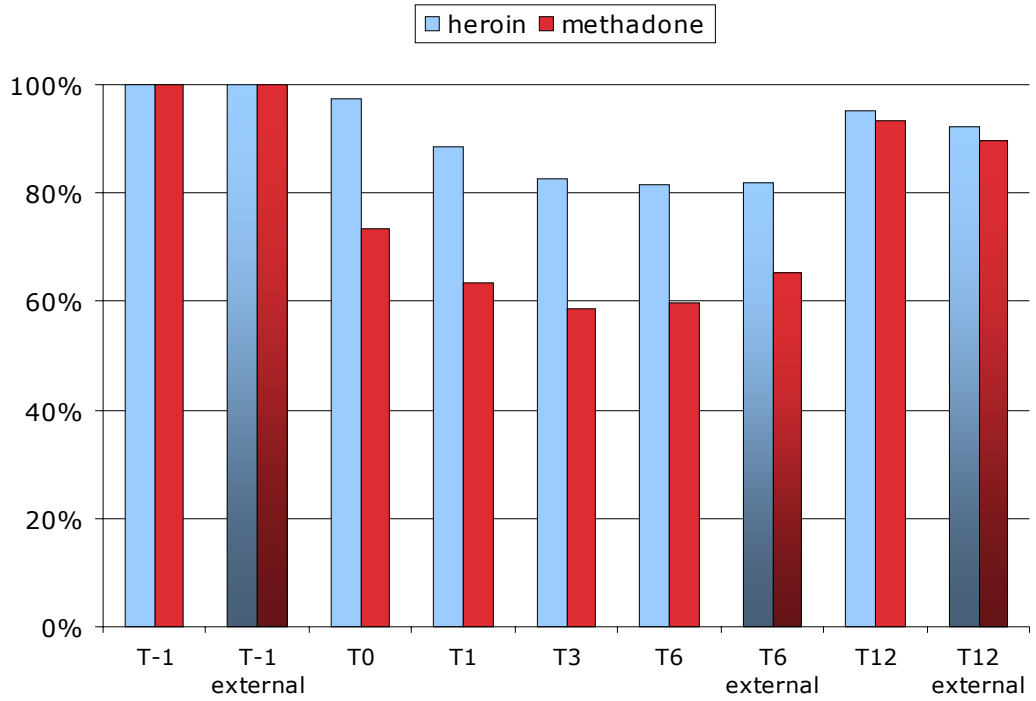
At T_{12}, 961 patients were examined by the medical investigators. This corresponds to 93.1% of the total of 1,032 randomised patients. 95.1% are heroin patients and 91.1% methadone patients, which corresponds to the expectations stated in the study protocol.[6]
With respect to the 1,015 patients of the *ITT sample*, the percentage is 94.2%, corresponding to n=956 patients. Figure 6.6 shows that, in this respect, there is hardly a difference between the experimental group (95.1%) and the control group (93.2%). The proportion of patients reached again for the examinations (and analyses) is more or less equal in the heroin and the methadone group. Due to the great efforts made by each study centre, the expected rates of patients reached again – 95% of the dropouts in the heroin group and 90% in the methadone group – were fulfilled and even slightly surpassed. The methodological bias that might occur in the statistical analysis (worst case) through the classification of dropouts, could thus be minimised.[7]
A marked decrease of examinations is perceived at T_3 and T_6. Due to successive recruitment (see above), increased efforts were made already at T_6 to carry out T_{12} examinations, in the attempt to fulfil the rates of patients reached again, which is of major importance for the primary analysis. This is reflected by the marked increase between T_6 and T_{12}. The increased

6 If the 12 patients, who died during the study treatment (rated as non-responders in the primary analysis), are included, the rate of patients reached again among all 1,032 randomised patients is even 94.3%. But a complete set of data is not available for all the patients reached again at T_{12}, so that, with respect to the primary outcome measures, a somewhat higher rate of missing values must be assumed (see table 6.5 and chapter 7).

7 Moreover, part of the patients with no T_{12} examination were reached by the external interviewers (see below) or valid data from the T_6 examination were available, which are used for the primary analysis by LOCF procedure.

rates among heroin patients are mainly due to the higher retention power of heroin treatment. Contrary to the original expectation that it would be easier to reach patients through external interviews than through medical investigators' examinations, more patients were medically examined than interviewed externally at T_{12} (heroin: 92.2%, methadone: 89.8%).

Figure 6.6
Participation in medical investigators' examinations and external interviews during the first study phase (ITT sample, n=1,015)



Following information is available on 59 patients (out of n=1,015), who were not medically re-examined after 12 months: 9 patients (heroin: 3, methadone: 6) were reached by the external interviewers (and are thus considered as valid cases in the primary analysis if the required data are available), and 10 patients died during the study period (and enter the analysis as non-responders), 5 from the experimental group and 5 from the control group.[8] Four study participants (heroin: 1, methadone: 3) were found to be in maintenance treatment, one was in prison (heroin), one was in contact with low-threshold addiction services (methadone) and one patient was homeless (heroin). These 7 patients were contacted several times but refused a follow-up examination. 4 study patients were abroad at T_{12} (all methadone), another 4 had „disappeared" (all heroin) to evade justice or other officials. The status of 25 patients is not known and no contact could be established (heroin: 10, methadone: 15).
It was endeavoured to keep as closely as possible to the scheduled times of examination, in order to have even intervals across the groups; nevertheless, major deviances developed

[8] Of the total number of 1,032 patients included in the study, 12 patients died during the first study phase. The analysis of the deaths (and other severe adverse events) occurs in paragraph 8.2.

between T_{-1} and T_0 and the subsequent examinations. It has to be considered that, on average, treatment was initiated only after one month following the baseline examination (see table 6.4). Therefore, the phase between the complex T_{-1} examination (often extending over several days) and treatment initiation had to be bridged as effectively as possible to avoid losing patients already examined. When considering average values up to T_6, they are more or less within the expected time frame. The final T_{12} examination was on average 13.4 months after treatment initiation (T_0). The standard deviations, particularly at T_{12}, point to individual variations of intervals. This concerns mainly dropped-out patients, who were sometimes reached again for an examination only after several months (in isolated cases up to 2 years).[9] No relevant differences can be detected between the study groups.

Table 6.4
Time intervals between baseline (T_{-1}) and treatment initiation (T_0) and between T_0 and the subsequent examination in days. Mean values and standard deviations (in brackets), only medical investigators' examinations performed

	Heroin	**Methadone**	**Total**
T-1 – T0	31.2 (32.8)	30.8 (30.2)	31.0 (31.7)
T0 – T1	31.2 (5.1)	36.3 (9.9)	33.3 (7.9)
T0 – T3	95.0 (12.2)	98.9 (14.9)	96.5 (13.5)
T0 – T6	187.8 (19.2)	192.4 (21.1)	189.6 (20.1)
T0 – T12	400.6 (95.9)	401.0 (92.8)	400.7 (94.6)

Apart from the rates of patients reached again, as represented above, complete data sets required for the primary analysis are not available for all the patients reached. Table 6.5 shows the number of patients with valid data for each study group. For a complete overview of patient data, we refer to the data listing in the annex.

[9] In Hanover in particular, the T_{12} examination occurred much later, on average 473.8 days after T_0 (standard deviation: 161.0 days). This cannot only be explained by the high proportion of dropouts, but the reason is also that only very late (towards the end of the first study phase in 2004) efforts were increased to reach again the study patients. The average T_0-T_{12} intervals of the other study centres are: Hamburg: 405.6 (96.6), Frankfurt: 378.5 (50.1), Cologne: 377.6 (41.8), Bonn: 368.3 (22.1), Karlsruhe: 363.9 (10.1), Munich: 400.7 (94.6).

Table 6.5
Number of patients with valid data for the primary outcome measures in each study group

Variable	Time, examination	Heroin		Methadone	
		N	%	N	%
OTI-HSS	T12	489	95.0	463	92.6
	T12 external	19	3.7	14	2.8
	T6	417	80.1	291	58.2
	T6 external	3	0.6	7	1.4
SCL-90-R, GSI	T12	485	94.2	460	92.0
	T12 external	16	3.1	11	2.2
	T6	412	80.0	290	58.0
	T6 external	2	0.4	6	1.2
Street heroin	T12 at least 3 urinalyses	344	66.8	186	37.2
	T6 at least 3 urinalyses	393	76.3	215	43.0
	T12 self-reports (med-CRF)	490	95.1	460	92.0
	T12 self-reports (ext-CRF)	472	91.7	444	88.8
	T6 self-reports (med-CRF)	418	81.2	293	58.6
	T6 self-reports (ext-CRF)	421	81.7	326	65.2
Cocaine	T12 HA	443	86.0	366	73.2
	T6 HA	38	7.4	39	7.8
	T12 self-reports (med-CRF)	490	95.1	460	92.0
	T12 self-reports (ext-CRF)	472	91.7	444	88.8
	T6 self-reports (med-CRF)	418	81.2	293	58.6
	T6 self-reports (ext-CRF)	422	81.9	326	65.2

As mentioned above, the rates of valid data at T_{12} are extraordinarily high. The consumption criterion reveals that it would not have been sufficient to calculate response rate solely based on urine and hair analyses. Only the (secondary) consideration of patients' reports concerning the 30-day consumption prevalence contributes to the high degree of exploitation of valid patient data so that response rates (and the primary analysis) can be calculated on a more reliable basis.

6.2 Protocol deviations

In addition to the 9 patients, who had withdrawn their consent prior to the treatment initiation (see paragraph 6.1), 9 patients were excluded from the analyses, because no external interview at T_{-1} is available (see also paragraph 5.8.1 concerning the statistical analysis plan). These patients had been randomised prior to completing the baseline investigation, which is a severe protocol breach. For most variables, no baseline data of these patients are available, and a valid analysis of the course of treatment was not possible. All 9 patients had previously been randomised to the control treatment (methadone). Disappointment at the "wrong" randomisation result is probably the reason for not participating in the baseline interview. However, the result of randomisation should have been communicated to the patient only

after the completion of the survey. Of the patients randomised without baseline interview, one was from Hamburg, six from Hanover and two from Munich.
In 10 of the 1,015 patients included in the analysis, deviations from the inclusion or exclusion criteria were found (see table 6.6). In each case, the regional expert committee voted for their inclusion in the study so that it was not necessary to exclude them from the analysis (see comment in table 6.6).

Table 6.6
Description of the 10 patients with formal breach of an inclusion or exclusion criterion

Rd-no	Centre	Strat.	Medic.	PsB	Gender	Age	Criterion	Comment
10068	HH	MTF	Heroin	PsE	m	44	Exclusion: in prison	Included only after prison release
10069	HH	MTF	Heroin	CM	f	41	Exclusion: Diabetes mellitus	Study inclusion approved by diabetes expert doctor
10096	HH	MTF	Metha	PsE	m	32	Inclusion: Residence in city/region since 12 months	Pt had lived in Hamburg since 6 months, was accepted as sufficient by committee
10178	HH	MTF	Heroin	CM	m	37	Exclusion: in prison	Included only after prison release
10306	HH	NR	Heroin	CM	m	37	Inclusion: Residence in city/region since 12 months	Pt was in prison in Freiburg until 8 months ago, normal residence in is HH
30013	Hann	MTF	Metha	PsE	m	39	Inclusion: Co-use under maintenance treatment	Inclusion approved by committee despite breach of criterion
30049	Hann	MTF	Heroin	PsE	m	52	Inclusion: continued i.v. heroin use	Inclusion recommended by committee despite breach of criterion
30057	Hann	NR	Metha	PsE	m	39	Inclusion: Residence in city/region since 12 months	Pt is homeless, according to mother had been staying in Hanover since at least 12 months
50003	Cologne	MTF	Metha	CM	m	44	Inclusion: continued i.v. heroin use	Pt was in in-patient treatment until shortly before treatment initiation, many years of previous heroin use
80038	Mü	NR	Metha	CM	m	44	Inclusion: no addiction treatment in the last 6 months	Pt was not in treatment in the last 4 months (before that in maintenance treatment)

Of 4 patients, 3 from Hanover, one from Karlsruhe, the second written consent, which should have been obtained directly before informing the patient of the randomisation result and before treatment initiation (T_0), is not available. These 4 patients had been randomised to the methadone group and did not show up for the study treatment.

In one patient (Rd-Nr. 10003, stratum MTF, methadone, CM, male, 47 years), an exclusion criterion occurred *in the course* of study treatment but did not lead to treatment exclusion. This patient was from Hamburg; he did not, at first, accept to be included in the control group but later reconsidered this decision. Due to a suicidal crisis, he was moreover advised by the treatment team to continue treatment. Therefore, the exclusion criterion of a longer treatment interruption was fulfilled at T_1. This patient concluded the first study phase and continued treatment in the second study phase.
In a number of patients, exclusion criteria were reported at the T_{12} examination (in particular that the patient cannot/will not continue the study treatment). However, this concerned only patients who dropped out at the end of the first study phase. Therefore, the criterion was the reason given for terminating the study treatment. All other patients, who fulfilled an exclusion criterion, had dropped out from study treatment prematurely.[10]

Among the patients of the MTF stratum, 23% (111 out of 492) were included in the study, although their methadone dose (or equivalence dose) was inferior to the required 60 mg per day. The regional expert committee explicitly approved the inclusion of each of these patients, because they certainly belonged to the target group of most severely dependent patients and their maintenance treatment was not satisfactory in terms of the other inclusion criteria (e.g. continuing co-use of heroin and/or cocaine). Moreover, the inclusion criterion related to the minimum methadone dose was changed by the 7th amendment (see paragraph 5.9.2). Table 6.7 shows the number of these patients and their mean daily doses for each study centre. According to a BfArM communication of 10.10.2003, it was agreed that these patients were included in the main analysis of the study. However, the team of the principal investigator was required to provide a description of these patients and their distribution to the different treatment groups. The latter is presented here, the description of patients' characteristics will be given in paragraph 7.2.1.

[10] Moreover, in some patients (who regularly concluded the first study phase), data on exclusion criteria were found to be missing. In 21 cases, information on lab deviations were missing, in one case information on severe somatic complications were missing, or, in isolated cases, a complete examination had not been carried out (n=8).

Table 6.7
MTF patients with a daily methadone dose inferior to 60 mg prior to treatment initiation, number and average dose per maintenance substance (n=111)

	d,l-Methadone		Levomethadone		Buprenorphine		Total[a)]	
Centre	**N**	**Dose mg**	**N**	**Dose mg**	**N**	**Dose mg**	**N**	**Dose mg**
Hamburg	44	39.9	5	21.5	13	5.8	62	39.2
Hanover	11	36.0	5	17.0	1	4.0	17	34.7
Frankfurt	9	37.2	-	-	1	4.0	10	36.0
Cologne	-	-	-	-	-	-	-	-
Bonn	-	-	-	-	-	-	-	-
Karlsruhe	10	33.1	-	-	2	7.5	12	35.1
Munich	10	44.0	-	-	-	-	10	44.0
Total	**84**	**38.8**	**10**	**19.3**	**17**	**5.8**	**111**	**38.2**

a) The mean total dose is analogously given in mg d,l methadone. As no equivalence doses can be determined for buprenorphine (Subutex®), the attributation is based on the dosage table of various maintenance substances, published in the Deutsche Ärzteblatt (Jg. 100, Heft 41, S. A2679) for reasons of price comparison.

Just above half of the "underdosed" MTF patients were from Hamburg representing 30% of the MTF stratum in Hamburg. In Hanover, their proportion was 34%, in Frankfurt only 10%. In Karlsruhe, the proportion of underdosed MTF patients was highest with 43%, in Munich, it was 34%. In Cologne and Bonn, all MTF patients had received at least 60 mg of methadone prior to the study initiation.
In terms of distribution to treatment groups, 35 patients were randomised to heroin treatment with psychoeducation, 20 to heroin treatment with case management (heroin total: n=55, corresponding to 50%). The second half of these patients was randomised to the control group, 25 patients received psychoeducation and 31 case management (methadone total: n=56, corresponding to 50%). As these patients were evenly distributed to the substance groups heroin and methadone, a distorting influence on the main effects of the study is not expected.

7. Efficacy analyses

The primary efficacy analyses are based upon n=1,015 patients of the ITT sample. They focus on the evaluation of the primary outcome measures "health" and "drug use" (see paragraph 7.4.1). The analysis of the secondary target criteria is based upon the valid data (see paragraph 7.4.3.4).
Following 17 patients were excluded from the ITT analysis (and further statistical evaluations). Nine of them are the patients already mentioned, whose baseline data (T_{-1}) were incomplete (no external interview, see paragraph 6.2), another 9 patients revoked their consent to study participation before starting treatment (patient no. 80057 fulfils both exclusion criteria) (see table 7.1).

Table 7.1
Description of the patients excluded from the ITT analysis (n=17)

Rd no	Centre	Strat.	Medic.	PsB	Gender	Age	Reason for exclusion
10130	HH	MTF	Metha	CM	m	43	Revocation prior to treatm. initiation
10292	HH	NR	Metha	PsE	m	28	Revocation prior to treatm. initiation
10441	HH	NR	Metha	CM	m	32	Revocation prior to treatm. initiation
10443	HH	NR	Metha	PsE	m	31	no baseline interview (T_{-1}) available
30040	Han	MTF	Metha	PsE	f	30	no baseline interview (T_{-1}) available
30087	Han	NR	Metha	CM	m	34	no baseline interview (T_{-1}) available
30105	Han	NR	Metha	CM	m	50	no baseline interview (T_{-1}) available
30126	Han	NR	Metha	CM	m	38	no baseline interview (T_{-1}) available
30129	Han	NR	Metha	PsE	f	34	no baseline interview (T_{-1}) available
30131	Han	NR	Metha	CM	m	36	no baseline interview (T_{-1}) available
40019	Fft	MTF	Metha	PsE	m	32	Revocation prior to treatm. initiation
40073	Fft	MTF	Metha	CM	m	39	Revocation prior to treatm. initiation
40124	Fft	NR	Metha	PsE	m	30	Revocation prior to treatm. initiation
50055	Cologne	NR	Metha	CM	f	36	Revocation prior to treatm. initiation
80027	Mu	MTF	Metha	CM	f	25	no baseline interview (T_{-1}) available
80032	Mu	NR	Metha	CM	f	28	Revocation prior to treatm. initiation
80057	Mu	NR	Metha	CM	f	39	No baseline interview / revocation

The majority of the patients excluded from the analysis are from Hanover; in Bonn and Karlsruhe, all patients could be included in the analyses. All of these patients had been randomised to the control group; this might be a reason for the incomplete baseline investigation as well as for the revocation of consent. Unlike the 9 patients with no interview at T_{-1}, who should not have been randomised in the first place (breach of protocol, see paragraph 6.2), a deviation from the (particularly robust) evaluation strategy „analysed as randomised" in patients, who revoked study participation, occurred, as their dropping out cannot be interpreted in connection with the study treatment (amendment ZIS-HA9/14 of 23.3.2005). As it is an open study, a higher number of revokers in the control group was

expected. Other revokers, who had started the treatment, were considered as dropouts in the statistical analyses (cf. paragraph 6.1.2).

7.1 Data sets

The *ITT analysis* includes all 1,015 patients. Dropouts, i.e. patients with no available data at T_{12} and whose data cannot be completed by LOCF procedure, are coded as non-responders in the experimental group and as responders in the control group with respect to the primary outcome measures (worst case). It can happen that the number of valid data for each target criterion is different for the patients of the ITT sample. In a second step, all dropouts are coded as non-responders, (realistically) assuming that dropouts not reached again most probably did not benefit from the treatment. It had been planned, in a third step, to code dropouts of the control group according to the valid data available for the primary outcome measures and to randomly assign them to responders or non-responders. Due to the low number of dropouts, this form of analysis was dropped (cf. paragraph 7.4.1).

The *per-protocol sample* includes all patients of the respective study branch, who completely concluded the first study phase. This includes all patients, who are reported, on page A1 of the CRF "patient data – study completion/end of treatment", to have regularly completed the study phase, and the patients, who were included in the second phase of the study. Restrictions in addition to the exclusion criteria mentioned in the study protocol are not applied (e.g. necessity of a minimum of heroin or methadone applications or a defined number of valid measures). This definition was agreed with the international advisory board and corresponds to the procedure of the Dutch heroin trial (CCBH 2002).
The per-protocol analysis is performed (in addition to the ITT analysis) in order to obtain an evaluation of the influence that dropouts exercice on the study outcome. Compared to the ITT analysis, the PP analysis is better able to produce results related to the treatment setting, in particular if retention rates differ between the groups. It should be investigated in a further step, in which ways patients retained in treatment differ from the dropouts (e.g. regarding their situation at admission), in order to draw conclusions in terms of predictors of regular treatment participation.

The *safety sample* is defined in terms of adverse events (AEs) and severe adverse events (SAEs) in patients, who started treatment. Only AEs and SAEs of the first study phase are analysed.

7.2 Patient characteristics at baseline

Demographic data and other patient characteristics at baseline (T_{-1}) for each target stratum and according to experimental and control groups are presented below (see table 7.2). The table includes only patients of the ITT sample (n=1,015). The data source is either the the medical investigator's examination (med-CRF) or the initial interview (ext-CRF).

Table 7.2

Patient characteristics of the ITT sample at baseline (T_{-1}) for each target stratum and group (n=1,015). The standard deviation is shown in brackets. The values marked in grey point out significant differences between the strata.

Characteristic	MTF stratum			NR stratum		
	Heroin	**Metha**	**Total**	**Heroin**	**Metha**	**Total**
Gender, male proportion	78.5%	77.2%	**77.8%**	81.4%	82.2%	**81.8%**
Age, years	36.7 (6.5)	37.1 (6.7)	**36.9 (6.6)**	35.7 (6.8)	36.0 (6.8)	**35.9 (6.8)**
Nationality Germany	91.5%	92.9%	**92.2%**	91.0%	91.1%	**91.0%**
Nationality EU country	4.1%	1.7%	**2.9%**	3.4%	3.5%	**3.4%**
Nationality not EU	4.5%	5.4%	**4.9%**	5.6%	5.4%	**5.5%**
Social situation						
Stable housing situation	74.8%	75.5%	**75.2%**	63.7%	64.2%	**63.9%**
Steady partnership	37.4%	30.3%	**33.9%**	28.4%	32.2%	**30.2%**
Children	38.6%	30.7%	**34.7%**	39.7%	41.1%	**40.4%**
Professional training completed	45.3%	44.5%	**44.9%**	45.7%	42.9%	**44.3%**
Main source of income employment	6.1%	3.7%	**4.9%**	4.1%	3.9%	**4.0%**
Main income unemployment funds	20.4%	18.7%	**19.5%**	17.8%	16.7%	**17.3%**
Main source of income welfare	35.5%	37.8%	**36.6%**	29.4%	26.7%	**28.1%**
Main income pension/sickness benefit	8.2%	7.9%	**8.0%**	2.2%	4.7%	**3.4%**
Main source of income illegal	17.1%	18.3%	**17.7%**	26.8%	28.7%	**27.7%**
Main source of income other	12.7%	13.7%	**13.2%**	19.7%	19.4%	**19.5%**
Employment last 30 days	17.1%	12.9%	**15.0%**	10.4%	11.7%	**11.0%**
Debts	86.2%	83.0%	**84.6%**	79.1%	82.9%	**81.0%**
Amount of debts, Euro	11,508 (14,953)	18,609 58,905)	**15,014 (42,824)**	13,981 (30,161)	25,470 (74,738)	**19,813 (57,519)**
Ever convicted	97.1%	96.2%	**96.6%**	96.6%	95.3%	**95.9%**
Ever in custody or sentenced to prison	74.2%	76.0%	**75.1%**	73.7%	74.3%	**74.0%**
In prison for narcotics offences	47.4%	37.9%	**42.8%**	34.8%	37.0%	**35.8%**
In prison for procuring offences	32.4%	34.2%	**33.2%**	33.2%	35.8%	**34.4%**
Illegal activities (for profit) last 30 days	70.1%	63.8%	**67.0%**	76.1%	80.2%	**78.1%**
Number of days	18.8 (11.0)	18.8 (10.5)	**18.8 (10.7)**	23.3 (9.5)	22.0 (10.0)	**22.6 (9.8)**
Physical health						
OTI health scale (0-50)	18.8 (5.1)	18.9 (5.5)	**18.9 (5.3)**	18.7 (5.3)	19.3 (5.3)	**19.0 (5.3)**
Karnofsky index (0-100)	71.2 (12.6)	70.6 (13.6)	**70.9 (13.1)**	72.0 (12.9)	71.7 (12.6)	**71.9 (12.7)**
Nutritional state BMI	23.0 (3.8)	22.9 (3.8)	**22.9 (3.8)**	22.5 (3.2)	22.2 (3.1)	**22.4 (3.2)**
HIV positive	11.8%	10.9%	**11.4%**	5.7%	8.1%	**6.9%**
HCV positive	82.8%	85.4%	**84.1%**	78.5%	78.6%	**78.5%**
Skin abscesses	4.1%	7.1%	**5.6%**	7.9%	7.8%	**7.9%**
Withdrawal symptoms (SOWS, 0-30)	9.1 (6.3)	9.4 (6.9)	**9.3 (6.6)**	9.9 (7.0)	10.8 (7.2)	**10.4 (7.1)**
Echocardiography pathol. finding [a)]	18.7%	15.4%	**17.0%**	14.1%	15.4%	**14.8%**
ECG pathol. finding [a)]	19.5%	16.6%	**18.1%**	17.8%	18.9%	**18.4%**
Abdominal sonogr. pathol. finding [a)]	59.8%	53.1%	**56.5%**	56.1%	52.5%	**54.4%**
Thorax x-ray pathol. finding [a)]	2.0%	0.4%	**1.2%**	2.6%	2.7%	**2.7%**
Mental health						
GSI value, SCL-90-R (T value)	69.5 (11.0)	69.7 (9.8)	**69.6 (10.4)**	68.4 (10.9)	69.7 (9.9)	**69.0 (10.4)**
GSI value, SCL-90-R (raw score, 0-4)	1.15 (0.61)	1.18 (0.64)	**1.17 (0.62)**	1.11 (0.65)	1.21 (0.68)	**1.16 (0.67)**
GAFS (0-100)	53.3 (10.5)	52.5 (11.9)	**52.9 (11.2)**	54.2 (12.1)	54.3 (11.5)	**54.2 (11.8)**
Previous suicide attempts	45.8%	43.5%	**44.6%**	37.4%	42.2%	**39.7%**
Clinical global impression (CGI, 0-7)	4.6 (0.9)	4.6 (1.0)	**4.6 (1.0)**	4.5 (1.0)	4.6 (0.9)	**4.6 (1.0)**
Lifetime diagnosis F2 disorder (at T_1) [b)]	0.5%	1.0%	**0.7%**	0.5%	0.9%	**0.6%**
Lifetime diagnosis F3 disorder (at T_1) [b)]	40.8%	35.1%	**38.9%**	32.2%	31.5%	**32.0%**
Lifetime diagnosis F4 disorder (at T_1) [b)]	43.7%	53.6%	**46.9%**	39.3%	50.0%	**42.9%**
Lifetime diagnosis F5 disorder (at T_1) [b)]	6.3%	7.2%	**6.6%**	1.4%	2.8%	**1.9%**
At least one of these lifet. diagnoses [b)]	62.1%	60.8%	**61.7%**	58.1%	62.0%	**59.4%**

Drug use						
Start regular heroin use, age	19.7 (5.2)	20.0 (5.0)	**19.8 (5.1)**	20.3 (5.5)	20.7 (5.5)	**20.5 (5.5)**
Start regular cocaine use, age	22.6 (7.5)	22.3 (7.2)	**22.5 (7.3)**	22.1 (7.7)	23.4 (6.8)	**22.7 (7.3)**
Years of regular heroin use	14.2 (6.2)	14.4 (6.3)	**14.3 (6.3)**	13.1 (6.4)	12.8 (6.2)	**13.0 (6.3)**
Years of regular cocaine use	6.1 (6.9)	5.9 (6.4)	**6.0 (6.7)**	5.0 (6.4)	5.3 (6.2)	**5.1 (6.3)**
Years of regular benzodiazepine use	6.2 (7.8)	7.3 (7.8)	**6.7 (7.8)**	4.0 (6.0)	3.8 (6.1)	**3.9 (6.0)**
Years of regular multiple use	13.4 (8.6)	15.0 (8.1)	**14.2 (8.4)**	12.8 (8.4)	12.9 (8.2)	**12.8 (8.3)**
Heroin use last 30 days [c)]	91.9%	92.1%	**92.0%**	99.6%	98.8%	**99.2%**
Number of days [c)]	17.1 (10.8)	17.6 (10.5)	**17.4 (10.7)**	26.8 (6.5)	26.2 (7.4)	**26.5 (6.9)**
Cocaine use last 30 days [c)]	76%	68%	**72.1%**	74.7%	72.0%	**73.4%**
Number of days [c)]	14.7 (11.0)	14.1 (10.8)	**14.4 (10.9)**	14.7 (11.4)	16.3 (11.7)	**15.5 (11.5)**
Benzodiazepine use last 30 days	62.2%	63.5%	**62.8%**	51.5%	50.6%	**51.0%**
Number of days [c)]	18.7 (11.2)	18.4 (11.5)	**18.6 (11.3)**	13.3 (11.3)	14.2 (11.4)	**13.8 (11.3)**
Alcohol use (harmful) last 30 days	16.3%	10.4%	**13.3%**	12.6%	13.2%	**12.9%**
Number of days [c)]	10.9 (11.3)	13.6 (12.2)	**11.9 (11.7)**	12.9 (11.5)	14.0 (13.1)	**13.4 (12.3)**
Multiple use last 30 days	87.5%	93.7%	**90.6%**	86.8%	89.9%	**88.3%**
Number of days [c)]	23.8 (9.3)	24.8 (8.7)	**24.3 (9.0)**	23.1 (9.5)	22.8 (9.6)	**22.9 (9.6)**
Intravenous use last 30 days	94.7%	92.5%	**93.6%**	98.5%	98.1%	**98.3%**
Number of days [c)]	19.7 (10.7)	20.3 (10.5)	**20.0 (10.6)**	26.6 (7.2)	26.3 (7.5)	**26.5 (7.4)**
Drug overdose up to now	74.5%	73.6%	**74.1%**	68.4%	61.9%	**65.2%**
Number of drug overdoses [c)]	6.1 (11.9)	5.7 (9.6)	**5.9 (10.8)**	5.6 (10.7)	5.7 (9.7)	**5.6 (10.2)**
Money spent on drugs last 30 days, Euro	880 (1,336)	738 (898)	**810 (1,142)**	1,304 (1,684)	1,346 (1,752)	**1,324 (1,716)**
Money spent on alcohol, last 30 d., Euro	30 (56)	33 (74)	**31 (66)**	29 (67)	28 (68)	**29 (67)**
Syringe sharing	11.3%	6.4%	**8.8%**	10.4%	8.2	**9.4%**
Sharing of injection equipment	19.6%	16.9%	**18.3%**	20.5%	20.4%	**20.5%**
Addiction treatment						
Outpatient detoxification up to now	38.3%	34.8%	**36.5%**	25.2%	34.4%	**29.7%**
Average number [d)]	7.8 (11.8)	7.6 (11.4)	**7.7 (11.5)**	8.8 (12.2)	8.0 (11.3)	**8.3 (11.7)**
Inpatient detoxification up to now	88.1%	90.4%	**89.2%**	82.3%	80.6%	**81.4%**
Average number [d)]	8.6 (7.9)	7.0 (6.8)	**7.8 (7.4)**	6.4 (6.5)	6.5 (6.9)	**6.5 (6.7)**
Maintenance treatment up to now	100.0%	99.6%	**99.8%**	77.8%	81.5%	**79.6%**
Average duration, months [d)]	63.6 (45.8)	63.9 (44.8)	**63.8 (45.3)**	32.9 (36.2)	29.3 (30.9)	**31.1 (33.7)**
Psychosocial treatment up to now	62.8%	68.2%	**65.5%**	37.3%	42.1%	**39.6%**
Average duration, months [d)]	45.9 (45.5)	46.2 (44.0)	**46.1 (44.6)**	30.3 (30.2)	28.9 (34.1)	**29.6 (32.3)**
Outpatient drugfree treatment up to now	11.6%	13.5%	**12.5%**	9.0%	11.1%	**10.0%**
Average number [d)]	1.5 (1.2)	1.7 (1.8)	**1.6 (1.5)**	1.6 (2.0)	1.4 (1.0)	**1.5 (1.5)**
Inpatient drugfree treatment up to now	62.6%	61.1%	**61.8%**	54.6%	53.0%	**53.8%**
Average number [d)]	2.2 (1.6)	2.3 (1.5)	**2.2 (1.6)**	2.1 (1.3)	2.2 (1.6)	**2.1 (1.4)**
Therapeutic flat sharing up to now	31.6%	29.3%	**30.5%**	19.6%	23.9%	**21.7%**
Average number [d)]	1.5 (0.8)	1.3 (0.8)	**1.4 (0.8)**	1.4 (0.7)	1.3 (0.7)	**1.3 (0.7)**
None of these treatments up to now	-	-	**-**	3.3%	3.1%	**3.2%**

[a)] Percentages relate to all patients (examination performed: echocardiography: n=890, ECG: n=940, sonography: n=935, x-ray: n=78).

[b)] Values relate to valid data; the CIDI was performed in 626 patients at T_1.

[c)] Heroin use in the last 30 days includes speedballs (heroin & cocaine). Cocaine use of the last 30 days includes crack and speedballs. The average number refers to patients with drug use (days) or overdoses (number).

[d)] The average number (or duration) of treatments refers to patients with experience of the respective type of treatment.

The majority of the study participants is male, in their mid-thirties and of German nationality. One fourth of the MTF patients and one third of the NR patients lived in instable housing conditions (guest-house, homeless, institutions) prior to treatment initiation, only one third had a steady partner. Less than half of the patients had completed professional training, and

the current employment situation is rather poor: only 15% of the MTF and 11% of the NR patients had been employed during the last month prior to the study treatment. Income sources are mainly social allowances; a considerable number of the NR report illicit gains as main source of income. More than four fifths were indebted with an average amount as high as 15,000 to 20,000 Euro. Almost all study participants had been previously convicted, three quarters had served a prison sentence, the reasons being mainly offences against the narcotics law and procuring offences.

Overall, patients are in poor health condition at baseline. With an average of 19 symptoms on the OTI health scale (inclusion criterion was at least 13 symptoms), physical impairments are rather severe. This is also reflected by the medical assessment of physical conditions: An average of 71-72 points on the Karnofsky index indicates that the patient is able to look after himself but that his fitness to work is strongly restricted. Accordingly, the medical investigators assess 35% of the MTF patients unfit to work and 43% fit with restrictions. The rates are similar among NR patients: 31% are not fit to work, 45% are considered fit in a restricted way. The nutritional state in terms of the Body-Mass-Index is normal with an average of 22-23 points. 21% of the MTF patients (BMI < 17.5: 2.9%) and 24% of the NR patients (BMI < 17.5: 3.4%) reach less than 20 points. A vast majority suffer from hepatitis C virus infection, 11.4% of the MTF and 6.9% of the NR patients are HIV positive. For 15%-17% of the patients, there were pathological echocardiography findings, almost exclusively referring to cardiac valves damages, mainly affecting the mitral valve (9%) and the tricuspid valve (8%). The ECG of 18% of the patients is medically conspicuous. Atrial conduction disturbances were found in 9%, recovery disturbances in 5% of the patients. Conspicuous sonography findings were found in more than half of the study participants. 24% suffer from hepatomegaly (more than 15 cm measured in the medioclavicular line; normal size according to Schmidt 2005: 13 cm), 30% from parenchymal piknosis, 9% from parenchymal coarsening. A congestion in the portal vein (corresponding to a flow rate of less than 10 cm/s) is found in 8% of the patients. At least 9% of the patients have an enlarged spleen. As only two values were recorded – 5 x 7 x 11 cm are assumed to be normal values (Schmidt 2005) –, megalosplenia is assumed only if larger than 80 cm^2 (lower standard limit corresponds to 7 x 11 cm = 77 cm^2). Only few patients have pathological thorax x-ray findings (e.g. pleural fibrosis, inflammatory infiltrates); this examination, however, was carried out only in 78 patients.

Patients' mental state is also very poor at baseline. Almost 70 points (T value) on the Global Severity Index of the SCL-90-R (inclusion criterion was a minimum of 60 points) indicate a high average degree of mental strain (Franke 1995). 30% even reach the highest score of 80 points. In the external assessment by the Global Assessment of Functioning Scale (GAFS), axis V of the DSM-IV, patients reach only an average score of 53 to 54 points. Accordingly, the clinical global assessment concerning the existence of a mental disease ranges from "moderate" to "distinctly ill". Two fifths of the study patients had attempted suicide at least once. The degree of previous mental disorders according to ICD-10 is considerable; they were investigated by CIDI only one month after treatment initiation (at T_1) in order to avoid inferences with current symptoms. About 60% of the patients have, in addition to the addiction diagnosis, a lifetime diagnosis of schizophrenic disorder, delusional disorder (F2),

affective disorder (F3), neurotic or anxiety disorder (F4) or eating disorder (F5). At least one of these mental disorders occurred in 52% of the MTF patients and 46% of the NR patients during the last 12 months (F2: MTF 1%, NR -, F3: MTF 34%, NR 26%, F4: MTF 35%, NR 29%, F5: MTF 4%, NR 1%).

The extent of patients' drug use prior to treatment is impressing. Almost all of them used i.v. heroin and almost three quarters cocaine in the last month prior to the baseline examination (T_{-1}). More than half of them used (prescribed or non-prescribed) benzodiazepines, multiple use was the rule. Alcohol was used by 13% beyond harmful limits. Heroin has regularly been used on average for 13 to 14 years, cocaine was used regularly for 5 to 6 years. The length of the drug career calculated from the beginning of regular heroin use is even 16 to 17 years. Two thirds to three quarters already experienced an overdose, on average about 6 times. Risky health behaviour in terms of shared use of syringes (9%) and/or injection equipment (18%-20%) in the last 6 months was still very widespread among the study participants.

A comparison of the two target groups or sample strata shows that, in general, differences are rather slight. When considering the scores marked in grey, which indicate significantly deviant values ($p<0.05$), the social situation is found to be distinctly better in the MTF stratum. MTF patients live in a more stable housing situation and draw their income mostly from social benefits such as unemployment benefit and welfare; NR patients particularly often report illegal or other sources of income. No great health related differences are found with the exception of a higher HIV rate among MTF patients that can be explained by the admission criteria for methadone treatment that had prevailed for a long time. As expected, current withdrawal symptoms are more marked among the NR patients, who are not being treated. Concerning drug use, MTF patients have a rather longer "user career", possibly because they are on average one year older. Currently, related to the last 30 days, NR patients use a large amount of heroin, which is also reflected in higher costs for drugs. Accordingly, i.v. drug use is more common among NR patients. MTF patients, on the other hand, use more benzodiazepines;[11] no differentiation is made between benzodiazepines prescribed in the context of (not satisfactory) maintenance treatment and benzodiazepines taken on the patient's own accord. As expected, MTF patients have greater experience of former addiction treatments. With the exception of drugfree outpatient treatment, patients coming from methadone maintenance treatment have tried almost all the usual types of treatment; the average number of therapies (or treatment attempts), however, is hardly different between the MTF stratum and the NR stratum. Only 3% of the NR patients, according to self-reports, had never experienced any addiction treatment, which corresponds to 1.7% of all the study participants.

For 439 MTF patients, data concerning the length of their current treatment are available showing that, immediately preceding study treatment, they had been in maintenance treatment already for an average of 39.9 (±41.8) months. One third had been in maintenance treatment up to one year (34%) and one third more than four years (32%). Patients, who had been in maintenance treatment for several years, are probably particularly eager to be admitted to the heroin treatment, because methadone treatment was not successful for many years, in some

[11] The EuropASI explores the use of „soothing psychopharmacological drugs", which are benzodiazepines as a rule.

cases more than 10 years, and maintenance treatment had been continued mainly for harm minimisation.

Randomisation produced two treatment groups that were largely comparable in terms of baseline characteristics across the two target group strata. Significant differences between heroin and methadone patients only exist in four of the described characteristics; a uniform tendency towards a subgroup with a heavier health or social burden cannot be discerned.
On average, methadone patients are significantly higher indebted (heroin: 12,725 Euro, methadone: 22,083 Euro; t=-2.60, df=487.7, p=0.010), but this is mainly due to the fact that three methadone patients are indebted with 500,000 Euro, with 450,000 Euro and one patient even with 750,000 Euro. A total of 12 methadone patients are indebted with more than 100,000 Euro. Only 6 patients of the heroin group ran up debts that high; the maximum is one patient with debts of 300,000 Euro. The proportion of indebted patients is 83% in both groups.
Another imbalance of baseline characteristics is the lifetime prevalence of mental disorders of the F4 group of diagnoses according to ICD-10. Neurotic, stress and somatoform disorders were, with 52%, significantly more frequent among methadone patients than among heroin patients (42%; Chi^2=5.7, df=1, p=0.017). As mental disorders according to ICD-10 were only diagnosed at T_1, the imbalance could also have been influenced by the different retention powers of the study treatment. After one month, the CIDI was performed only in n=205 patients of the methadone group, while n=421 of the heroin patients still participated in the diagnostic examination. However, an overall higher level of mental disorders or disturbances in the methadone group could not be found.
Consumption patterns between the groups differ in a statistically significant way only where multiple use in the last 30 days is concerned. With a 30-day prevalence of 92%, the already high level of polyvalent substance use prior to treatment was even more widespread among methadone patients than among heroin patients (87%; Chi^2=5.5, df=1, p=0.020). The level of risk behaviour was higher among heroin patients prior to treatment. “Needle sharing” was reported by almost 11% of the heroin patients within the last 6 months (“sometimes”: 8.5%, “frequently”: 2.4%), but only just above 7% of the methadone patients shared syringes (“sometimes”: 6.7%, “frequently”: 0.6%; Chi^2=6.4, df=2, p=0.040). Other consumption variables do not differ significantly between methadone and heroin groups.
Thus, an imbalance at baseline influencing the central study results cannot be found in the two treatment groups. Nonetheless, explorative analyses of the individual variables at the base of the primary outcome measures *health* and *drug use* are performed to statistically control the influence of potential group differences at baseline on the results at T_{12} using a covariance analysis (see table 7.4).

7.2.1 Patient characteristics – special evaluation of MTF patients with previous daily methadone dose of less than 60 mg

111 MTF patients were included in the study though their methadone dose (or equivalence dose) was less than the required 60 mg per day. This number is reduced to n=110 among the

1,015 patients included in the analysis. Table 7.3 compares the characteristics of the previously "underdosed" patients with the other patients of the MTF stratum at baseline.

Table 7.3
Characteristics of MTF patients at baseline (T_{-1}): Patients with less than 60 mg methadone (analogous) daily dose are compared to patients with higher doses (total n=487). Standard deviation in brackets. Values marked in grey highlight significant differences between the dosage groups.

Characteristics	MTF patients, dose < 60 mg			MTF patients, dose ≥ 60 mg		
	Heroin	Metha	Total	Heroin	Metha	Total
Gender, male proportion	83.6%	78.2%	**80.9%**	77.0%	76.9%	**76.9%**
Age, years	36.5 (6.8)	37.0 (7.2)	**36.8 (7.0)**	36.8 (6.4)	37.1 (6.6)	**37.0 (6.5)**
Nationality Germany	81.8%	98.2%	**90.0%**	94.2%	91.4%	**92.8%**
Social situation						
Stable housing situation	92.7%	87.3%	**90.3%**	69.6%	72.0%	**70.8%**
Steady partnership	47.3%	29.1%	**38.2%**	35.6%	32.3%	**34.0%**
Children	29.1%	27.3%	**28.2%**	41.4%	31.7%	**36.6%**
Professional training completed	58.2%	60.0%	**59.1%**	53.7%	54.1%	**53.9%**
Main source of income employment	9.1%	9.1%	**9.1%**	5.3%	2.2%	**3.7%**
Main income unemployment funds	18.2%	25.5%	**21.8%**	21.1%	16.7%	**18.9%**
Main source of income welfare	38.2%	38.2%	**38.2%**	34.7%	37.6%	**36.2%**
Main income pension/sickness benefit	10.9%	7.3%	**9.1%**	7.4%	8.1%	**7.7%**
Main source of income illegal	9.1%	16.4%	**12.7%**	19.5%	18.8%	**19.1%**
Main source of income other	14.5%	3.6%	**9.1%**	12.1%	16.7%	**14.4%**
Employment last 30 days	18.2%	18.2%	**18.2%**	16.8%	11.4%	**14.1%**
Debts	80.0%	94.5%	**87.3%**	88.0%	79.6%	**83.8%**
Ever convicted	94.4%	96.4%	95.4%	97.9%	96.1%	97.0%
Ever in custody or sentenced to prison	60.4%	72.7%	**66.7%**	78.1%	77.0%	**77.6%**
Illegal activities (for profit) last 30 days	70.6%	79.6%	**75.2%**	70.0%	59.1%	**64.5%**
Physical health						
OTI health scale (0-50)	17.8 (4.1)	18.4 (5.0)	**18.1 (4.6)**	19.1 (5.3)	19.1 (5.6)	**19.1 (5.5)**
Karnofsky index (0-100)	70.2 (11.8)	68.1 (12.2)	**69.2 (12.0)**	71.5 (12.9)	71.3 (14.0)	**71.4 (13.4)**
HIV positive	5.6%	3.7%	**4.6%**	13.6%	13.0%	**13.3%**
HCV positive	85.2%	85.5%	**85.3%**	82.1%	85.4%	**83.7%**
Skin abscesses	1.9%	3.6%	**2.8%**	4.8%	8.1%	**6.4%**
Withdrawal symptoms (SOWS, 0-30)	7.7 (5.2)	8.8 (5.6)	**8.3 (5.4)**	9.5 (6.5)	9.6 (7.2)	**9.5 (6.9)**
Echocardiography pathol. findings [a)]	23.6%	20.0%	**21.8%**	17.3%	14.0%	**15.6%**
ECG pathol. findings [a)]	12.7%	7.3%	**10.0%**	21.5%	19.4%	**20.4%**
Abdominal sonogr. pathol. findings [a)]	67.3%	60.0%	**63.6%**	57.6%	51.1%	**54.4%**
Thorax x-ray pathol. findings [a)]	-	-	**-**	2.6%	0.5%	**1.6%**
Mental health						
GSI score, SCL-90-R (T-value)	68.3 (10.4)	69.0 (10.1)	**68.7 (10.2)**	69.8 (11.2)	69.9 (9.7)	**69.8 (10.5)**
GSI score, SCL-90-R (raw score, 0-4)	1.04 (0.55)	1.16 (0.56)	**1.10 (0.55)**	1.19 (0.62)	1.19 (0.66)	**1.19 (0.64)**
GAFS (0-100)	53.6 (9.6)	52.3 (11.5)	**52.9 (10.6)**	53.3 (10.8)	52.6 (12.1)	**52.9 (11.5)**
Previous suicide attempts	41.5%	44.4%	**43.0%**	47.0%	43.2%	**45.1%**
Clinical global impression (CGI, 0-7)	4.5 (0.8)	4.6 (1.1)	**4.6 (1.0)**	4.6 (1.0)	4.7 (1.0)	**4.6 (1.0)**
Lifetime diagnosis F2 disorder (at T_1) [b)]	2.3%	7.1%	**3.5%**	-	-	**-**
Lifetime diagnosis F3 disorder (at T_1) [b)]	44.2%	50.0%	**45.6%**	39.9%	32.5%	**37.4%**
Lifetime diagnosis F4 disorder (at T_1) [b)]	34.9%	64.3%	**42.1%**	46.0%	51.8%	**48.0%**
Lifetime diagnosis F5 disorder (at T_1) [b)]	2.3%	14.3%	**5.3%**	7.4%	6.0%	**6.9%**
At least one of these lifet. diagnoses [b)]	51.2%	71.4%	**56.1%**	65.0%	59.0%	**63.0%**

Drug use						
Start of regular heroin use, age	20.7 (5.6)	20.4 (5.9)	**20.6 (5.7)**	19.4 (5.0)	19.8 (4.7)	**19.6 (4.8)**
Start of regular cocaine use, age	24.1 (8.2)	23.6 (8.3)	**23.8 (8.2)**	22.2 (7.3)	21.9 (6.8)	**22.1 (7.0)**
Years of regular heroin use	12.9 (6.7)	13.9 (6.2)	**13.4 (6.5)**	14.6 (6.1)	14.6 (6.4)	**14.6 (6.2)**
Years of regular cocaine use	4.6 (6.1)	5.0 (6.2)	**4.8 (6.1)**	6.5 (7.1)	6.2 (6.5)	**6.3 (6.8)**
Years of regular benzodiazepine use	4.3 (7.0)	6.2 (7.9)	**5.3 (7.5)**	6.7 (7.9)	7.6 (7.7)	**7.2 (7.8)**
Years of regular multiple use	13.1 (9.2)	14.3 (8.8)	**13.7 (8.9)**	13.5 (8.4)	15.2 (7.8)	**14.4 (8.2)**
Heroin use last 30 days [c)]	94.5%	94.5%	**94.5%**	91.1%	91.4%	**91.2%**
Number of days [c)]	18.2 (10.5)	16.6 (10.2)	**17.4 (10.4)**	16.8 (10.9)	17.9 (10.6)	**17.4 (10.8)**
Cocaine use last 30 days [c)]	72.7%	74.5%	**73.6%**	77.0%	66.1%	**71.6%**
Number of days [c)]	13.4 (9.8)	12.4 (10.5)	**12.9 (10.1)**	15.0 (11.4)	14.6 (10.8)	**14.8 (11.1)**
Benzodiazpeine use last 30 days	47.3%	54.5%	**50.9%**	66.5%	66.1%	**66.3%**
Number of days [c)]	16.8 (11.7)	15.6 (11.8)	**16.2 (11.7)**	19.1 (11.1)	19.1 (11.4)	**19.1 (11.2)**
Alcohol use (harmful) last 30 days	14.5%	9.1%	**11.8%**	16.8%	10.8%	**13.8%**
Number of days [c)]	15.4 (13.4)	5.8 (5.9)	**11.7 (11.8)**	9.8 (10.7)	15.6 (12.7)	**12.0 (11.7)**
Multiple use last 30 days	87.0%	90.7%	**88.9%**	87.6%	94.5%	**91.1%**
Number of days [c)]	22.7 (9.8)	25.2 (8.9)	**24.0 (9.4)**	24.1 (9.1)	24.8 (8.7)	**24.4 (8.9)**
Intravenous use last 30 days	92.7%	90.1%	**91.8%**	95.2%	92.9%	**94.1%**
Number of days [c)]	21.1 (10.9)	19.8 (10.1)	**20.4 (10.5)**	19.4 (10.6)	20.5 (10.6)	**19.9 (10.6)**
Drug overdose up to now	66.7%	71.7%	**69.2%**	76.7%	74.2%	**75.5%**
Money spent on drugs last 30 d., Euro	680 (746)	635 (744)	**658 (742)**	938 (1,460)	770 (938)	**855 (1,233)**
Money spent on alcohol last 30 d., Euro	35 (75)	35 (55)	**35 (65)**	28 (50)	32 (79)	**30 (66)**
Syringe sharing	15.4%	11.1%	**13.2%**	10.1%	4.9%	**7.6%**
Sharing of injection equipment	32.7%	24.1%	**28.3%**	16.0%	14.8%	**15.4%**
Addiction treatment						
Outpatient detoxification up to now	38.0%	37.7%	**37.9%**	38.3%	33.9%	**36.1%**
Inpatient detoxification up to now	90.7%	94.5%	**92.7%**	87.3%	89.1%	**88.2%**
Maintenance treatment up to now	100.0%	100.0%	**100.0%**	100.0%	99.5%	**99.7%**
Psychosocial treatment up to now	61.5%	74.5%	**68.2%**	63.1%	66.3%	**64.7%**
Outpatient drugfree treatment up to now	6.5%	17.3%	**12.2%**	12.9%	12.3%	**12.6%**
Inpatient drugfree treatment up to now	62.7%	70.4%	**66.7%**	62.5%	58.3%	**60.4%**
Therapeutic flat sharing up to now	29.2%	25.0%	**27.0%**	32.2%	30.6%	**31.4%**
None of these treatments up to now	-	-	**-**	-	-	**-**
Length of current maint. treatm., months	38.5 (40.8)	36.8 (41.3)	**37.7 (40.8)**	40.2 (41.8)	40.8 (43.2)	**40.5 (42.4)**

[a)] Percentage relates to all patients (examinations performed: echocardiography: n=442, ECG: n=463, sonography: n=449, x-ray: n=36).

[b)] The values relate to valid data; the CIDI was performed in 303 MTF patients at T_1.

[c)] Heroin use of the last 30 days including speedballs (heroin & cocaine). Cocaine use of the last 30 days including crack and speedballs. The average number refers to patients with consumption (days) or overdoses (number).

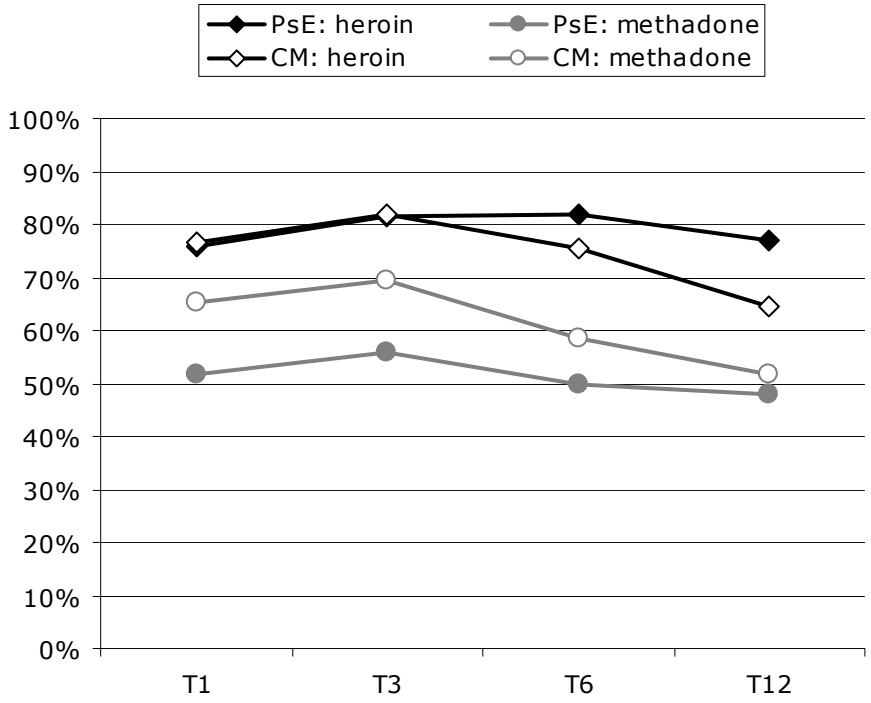
MTF patients with a maintenance dose of less than 60 mg prior to the study treatment differ from other participants of the MTF stratum only in few aspects. They live in more stable housing conditions and were less often in custody or sentenced to prison. On the other hand, they were deeper involved in illegal activities during the last month prior to the baseline examination. The low-dosed patients are less often HIV positive and have less often conspicuous ECG findings. Pathological findings in abdominal sonography are more frequent among higher-dosed MTF patients. The length of drug use shows a homogenous tendency, which was longer among the higher-dosed patients, mostly regarding cocaine and benzodiazepines. There is no difference in the current consumption pattern except for a higher benzodiazepine use in higher-dosed MTF patients. Risk behaviour is, however, more marked among low-dosed patients as shown by a higher rate of needle sharing.

Uniform differences cannot be detected, for instance to the effect that low-dosed patients would be in markedly better health or have less consumption-related problems (or be in treatment only for a short time). Apparently, these patients had also been individually stabilised to an appropriate dose. Assumptions that higher doses of the maintenance substance would have led to better effects (perhaps not justifying admission to the heroin study) cannot be deduced from this group comparison. Moreover, the overall slight differences are not expected to distort the study results. As presented in table 7.2, NR and MTF strata differ only marginally despite the quite relevant proportion of 23% of patients with a (too) low dose of the maintenance substance.

7.3 Compliance

Contrary to the retention rate (see paragraph 6.1.1), the figures on treatment compliance refer to n=1,015 patients of the analysis sample.
546 patients regularly concluded the first phase of the study (total: 54%, heroin: 67%, methadone: 37%), which was recorded as *regular conclusion* on the med-CRF. 434 of them entered the second study phase of the heroin treatment (43%). Treatment compliance is clearly influenced by the group the patient belongs to, i.e. by the randomisation result. This was to be expected in face of the open study design and the patients' baseline conditions.
As regards participation in concomitant psychosocial treatment (case management vs. psychoeducation), the differences between the groups are a bit less pronounced. This can be explained by the fact that they reproduce information from the medical investigators, who were required to record for each visit whether PST had been initialised (T_1) and whether the patient had participated in his specific type of treatment within the preceding time interval (T_3 to T_{12}, see figure 7.1). A more detailed description of utilisation behaviour (and the specific effects) will be presented in the context of the special study on psychosocial treatment.

Figure 7.1
Utilisation of psychosocial treatment according to subgroups and kind of PST, records of medical investigators (n=1,015)



Part of the patients never even initiated psychosocial treatment (up to T_3): among heroin patients almost one fifth; among methadone patients, 31% did not take up case management and 44% psychoeducation. The emerging trend of a slightly higher utilisation of PsE (compared to CM) among heroin patients and apparently a lower utilisation of PsE among methadone patients is only preliminary and will be verified by the results of the special study. Moreover, the differing retention rates of the study centres should be kept in mind, which might also mask the results concerning the utilisation of PST.

Without anticipating the results of the special study concerning psychosocial treatment, patients' treatment satisfaction will be shortly touched upon. It was explored by the Treatment Perception Questionnaire, TPQ (Marsden et al. 2000) during the external interviews. With a mean score of 2.46 in the heroin group and 2.45 in the methadone group (on a scale from 0 to 4), the overall assessment of PST at T_{12} is quite positive. In both groups, the score for the treatment team is 2.56 on average and slightly higher than the score for the treatment programme (heroin: 2.35, methadone: 2.34). It is conspicuous that the groups do not differ in their assessment of PST. This is still the case, if only treatment concluders are considered (n=546, cf. paragraph 7.4.3.1): The overall score among heroin patients is then 2.51, among methadone patients 2.55.

7.4 Efficacy results

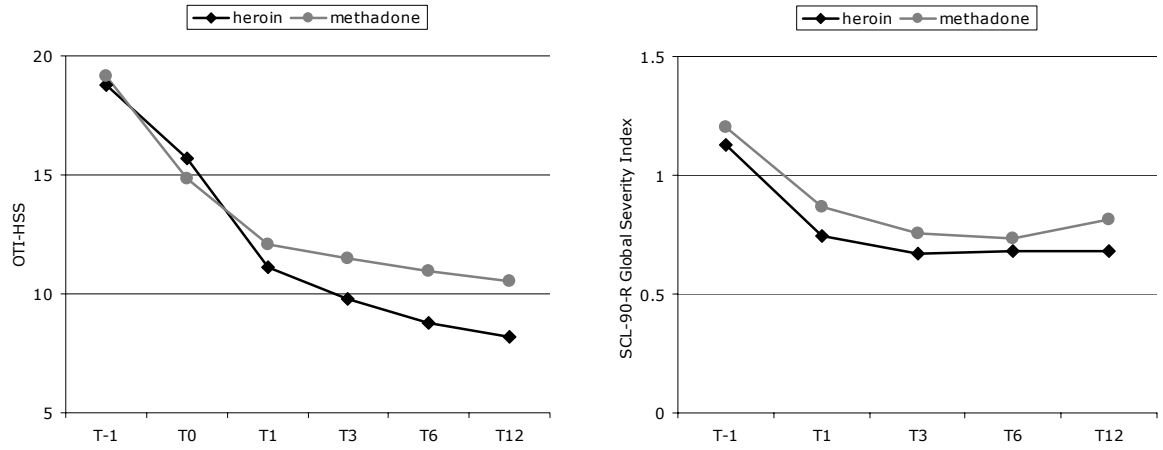
The efficacy results of heroin treatment are presented first of all according to the primary outcome measures "health" and "drug use" and the individual variables they are based upon. The latter are presented as a descriptive comparison of the experimental and control group between baseline (T_{-1}) and 12-month (T_{12}). The response rates are then considered and the statistical hypothesis testing carried out for each POM (primary analysis).

The POM *health improvement (A)* is based upon the score of the OTI health scale (physical health) and the Global Severity Index (GSI) of the SCL-90-R (mental health) (cf. paragraph 5.6). A marked improvement of both the physical and mental health is found within the first weeks of study treatment (see figure 7.2). The OTI health scale discovers this effect already between the baseline examination (T_{-1}) and the actual start of treatment (T_0).[12] This phenomenon can be explained by the fact that patients, who initiate a new treatment, are encountered in a state of crisis, which can even be subjectively enhanced by the expectation to be admitted to heroin treatment. Then, the comprehensive baseline examination can be experienced as an intervention with a positive influence on patients' wellbeing. As a rule, patients, who participated in the baseline examination, could not immediately start treatment but (on average) only after one month (see paragraph 6.1.2). Various medical examinations were conducted, and it can be assumed that contacts with the treatment staff were experienced by the patient as a kind of care. Some patients of the NR stratum even received methadone to bridge the interval between T_{-1} and T_0. Last not least, the statistical artefact of regression to the mean might also play a part, stating that is not probable that very extreme values are obtained again in a re-investigation. In the further course, the two groups drift apart during treatment, mainly regarding physical health. While the two curves run mostly parallel until T_1, health improvement is greater in heroin patients than in methadone patients during the first 12 months.

The improvement of mental health runs mostly parallel in the experimental and control group. During the study treatment (from the 3rd month onwards), hardly any differences of the mental symptoms can be detected. However, it is conspicuous that the curves drift apart between T_6 and T_{12}. The condition of methadone patients declines again towards the end of the first study phase, possibly due to the greater proportion of dropouts (cf. paragraph 6.1.1).

[12] Distinct improvements prior to T_0 are found mainly for the symptoms loss of appetite (decrease by 43.6%), loss of weight (40.8%), night sweat (39.0%), joint pains (35.2%) muscular pain (43.6%), giddiness (33.8%) and head injuries (34.1%). But also symptoms directly related to (unhygienic) injection conditions such as a feeling of illness after injection („dirty hit") (38.7%), scars/hematomae (34.6%) and problems with hitting blood vessels (36.6%) strongly decline prior to the actual initiation of study treatment. The positive effect of the preparation phase between T_{-1} and T_0, comparable to an intervention, is particular evident for the last-named symptoms; patients obviously start changing their consumption behaviour prior to the initiation of treatment.

Figure 7.2
Changes of physical health according to the OTI health scale (left-hand) and mental health according to the Global Severity Index (GSI) of the SCL-90-R[a)] (right-hand) in the course of the study[b)]

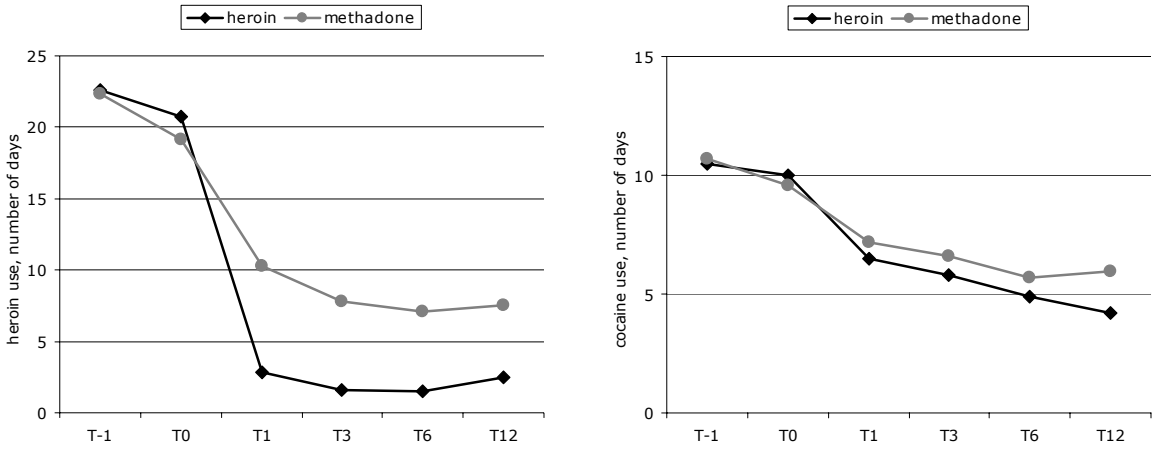


a) At T_0, SCL-90-R was not indicated, since the symptom recording relates to the last 7 days and investigational overlaps should be avoided.

b) Missing data at T_6 and T_{12} were, if possible, completed by information collected in the context of the external interview. OTI-HSS: n_{-1}=1,015, n_0=841, n_1=762, n_3=709, n_6=716, n_{12}=955, SCL-90-R: n_{-1}=1,015, n_1=762, n_3=705, n_6=707, n_{12}=948.

The POM *reduction of illicit drug use (B)* is defined, on the one hand, by objective data such as urinalyses (heroin) and hair analyses (cocaine), but, if the latter are missing, also based on patients' reports concerning drug use within the last 30 days (cf. paragraph 5.6). The latter was explored in the context of medical investigators' examinations and external interviews.
Street heroin use changed as follows, largely based on patients' self-reports: In the experimental and the control group, a drastic decline of the number of consumption days is recorded already at the beginning of treatment; as expected, it is even more marked among heroin patients (see figure 7.3). In about the third month of treatment, the curves start to run parallel, with an average of 7-8 days of heroin use among methadone patients and 1-3 days among heroin patients related to the 30-day prevalence. The subgroups differ less markedly with respect to cocaine. After a marked decline in both groups at the beginning of treatment, use among heroin patients decreases from an average of almost 7 days at T_1 to 4 days at T_{12}. In the methadone group, there is only a slight decrease between T_1 (average of 7 days) and T_{12} (6 days).

Figure 7.3
Changes of the use of street heroin (left-hand) and cocaine (right-hand) within the last 30 days based on self-reports in the context of medical investigators' examinations[a)] in the course of the study[b)]

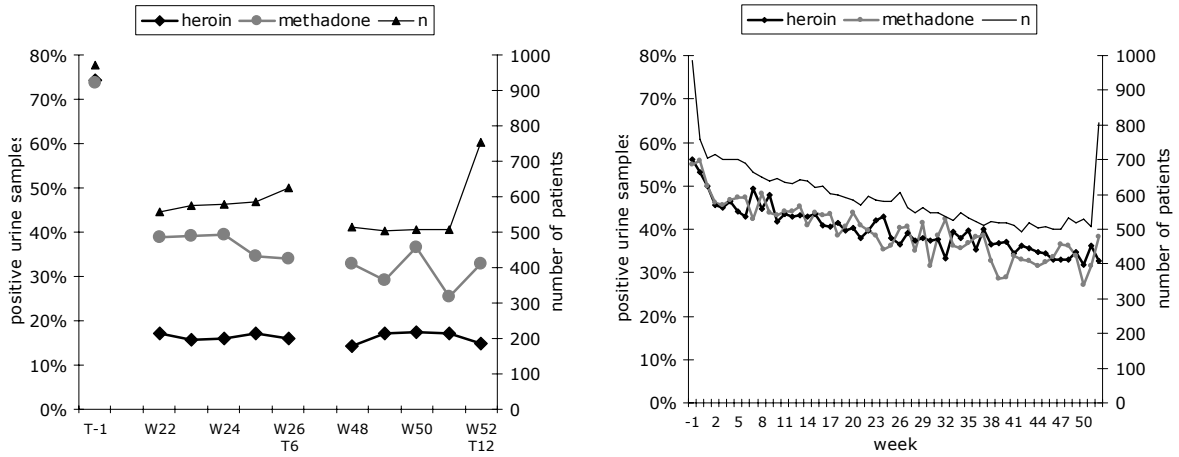


a) For reasons of comparability across all examination times, data from medical investigators are presented; missing data are completed by information of the external interviews. Between T_{-1}, T_6 und T_{12}, there are hardly any differences between data from medical examinations and external interviews (Pearson-Corr: street heroin: r_{-1}=.78, r_6=.77, r_{12}=.83, cocaine: r_{-1}=.82, r_6=.77, r_{12}=.80).

b) Street heroin: n_{-1}=1,014, n_0=859, n_1=769, n_3=712, n_6=771, n_{12}=963, cocaine: n_{-1}=1,015, n_0=859, n_1=769, n_3=712, n_6=771, n_{12}=963.

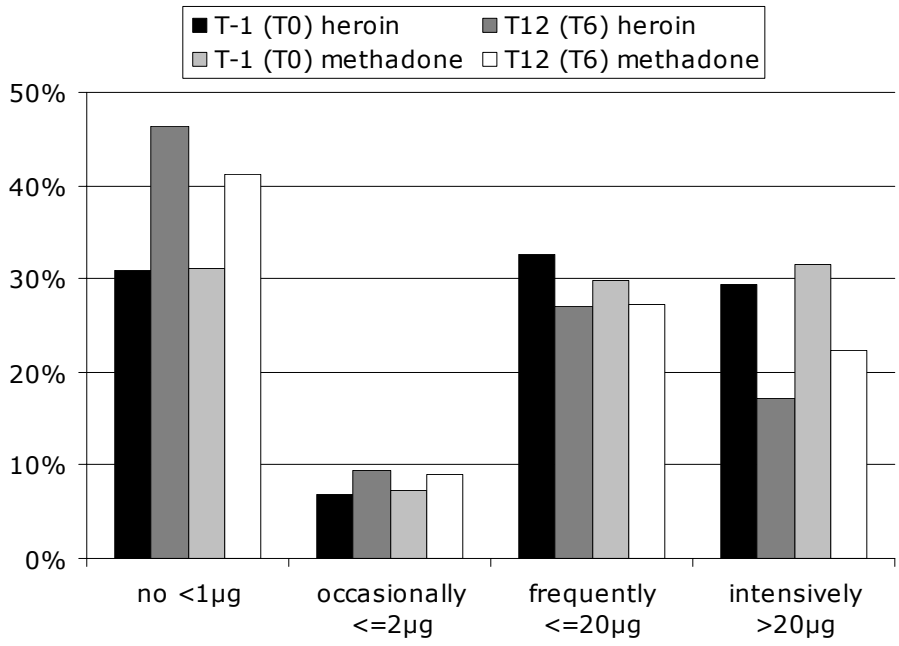
The results of urinalyses confirm the results based on patients' self-reports. Controls for street heroin occurred eleven times: at T_{-1}, in the five weeks prior to T_6 (weeks 22-26) and in the five weeks prior to T_{12} (weeks 48-52). Cocaine controls were performed weekly during the entire 12-month period. Figure 7.4 shows that the use of street heroin is constantly higher in the methadone group. Cocaine use continuously declined (largely parallelly) in both groups. It is also conspicuous that the proportion of cocaine-positive urinalyses corresponds to the number of controls carried out. Therefore, the results of urinalyses for cocaine are probably rather an underestimation. According to patients' self-reports, 63.6% of heroin patients and 55.6% of methadone patients had used cocaine in the last 30 days prior to T_6 (positive USs at T_6/week 26: heroin: 36.5%, methadone: 40.4%). In the last 30 days prior to T_{12}, the prevalence in the heroin group was 51.3% and in the methadone group 55.3% (positive USs at T_{12}/week 52: heroin: 32.7%, methadone: 38.2%).

Figure 7.4
Use of street heroin (left-hand) and cocaine (right-hand) during the first study phase based on weekly urine samples



The evaluation of hair analyses also shows a decline of cocaine use during study treatment. However, the decline is greater in heroin patients than methadone patients (see figure 7.5). The proportion of heroin patients with no cocaine use increases from 31% to 46%, in methadone patients from 31% to 41%. At the same time, the percentage of intensive cocaine use decreases from 29% to 17% in the heroin group and from 32% to 22% in the methadone group.

Figure 7.5
Cocaine use during the first study phase based on hair analyses (T_{-1}: n=898, T_{12}: n=842)[a)]



a) The values at T_{-1} include the hair analyses performed at T_0. Missing data at T_{12} are completed by analysis results at T_6

Table 7.4 summarises the baseline and T_{12} values of the variables at the base of the primary outcome measures. The table moreover includes the significance test between the heroin and the methadone group performed at T_{12} (2-factor ANCOVA taking into account the initial score). It shows that the differences of mean values for OTI-HSS and SCL-90-R are statistically significant. This is also true for the frequency of street heroin and cocaine use during the last 30 days according to patients' self-reports. Interaction effects between treatment group and stratum cannot be found. Urinalyses for street heroin are represented according to the average percentage of positive samples per patient at T_6 and T_{12}. The calculation was independent of the number of USs (1 to 5) performed. The difference between the heroin and methadone group is statistically significant at the two times of examination (T-test: T_6: $t=-6.9$, $p<0.001$, T_{12}: $t=-5.8$, $p<0.001$). The results of hair analyses for cocaine concentration do not differ significantly, taking into account the baseline values. A clear decline of the intensity of cocaine use is found in the experimental and the control group. The medians (additionally shown because of the distribution lopsided to the left) also prove a strong decline of cocaine use under study treatment. Contrary to the above categorisation (cf. figure 7.5), average and median values show no advantage of heroin treatment.
Paragraph 7.4.1.3 (table 7.6) presents the response data for the individual criteria.

Table 7.4
Change of health state according to OTI health scale and GSI of the SCL-90-R and of street heroin and cocaine use between T_{-1} and T_{12}.[a)] Mean values per stratum and covariance analysis taking into account the baseline score.

Characteristic		MTF Stratum		NR Stratum		Total		Sign.
		Heroin	Metha-done	Heroin	Metha-done	Heroin	Metha-done	ANCOVA at T12
OTI-HSS	T-1	18.8 (5.1)	18.9 (5.5)	18.7 (5.3)	19.3 (5.3)	18.7 (5.2)	19.1 (5.4)	F=41.2, df=1, p<0.001
	T12	8.4 (5.9)	10.8 (5.9)	7.9 (5.7)	10.3 (6.8)	8.2 (5.8)	10.6 (6.4)	
GSI, SCL-90-R	T-1	1.15 (0.61)	1.18 (0.64)	1.11 (0.65)	1.21 (0.68)	1.13 (0.63)	1.20 (0.66)	F=11.5, df=1, p=0.001
	T12	0.74 (0.58)	0.85 (0.58)	0.63 (0.56)	0.79 (0.65)	0.68 (0.57)	0.82 (0.62)	
Street heroin, number of days	T-1	17.0 (10.7)	16.9 (10.7)	27.7 (5.4)	27.3 (6.3)	22.6 (9.9)	22.3 (10.1)	F=77.4, df=1, p<0.001
	T12	1.9 (5.8)	5.9 (9.5)	3.0 (7.5)	9.0 (11.7)	2.5 (6.8)	7.5 (10.8)	
Street heroin, positive urinalyses	T6	12.5%	29.4%	20.1%	42.8%	16.3%	36.0%	
	T12	14.9%	26.0%	20.2%	38.9%	17.6%	32.8%	
Cocaine, number of days	T-1	10.6 (10.7)	10.1 (11.0)	10.4 (11.4)	11.3 (11.9)	10.5 (11.1)	10.7 (11.5)	F=11.6, df=1, p=0.001
	T12	4.1 (7.5)	5.2 (8.5)	4.2 (7.5)	6.7 (10.2)	4.2 (7.5)	6.0 (9.4)	
Cocaine, HA, µg/g, mean value	T-1	23.5 (44.2)	33.2 (108.6)	23.8 (44.8)	35.5 (82.2)	23.7 (44.5)	34.3 (96.3)	F=2.6, df=1, p=0.107
	T12	13.2 (32.5)	18.6 (42.8)	19.3 (50.4)	30.6 (88.0)	16.4 (42.9)	24.8 (70.2)	
cocaine, HA, µg/g, median	T-1	4.8	4.8	5.0	5.4	4.9	5.3	
	T12	1.3	1.6	1.8	2.2	1.5	1.9	

a) Missing data at T_{12} were completed, if possible, by information collected at the external interview. For heroin and cocaine use, the data provided by the examination of medical investigators are represented, missing data were completed from the external interview. The values at T_{-1} include the hair analyses performed at T_0. Missing HA data at T_{12} are completed by examination results at T_6. The percentage of urine samples is related to all available USs at the respective time, irrespective of the number (1-5).

7.4.1 Primary analysis

According to the analysis plan laid down in the study protocol (cf. paragraph 5.8.1), the primary analysis is carried out as an ITT analysis with a total of n=1,015. With the stipulated worst case strategy, according to which dropouts of the experimental group are assessed as non-responders and dropouts of the control group as responders, a very conservative evaluation strategy was chosen (analysis 1). In a lower-ranking analysis, all dropouts are assessed as non-responders (analysis 2). This procedure is less robust, but is probably closer to reality, as it can normally be assumed that patients of both groups with no analysable data due to premature discontinuation of the study did not benefit from the treatment. In both analyses, missing data at T_{12} are completed by data at T_6 according to „last observation carried forward“ (LOCF).[13]

[13] For the POM *health*, valid data are available for 970 patients (95.6%) according to LOCF (including deaths) (heroin: n=497, methadone: n=473), the missing 45 are completed by the worst case procedure. For the

Analysis 1: Table 7.5 shows that for both primary outcome measures, there is a significant difference between the experimental and the control group indicating that heroin patients benefited more from their treatment than methadone patients. For the criterion ***health***, the response rate is 80.0% in the heroin group versus 74.0% in the methadone group (see also figure 7.6). With an odds ratio of 1.41 (95%-KI: 1.05-1.89, p=0.023), the difference between the groups is statistically significant. The logistic regression shows no significant influence of the factors sample stratum (p=0.320), study centre (p=0.143) and kind of PST (p=0.269).[14] There is no interaction between the effects of medication and the MTF or NR stratum affiliation
(interaction: OR=0.83, 95%-KI: 0.46-1.50, p=0.544), the main effect remains significant after adjustment with an odds ratio of 1.54 (95%-KI: 1.02-2.34, p=0.042).[15]
For the POM ***drug use***, the response rate is 69.1% in the heroin group and 55.2% in the methadone group (see figure 7.6). This difference is also statistically significant with an odds ratio of 1.85 (95%-KI: 1.43-2.40, p<0.001). However, a study centre effect is evident here (p=0.002), as the success rates are not homogenous across the study centres (see below).[16] There is no interaction between stratum and study medication (interaction: OR=0.95, 95%-KI: 0.56-1.60, p=0.840), the main effect remains significant after adjustment with an odds ratio of 1.91 (95%-KI: 1.30-2.79, p=0.001).[17]

Table 7.5
Response rates for the primary outcome measures health improvement and reduction of illicit drug use. ITT analysis, LOCF (n=1,015) with different response assumptions among dropouts

Analysis strategy	**POM**	**Heroin**		**Methadone**		**Significance, Log. regression**
		N	**%**	**N**	**%**	
Worst case	Health	412	80.0	370	74.0	OR=1.41, p=0.023
	Drug use	356	69.1	276	55.2	OR=1.85, p<0.001
Non response	Health	412	80.0	343	68.6	OR=1.84, p<0.001
	Drug use	356	69.1	254	50.8	OR=2.22, p<0.001
Total		**515**	**100.0**	**500**	**100.0**	

Analysis 2: If all dropouts were considered as non-responders, the differences between experimental and control groups are even more marked. For the POM ***health***, table 7.5 shows 80.0% of responders in the heroin group versus 68.6% in the methadone group (see also

criterion drug use, valid data are available for 982 patients (96.7%) (heroin: n=504, methadone: n=478), 33 data are completed.

[14] Goodness of Fit following Hosmer & Lemeshow: χ^2=2.23, df=8, p=0.973. The univariate result for the POM *health* is not deviant from the result of the multivariate analysis, with OR=1.41 (95%-KI: 1.05-1.89).

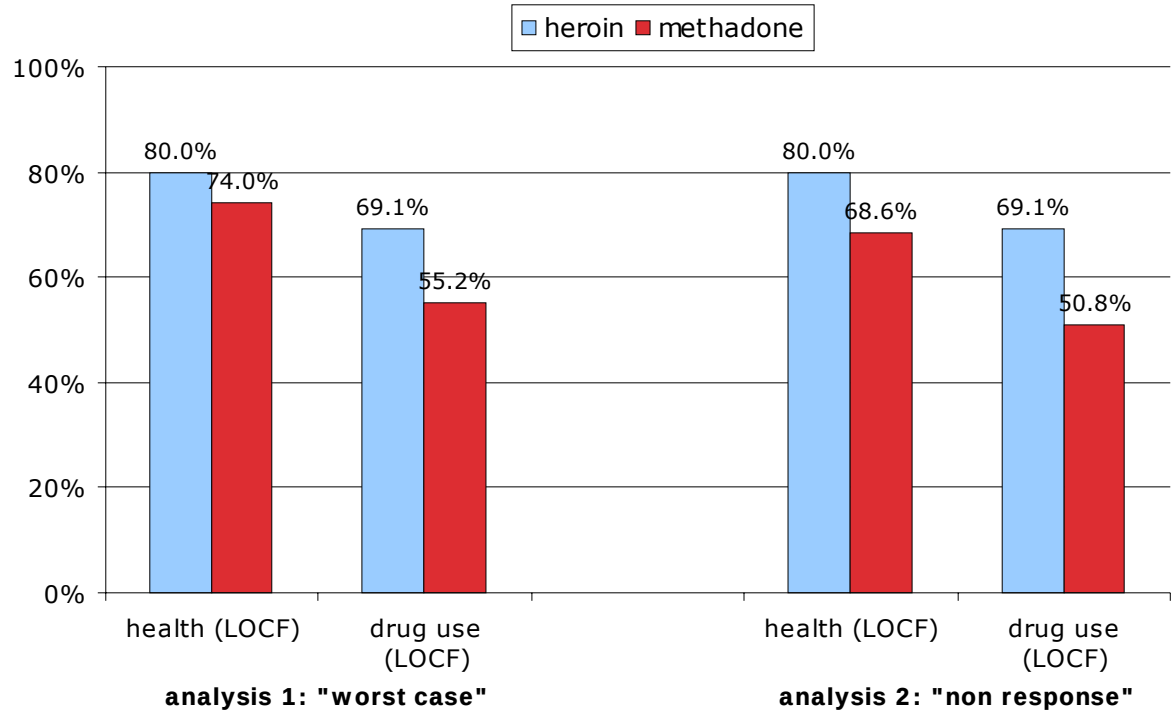
[15] Goodness of Fit following Hosmer & Lemeshow: χ^2=6.96, df=8, p=0.541 (the variable kind of PST is no longer included in this model).

[16] Goodness of Fit following Hosmer & Lemeshow: χ^2=11.06, df=8, p=0.198. The univariate result for the POM *drug use* is, with OR=1.82 (95%-KI: 1.41-2.35), virtually not deviant from the result of the multivariate analysis.

[17] Goodness of Fit following Hosmer & Lemeshow: χ^2=2.93, df=8, p=0.939 (the variable kind of PST is no longer included in this model).

figure 7.6). The odds ratio is 1.84 (95%-KI: 1.38-2.46, p<0.001) and points to a statistically significant difference. For the POM *drug use*, response rates of 69.1% in the experimental group and 50.8% in the control group also indicate a significant difference between the groups (OR=2.22, 95%-KI: 1.71-2.88, p<0.001). The above mentioned study centre effect is also evident in this analysis (p=0.002).

Figure 7.6
Efficacy of heroin vs. methadone treatment according to the primary outcome measures health improvement and reduction of illicit drug use. ITT analysis, LOCF (n=1,015) with different responses assumed for dropouts (left-hand: analysis 1: worst case strategy, right-hand: analysis 2: non-response strategy)



The statistical analysis plan described a third variety of primary evaluation, where patients, whose data could not be completed by LOCF, were assessed as non-responders in the experimental group, and in the control group, in proportion to the known data (included in the analysis), as responders and non-responders respectively; however, this procedure was dropped due to the small number of dropouts.[18]

[18] According to the definition, this analysis result is situated between the worst case analysis and the analysis defining all dropouts as non-responders.

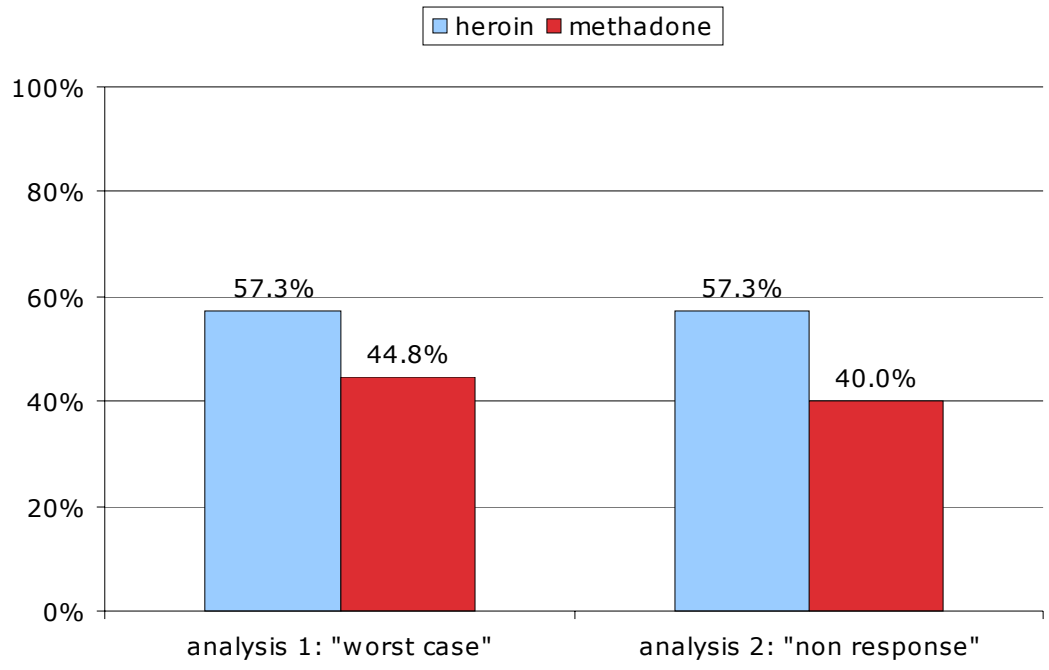
7.4.1.1 Patients with a response in both primary outcome measures

Although the presentation of patients, who fulfil *both primary outcome measures*, is not the focus of the primary analysis, a comparison of the groups will be presented here.[19] This combined target criterion is particularly useful for a comparison with the Dutch results, as health and cocaine use were a.o. also included in the POM of the Dutch study. Figure 7.7 shows a response for both POM in 57.3% of the heroin patients versus 44.8% of the methadone patients (LOCF, worst case). The odds ratio is 1.67 (95%-KI: 1.30-2.14, p<0.001). No significant influence of the factors sample stratum (p=0.853), study centre (p=0.146) and kind of PST (p=0.508), and no interaction between stratum and main effect (interaction: OR=1.07, 95%-KI: 0.45-1.76, p=0.797) are found. Therefore, heroin treatment proves superior to methadone treatment even if an overall success according to the definition is only associated with improvement of *both* POM.

If dropouts are evaluated as non-responders, the response difference is 57.3% in the heroin group vs. 40.0% in the methadone group (OR=2.03, 95%-KI: 1.58-2.61, p<0.001). Again, there is no influence by the factors sample stratum (p=0.931), study centre (p=0.190) and kind of PST (p=0.414) and no interaction between stratum and effects of medication (interaction: OR=0.99, 95%-KI: 0.60-1.63, p=0.961).

Figure 7.7

Efficacy of heroin vs. methadone treatment according to the response rates of patients fulfilling both primary outcome measures. ITT analysis, LOCF (n=1,015) assuming a different response among dropouts (left-hand: worst case strategy, right-hand: non-response strategy)



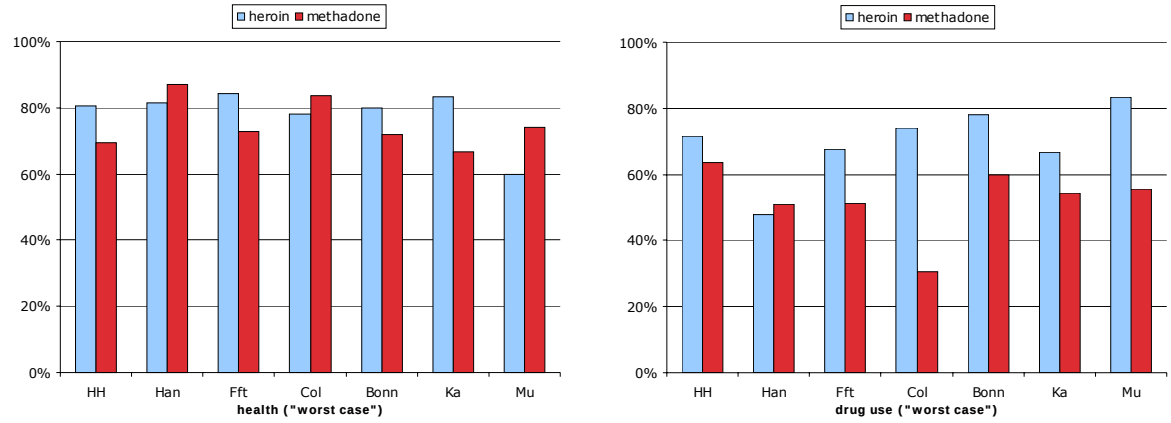
[19] The primary evaluation strategy of this medical drug trial plans separated analyses for the two primary outcome measures. The power analysis for calculating the sample size is also based on separated analyses. *An overall POM* based on *identical* effect sizes would have resulted in lower case numbers.

7.4.1.2 Differences related to study centres in primary outcome measures

Potential *differences related to study centres* were tested for significance in the multivariate primary analysis. There is no significant influence for the POM health, but a significant relationship is found for the POM drug use (see above).

Figure 7.8 shows that, for the POM *health*, methadone treatment achieved somewhat higher response rates than heroin treatment in the study centres Hanover, Cologne and Munich. But since the mean response rates of both groups hardly differ across all centres, no significant effect is found in the multivariate analysis model.[20] It is remarkable (though statistically inconspicuous) that the superiority of heroin treatment with respect to health cannot be represented uniformly across all centres.

Figure 7.8
Efficacy of heroin vs. methadone treatment with respect to the target criteria health improvement (left-hand) and decrease of illicit drug use (right-hand) according to study centres. ITT analysis, worst case, LOCF (n=1,015)



For the POM *drug use*, no contrary trends can be found in the study centres with the exception of Hanover. The significant study centre effect found in the primary analysis (see above) is due to the fact that the mean response rate (independent of the distribution among methadone and heroin groups) is overall lower in the centres of Hanover and Cologne.

7.4.1.3 Subanalysis of individual variables at the base of the primary outcome measures in patients with valid data

Since each POM consists of two components – physical and mental health and use of street heroin and cocaine – the respective individual criteria will be considered. Conclusions might be deduced whether the two variables contributed to equal parts or one more than the other to the fulfilment of the response criterion. As the logic of the worst case definition relates only to the entire POM, only valid data (i.e. without missing values) are represented here. Due to different survey procedures concerning the consumption criterion, response rates for lab results (USs, HAs) and self-reports on 30-day prevalence are indicated separately (see table 7.6).

[20] Even if each study centre is considered separately, these differences do not reach statistical significance.

Table 7.6
Representation of response rates for the individual criteria of each POM according to groups in patients with valid data

Criterion	Value (response)	Heroin		Methadone	
		N	%	N	%
OTI-HSS (n=969)	Improved by 20%	435	87.3	362	76.9
	No change	54	10.8	86	18.3
	Declined by 20%	9	1.8	23	4.9
SCL-90-R, GSI (n=965)	Improved by 20%	347	70.2	287	60.9
	No change	84	17.0	101	21.4
	Declined by 20%	63	12.8	83	17.6
Street heroin, urines (n=612)[a)]	Response yes	339	87.6	149	66.2
	Response no	48	12.4	76	33.8
Street heroin, self-reports (n=975)	Response yes	461	92.2	331	69.7
	Response no	39	7.8	144	30.3
Cocaine, HAs (n=770)[b)]	Response yes	336	80.4	266	75.6
	Response no	82	19.6	86	24.4
Cocaine, self-reports (n=975)	Response yes	448	89.6	406	85.5
	Response no	52	10.4	69	14.5

a) If at least 3 valid urinalyses are available at T_{12} or T_6.
b) If one valid HA is available at T_{-1} (or T_0) and T_{12} (or T_6).

The two individual criteria of the POM *health* show that the response rate is about 10% higher in the heroin group. Moreover, the proportion of patients, whose physical or mental health deteriorated (by at least 20%), is markedly higher in the control group.
For the POM *drug use*, a marked difference between the experimental and control group exists mainly regarding the decrease of street heroin use. This refers both to the evaluation of urinalyses and patients' self-reports on the 30-days prevalence. Differences regarding the non-increase of cocaine use are less marked – also irrespective of whether they are based on hair analyses or patients' self-reports. However, self-reports lead to higher response rates in both groups.
If results for the POM drug use were solely based on (objective) laboratory results (urinalyses, HAs), the response difference between experimental and control group would be much greater: 71.6% of the heroin group vs. only 46.1% of the methadone group would have fulfilled the target criterion of decrease of street heroin and simultaneous non-increase of cocaine use. However, it must be considered that lab information on both substances are only available for n=530 patients, which represents 52% of all the patients of the analysis sample.

7.4.1.4 Explorative analyses regarding POM health and potential artefacts

The POM health was explored in terms of the components physical and mental health using standardised survey instruments (OTI health scale, SCL-90-R). The reasons for this procedure were explained and discussed in the study protocol (Krausz et al. 2001). The very high response rate (considering the selected target group) could indicate that the operationalisation

of POM health (20% improvement of physical and mental health) was possibly not adequately chosen to allow a differentiated representation of positive treatment effects. Therefore, the issue of artefacts, which might have influenced the high response rates, will be addressed.

A) Improvement of health prior to treatment
It has already been described that physical health (cf. figure 7.2) markedly improved between baseline examination (T_{-1}) and treatment initiation (T_0). Possible and plausible explanations of this phenomenon have also been discussed above. It will be described below, how the response rates would change, if the conditions at the beginning of treatment (T_0) were considered as baseline value for the definition of the POM and the discussed recruitment and intervention effects of the pre-phase were not taken into account.[21]
77.1% of the heroin group vs. 69.2% of the methadone group fulfil the response criterion operationalised in this way. With an odds ratio of 1.50 (95%-KI: 1.13-1.99, p=0.005) in the logistic regression model, this difference of almost 8% is significant. An interaction effect between medication and stratum does not exist. This setup thus not only results – as expected – in an overall lower response rate, but also in greater differences between the groups. If the initial value at treatment initiation (T_0) were considered for the definition of the POM health, this would result in a greater superiority of heroin over methadone treatment.

B) Response criterion changed to an improvement of 30% and 40% respectively
Another explanation for the high response rates is the sensitivity of the criterion. The 20% improvement of condition between baseline (T_{-1}) and T_{12}, initially defined as adequate considering patients' poor condition of health, is possibly too low, and the criterion would be too easily fulfilled by the majority of patients (irrespective of the type of treatment). By modifying the criterion to 30% or even 40% health improvement (and no worsening by 30% and 40% respectively), the effects of this stricter definition on the response are tested.
A response rate for the POM health based on an improvement by at least 30% is reached by 79.2% of the heroin patients and 73.8% of the methadone patients (OR=1.36, 95%-KI: 1.01-1.82, p=0.042, no interaction between stratum and medication). There is hardly any difference between a response definition of 30% and a response definition of 20% as stated in the study protocol. Thus, patients, who reached at least 20% of health improvement, most probably also achieved 30% of improvement.[22] In other words, the degree of physical health improvement is, on average, clearly higher (cf. also table 7.4). If the response criterion is heightened to 40% improvement, a response is achieved by 75.7% of the heroin patients and 68.0% of the methadone patients (OR=1.48, 95%-KI: 1.12-1.96, p=0.006, no interaction between stratum and medication). As expected, the number of responders in both groups decreases with higher percentage of success definition. However, differences between the response rates in favour

[21] At T_0, data from n=806 patients were available for the response criterion health. Missing data were completed from the original analysis based on T_{-1} as baseline examination (including LOCF and worst case).

[22] 22 responders of the 20% POM become non-responders under the 30% criterion, 17 of the original non-responders become responders.

of heroin treatment are only slight and a stricter response definition would confirm the study result.

C) Influence of prison detention on treatment success
At T_{12}, 60 patients (30 of the heroin group) were medically examined in prison (5.9%), at T_6, 9 patients (4 of the heroin group) were examined in prison (0.9%). Imprisonment of study patients, irrespective of the reasons of imprisonment, is without any doubt an adverse situation in the context of the study treatment (which was then normally discontinued). Depending on the conditions, imprisonment can have a deteriorating effect on patients' physical and/or mental health thus influencing the POM. But health improvement could also happen, if e.g. patients, who had dropped out of treatment, receive good medical care in prison (possibly with maintenance treatment). Since it is not always possible to discern which offence is responsible for the conviction and prison sentence, imprisonment was not a priori assessed as non-response, but the defined primary outcome measures were calculated independent of the patient's state of residence. However, the high rate of imprisonment at T_{12} came as a surprise, since heroin addicts whose imprisonment could be expected were not to be included in the study.
If patients imprisoned at T_{12} are not considered for the primary analysis, response rates for the POM health change as follows: 80.2% in the heroin group compared to 73.4% in the methadone group (OR=1.47, 95%-KI: 1.09-2.00, p=0.013, n=955, no interaction between stratum and medication). Response rates thus hardly change compared to the primary analysis in accordance with the study protocol, there is only a slight increase of 0.8% between experimental and control group.
If all patients imprisoned at T_{12} were assessed as non-responders, the response rate would decline to 75.6% in the heroin group and 69.0% in the methadone group (OR=1.39, 95%-KI: 1.05-1.83, p=0.021, no interaction between stratum and medication). Except for lower response rates in both groups, the study results for the POM health are thus hardly influenced by the imprisonment issue.

7.4.2 Primary analysis – special evaluation of MTF patients with a previous daily dose of methadone lower than 60 mg

It has been shown that MTF patients with a methadone dose of less than 60 mg prior to the study (n=110) differ from other study participants of the MTF stratum only in few areas (cf. paragraph 7.2.1); the following is an analysis of the primary outcome measures limited to these low-dose patients. The 12-month retention rate of these patients in the heroin group is 78.2% and higher than that of other MTF patients (68.8%); in the methadone group, it is 26.8% and markedly lower that the retention rate of other MTF patients (41.6%).
Differences between the experimental and the control group are more pronounced in this subgroup. For the POM *health*, the response rate is 85.5% of n=55 in the heroin group compared to 69.1% of n=55 in the methadone group. With an odds ratio of 2.53 (95%-KI: 0.96-6.67, p=0.061), this group difference is not statistically significant, which is mainly due to the small sample size (low statistical power). For the POM *drug use*, the response rate is 80.0% in the heroin group and 56.4% in the methadone group. Similar to the primary analysis

of all patients, this difference with an odds ratio of 3.42 (95%-KI: 1.41-8.31, p=0.007) is statistically significant, despite the smaller sample size.
With respect to patients with a response for both primary outcome measures, there is also a marked difference between the experimental and control group among previously low-dosed patients: 69.1% response among heroin patients versus 43.6% among methadone patients (OR=2.93, 95%-KI: 1.30-6.59, p=0.009).[23]
These rather clear results of the primary analysis of the primary outcome measures concerning response rates and deviant retention rates in the subgroup of previously "underdosed" MTF patients allow the conclusion that the criterion of a minimum dose of 60 mg methadone in non-responders to maintenance treatment is not necessarily a precondition for the inclusion in heroin treatment. In patients with an unsatisfactory course of methadone treatment, the methadone dose is not necessarily increased, but treatment is continued with a low dose (in terms of harm reduction; the average duration of previous treatment of these patients was more than three years). It should also be considered that in some patients, the methadone dose was deliberately reduced prior to the study treatment, in order to avoid possible complications when switching to diacetylmorphine.

7.4.3 Secondary analyses

Out of the range of secondary analyses, the per-protocol analysis is presented, and the two kinds of psychosocial treatment are compared (with reference to the primary outcome measures). Moreover, POM results will be compared according to gender, and other (secondary) target criteria such as change of social situation or development of delinquency will be considered as well as potential withdrawal symptoms under study medication and direct effects of study medication. Finally, baseline situations of responders and non-responders will be compared.

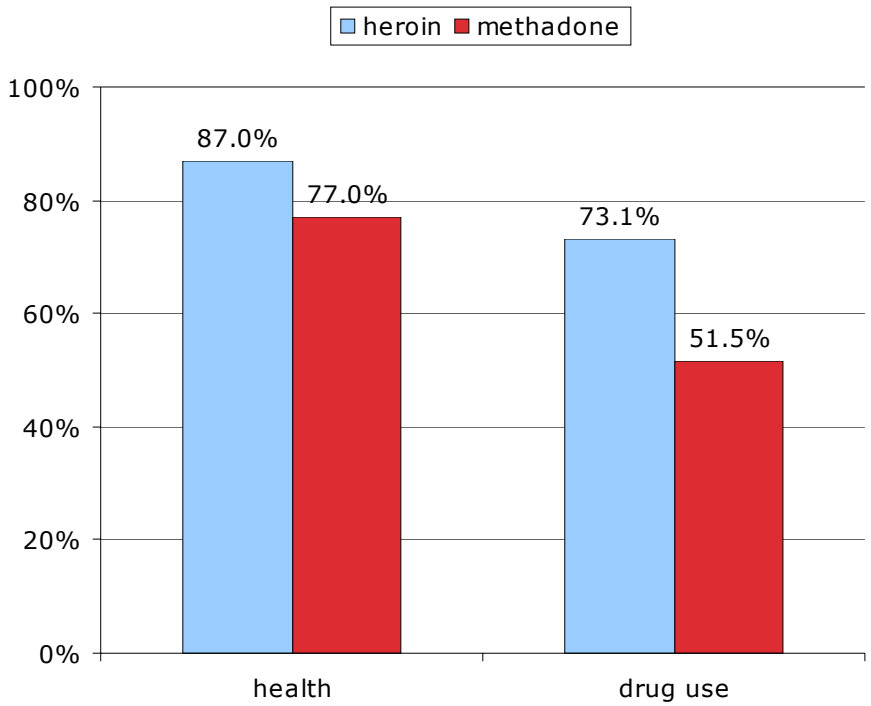
7.4.3.1 Per-protocol analysis and comparison of dropouts and concluders

As mentioned earlier, 546 patients – 346 of the heroin group and 200 of the methadone group – regularly concluded the first phase of study treatment. Although the analysis results of this sample are probably more closely related to treatment conditions than the results of the whole sample (among them dropouts who hardly benefited from the study treatment) there is no great difference compared to the ITT sample (cf. paragraph 7.4.1).
As expected, response rates of the PP sample are generally higher. For the POM *health*, 87.0% of the heroin patients and 77.0% of the methadone patients fulfil the response criterion (see figure 7.9). This difference of 10% is statistically significant with an odds ratio of 2.05 (95%-KI: 1.28-3.27, p=0.003). There is no interaction between stratum and study medication (interaction: OR=0.92, 95%-KI: 0.37-2.33, p=0.863).
For the target criterion *drug use*, the difference between experimental and control groups markedly increased compared to the ITT analysis: The response rate of the heroin group is

[23] MTF patients with a minimum of 60 mg (n=378): POM *health*: heroin patients: 77.6%, methadone patients: 72.0%; POM *drug use*: heroin patients: 69.3%, methadone patients: 58.1%. Both POM: heroin patients: 54.2%, methadone patients: 46.8%.

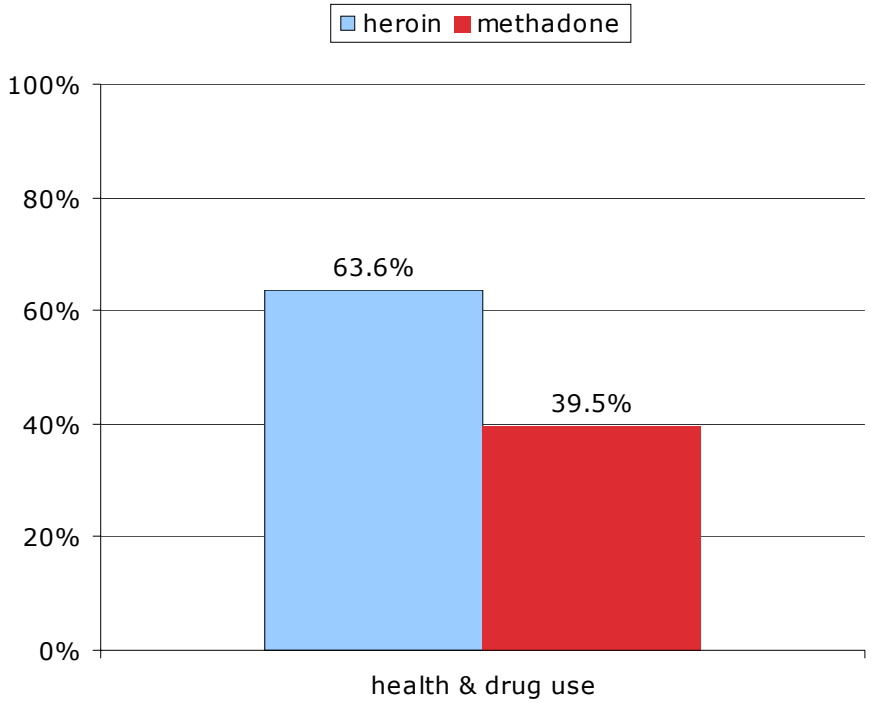
73.1% and thus more than 20% higher than that of the methadone group, where it is 51.5% (OR=2.64, 95%-KI: 1.80-3.88, p<0.001, see figure 7.9). Again, there is no interaction between stratum and medication (interaction: OR=0.66, 95%-KI: 0.31-1.41, p=0.283).

Figure 7.9
Effects of heroin vs. methadone treatment with respect to the target criteria health improvement und reduction of illicit drug use. Per-protocol analysis (n=546)



An evaluation of response rates concerning the *two primary outcome measures* will also be performed for the per-protocol sample. This analysis brings forth the greatest deviations compared to the ITT analysis; the response rates of experimental and control groups are distinctly different.
In the PP sample, 63.6% of the heroin patients, but only 39.5% of the methadone patients fulfil both target criteria (see figure 7.10). This difference of effects is statistically significant (OR=2.73, 95%-KI: 1.88-3.97, p<0.001). There is no interaction between stratum (MTF or NR) and medication (interaction: OR=0.86, 95%-KI: 0.41-1.78, p=0.677).

Figure 7.10
Effects of heroin vs. methadone treatment according to the response rates of patients, who fulfil both target criteria. Per-protocol analysis (n=546)



Apart from the expected fact that, in the PP analysis, response rates of both groups are in general higher than in the ITT analysis, the results of the primary analysis are confirmed by the analysis of the treatment sample in such a sense that heroin treatment proves to be clearly superior to methadone treatment for both primary outcome measures. Effect differences increase; continuous heroin treatment over 12 months sets off the positive effects compared to the effects of 12-month methadone maintenance treatment.

The individual criteria related to health and drug use highlight again the differences between regular concluders and dropouts in the per-protocol sample. Improvements related to health and use of street heroin are in general greater in concluders (see table 7.7). Differences between heroin ad methadone patients are, however, evident both in concluders and dropouts. Though the effects related to a decrease of cocaine use are comparable, dropouts used cocaine more heavily prior to the study. This indicates that a (too) high degree of cocaine use might be a negative predictor for a sufficiently long adherence to maintenance treatment.

Table 7.7
Changes of the state of health according to OTI health scale and GSI of the SCL-90-R and of the use of street heroin and cocaine between T_{-1} and T_{12}[a)]. Mean values and standard deviations (in brackets) of regular concluders (per-protocol sample) compared to dropouts.

Characteristic		Concluders (PP sample)		Dropouts		Total	
		Heroin	Methadone	Heroin	Methadone	Heroin	Methadone
OTI-HSS	T-1	18.5 (5.2)	18.7 (5.1)	19.2 (5.1)	19.4 (5.5)	18.7 (5.2)	19.1 (5.4)
	T12	7.4 (5.1)	9.9 (6.3)	9.9 (6.8)	11.1 (6.4)	8.2 (5.8)	10.6 (6.4)
GSI, SCL-90-R	T-1	1.13 (0.65)	1.17 (0.64)	1.13 (0.60)	1.22 (0.67)	1.13 (0.63)	1.20 (0.66)
	T12	0.63 (0.54)	0.74 (0.56)	0.81 (0.62)	0.87 (0.65)	0.68 (0.57)	0.82 (0.62)
Heroin, Number of days	T-1	22.9 (9.8)	23.0 (9.8)	22.0 (10.3)	21.9 (10.3)	22.6 (9.9)	22.3 (10.1)
	T12	1.0 (3.5)	6.5 (9.4)	5.9 (10.4)	8.3 (11.7)	2.5 (6.8)	7.5 (10.8)
Cocaine, Number of days	T-1	9.2 (10.7)	8.1 (10.1)	13.1 (11.3)	12.5 (12.0)	10.5 (11.1)	10.7 (11.5)
	T12	4.1 (7.4)	4.9 (8.1)	4.4 (7.6)	6.8 (10.3)	4.2 (7.5)	6.0 (9.4)
Cocaine, HA, µg/g, mean value	T-1	19.9 (37.7)	22.1 (68.7)	31.8 (55.8)	42.8 (110.8)	23.7 (44.5)	34.3 (96.3)
	T12	16.1 (45.5)	20.0 (74.6)	17.1 (34.5)	28.5 (66.5)	16.4 (42.9)	24.8 (70.2)
Cocaine, HA, µg/g, median	T-1	3.9	2.6	8.9	7.6	4.9	5.3
	T12	1.3	1.7	1.8	2.4	1.5	1.9

[a)] Missing data at T_{12} were completed, if possible, by information collected at the external interview. Heroin and methadone use is based upon data of the medical examinations; missing values are substituted from the external interview. The values at T_{-1} include the hair analyses performed at T_0. Missing HA data at T_{12} are completed by results at T_6.

Certain characteristics, which describe patients' initial status, are selected to explore the influence that the baseline situation of drug users might have on their treatment participation. Table 7.8 compares the social situation, health, user behaviour and treatment experience of concluders and dropouts.
When focusing on the characteristics marked in grey to highlight significant differences, only few areas hint to possible predictors for continued treatment participation. These are mainly a stable housing situation and a stable partnership, which are indicators of an overall more stable social initial situation in the experimental and the control group. The proportion of gainfully employed persons (in heroin and methadone group) also tends to be higher among concluders (but not significantly different). Health and user behaviours show no uniform tendency. Concluders seem to have had more health problems at baseline. However, similar initial OTI scores and SCL-90-R scores (cf. table 7.7) and in tendency lower HIV and HCV infection rates do not confirm this. As for addiction behaviour, dropouts currently use cocaine and did so for a long time, which corresponds to the higher amounts of money spent on drugs.
The expectation that concluders have more previous treatment experience is not confirmed. Dropouts had utilised an equal degree of detoxification, maintenance and drugfree treatment.
Apart from the more stable social situation prior to the study, no factors can be discerned that might have a positive effect on treatment adherence. The evaluation of possible predictors only refers to treatment delivered under the study conditions of the German model project and not to the participation in heroin or methadone treatment in general.

Table 7.8

Patient characteristics of concluders (n=546) and dropouts (n=469) at baseline (T_{-1}). Standard deviation is indicated in brackets. The values marked in grey indicate significant differences between concluders and dropouts.

Characteristic	Concluders (PP sample)			Dropouts		
	Heroin	Metha	Total	Heroin	Metha	Total
Gender, male proportion	80.9%	79.5%	**80.4%**	78.1%	80.0%	**79.3%**
Age, years	36.6 (6.6)	36.7 (6.9)	**36.6 (6.7)**	35.4 (6.7)	36.5 (6.7)	**36.1 (6.7)**
Social situation						
Stable housing situation	72.8%	72.5%	**72.7%**	61.3%	67.8%	**65.5%**
Stable partnership	36.7%	38.0%	**37.2%**	27.4%	28.4%	**28.1%**
Children	40.0%	33.5%	**37.6%**	37.5%	37.8%	**37.7%**
Employment last 30 days	15.4%	13.1%	**14.5%**	10.1%	11.7%	**11.1%**
Illegal activities (for profit) last 30 days	71.5%	71.8%	**71.6%**	76.7%	72.6%	**74.1%**
Health [a]						
Karnofsky index (0-100)	72.6 (12.6)	73.5 (13.0)	**73.0 (12.8)**	69.7 (12.8)	69.6 (13.0)	**69.6 (12.9)**
HIV positive	7.6%	8.1%	**7.8%**	10.7%	10.4%	**10.5%**
HCV positive	79.5%	79.8%	**79.6%**	82.7%	83.3%	**83.1%**
Skin abscesses	6.7%	6.6%	**6.7%**	4.8%	8.0%	**6.9%**
Echocardiography pathol. finding [b]	16.8%	16.5%	**16.7%**	15.4%	14.7%	**14.9%**
ECG pathol. finding [b]	21.7%	21.5%	**21.6%**	12.4%	15.3%	**14.3%**
Abdominal sonogr. pathol. finding [b]	57.5%	60.5%	**58.6%**	58.6%	47.7%	**51.6%**
Thorax x-ray pathol. finding [b]	2.9%	2.5%	**2.7%**	1.2%	1.0%	**1.1%**
GAFS (0-100)	54.2 (11.2)	53.4 (11.9)	**53.9 (11.5)**	52.9 (11.7)	53.4 (11.7)	**53.2 (11.7)**
Global clinical impression (CGI, 0-7)	4.5 (1.0)	4.6 (1.0)	**4.6 (1.0)**	4.6 (1.0)	4.6 (0.9)	**4.6 (1.0)**
Drug use [a]						
Start regular heroin use, age	20.3 (5.4)	20.2 (5.2)	**20.3 (5.3)**	19.4 (5.3)	20.4 (5.2)	**20.0 (5.3)**
Start regular cocaine use, age	22.7 (7.5)	23.2 (6.6)	**22.9 (7.2)**	21.8 (7.7)	22.6 (7.2)	**22.3 (7.4)**
Years regular heroin use	13.7 (6.2)	13.7 (6.6)	**13.7 (6.4)**	13.5 (6.5)	13.6 (6.2)	**13.5 (6.3)**
Years regular cocaine use	5.1 (6.5)	4.6 (5.8)	**4.9 (6.3)**	6.2 (7.0)	6.3 (6.5)	**6.3 (6.7)**
Heroin use last 30 days	96.0%	94.5%	**95.4%**	95.9%	96.3%	**96.2%**
Cocaine use last 30 days	72.0%	62.3%	**68.4%**	82.2%	75.3%	**77.8%**
Benzodiazepine use last 30 days	54.9%	59.3%	**56.5%**	60.1%	55.2%	**57.0%**
Alcohol use (harmful) last 30 days	16.5%	15.6%	**16.1%**	10.1%	9.4%	**9.6%**
Multiple use last 30 days	87.2%	93.9%	**89.6%**	87.1%	90.2%	**89.1%**
Intravenous use last 30 days	96.8%	94.4%	**95.9%**	96.4%	96.0%	**96.1%**
Drug overdose up to now	68.9%	68.7%	**68.8%**	76.2%	66.7%	**70.1%**
Money spent on drugs last 30 days, Euro	1,022 (1,208)	901 (1,081)	**978 (1,164)**	1,263 (2,053)	1,155 (1,626)	**1,194 (1,791)**
Money spent on alcohol last 30 d., Euro	29 (56)	35 (82)	**31 (66)**	31 (74)	27 (63)	**28 (67)**
Needle sharing	9.4%	8.2%	**8.9%**	13.9%	6.8%	**9.3%**
Sharing of injection equipment	17.5%	17.9%	**17.7%**	25.3%	19.3%	**21.4%**
Addiction treatment						
Outpatient detoxification up to now	34.8%	36.8%	**35.5%**	24.4%	33.1%	**30.0%**
Inpatient detoxification up to now	84.7%	88.9%	**86.3%**	85.7%	82.9%	**83.9%**
Maintenance treatment up to now	90.4%	87.9%	**89.5%**	84.6%	91.9%	**89.2%**
Psychosocial treatment up to now	48.8%	62.4%	**53.8%**	50.9%	49.7%	**50.1%**
Outpatient drugfree treatment up to now	12.3%	10.2%	**11.5%**	6.2%	13.6%	**10.9%**
Inpatient drugfree treatment up to now	56.8%	57.2%	**57.0%**	61.6%	56.7%	**58.5%**
Therapeutic flat sharing up to now	24.9%	24.9%	**24.9%**	25.9%	27.6%	**27.0%**
None of these treatments up to now	0.9%	2.0%	**1.3%**	3.6%	1.3%	**2.1%**

[a] The individual criteria already mentioned in table 7.7 as characteristics of the corresponding POM are not considered here.

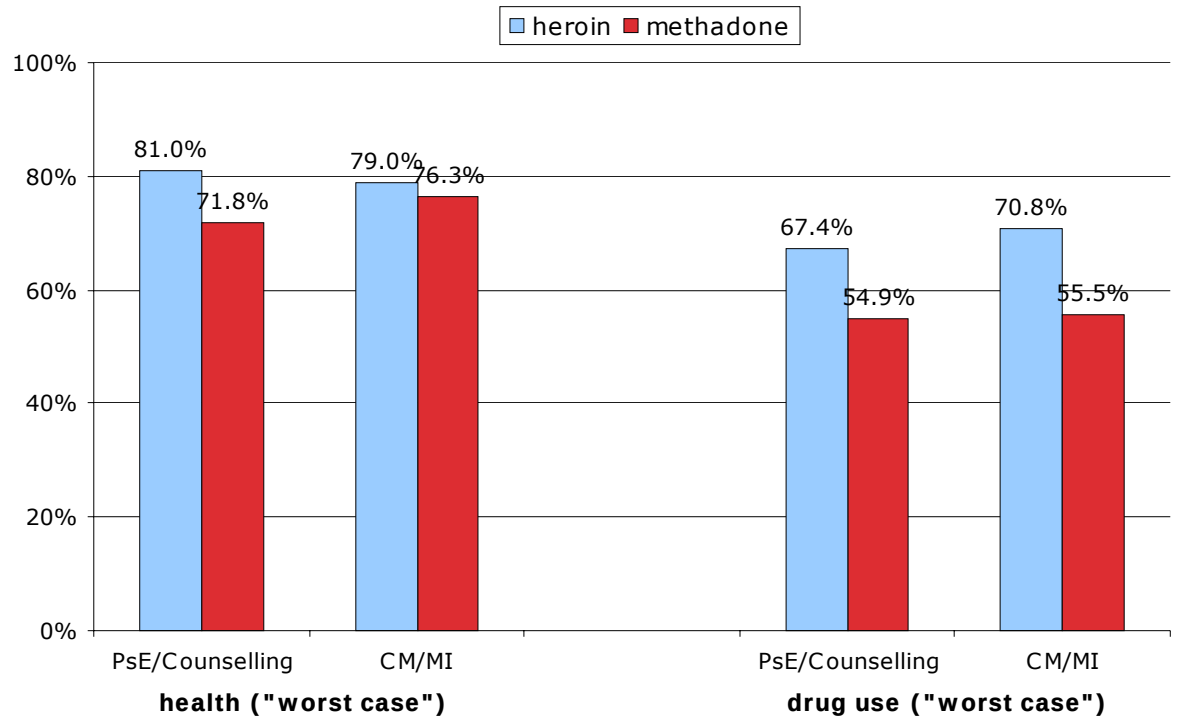
[b] Percentage related to all patients (examinations performed: echocardiography: n=890, ECG: n=940, sonography: n=935, x-ray: n=78).

7.4.3.2 Comparison of the two types of psychosocial treatment

The initial hypothesis concerning the two different types of psychosocial treatment – psychoeducative groups with drug counselling and case management with motivational interviewing – used in the German model project was that their influence on the primary study result would be low. In other words: No difference between heroin and methadone patients was expected regarding the response ratio of the two primary outcome measures. The multivariate primary analysis could not detect any influence by the type of PST (cf. paragraph 7.4.1). This becomes evident by the fact that the overall response rates (irrespective of experimental or control group) do not differ: For the POM *health*, the overall response rate among PsE patients is 76.4%, among CM patients 77.7%. Results are similar for the POM *drug use*: 61.2% of the PsE patients fulfil this target criterion compared to 63.3% of the CM patients.

Figure 7.11 presents the response rates for each group according to the kind of PST. For the TMC health, there seems to be a deviance, at first sight, in the response rates of PsE and CM patients to the effect that differences between the experimental and control group are less pronounced among CM patients. For the POM drug use, such differences are not found.

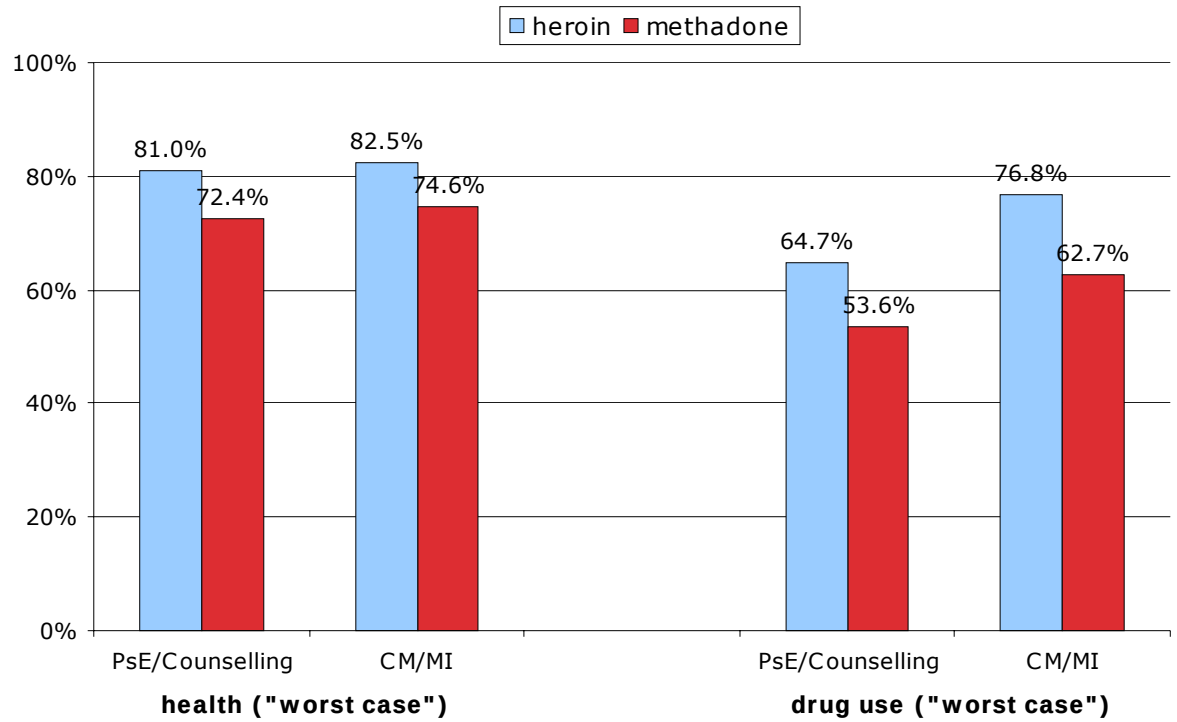
Figure 7.11
Effects of heroin vs. methadone treatment for the target criteria improvement of health and reduction of illicit drug use according to the kind of psychosocial treatment. ITT analysis (n=1,015)



Calculations of the Mantel-Haenszel statistics, show, however, significant differences in the response rates between heroin and methadone group across *both groups of PST* both for the POM health (Mantel-Haenszel-Chi^2=4.8, p=0.028) and for the POM drug use (Mantel-

Haenszel-Chi^2=20.3, p<0.001), that is, there are no deviances of homogeneity of the odds ratios. The *overall odds ratio* for the POM health (OR=1.40 (p=0.024)) hardly differs from the odds ratio of the primary analysis (cf. paragraph 7.4.1). This is also true for the POM drug use: The *overall odds ratio* (OR=1.82 (p<0.001)) corresponds to that of the primary analysis.
When comparing the two forms of psychosocial treatment, it must be considered that, for organisational reasons, not all study centres offered both PST types. The centres of Bonn and Karlsruhe only offered PsE/drug counselling, Cologne and Munich only case management/MI. Therefore, potential differences between PST groups could be masked by centre effects. This could be clarified by a comparison among patients of the larger study centres (Hamburg, Hanover and Frankfurt), where both kinds of PST were offered. Figure 7.12 shows that the response rates, that is the ratio of these rates in heroin and methadone patients, hardly differ between the kinds of PST. For the POM health (Mantel-Haenszel-Chi^2=6.5, p=0.011; overall OR=1.62, p=0.008) as well as for the POM drug use (Mantel-Haenszel-Chi^2=4.7, p=0.030; overall OR=1.42, p=0.025), there are significant differences between the response rates across both PST groups. The obvious differences for the criterion drug use are mainly due to the lower response rates in Hanover (see paragraph 7.4.1.2).

Figure 7.12
Response for target criteria health improvement and reduction of illicit drug use according to the kind of psychosocial treatment in the study centres (Hamburg, Hanover and Frankfurt), where both kinds of PST were offered. ITT analysis (n=711)



If the response rates, which are based on the fulfilment of *both* primary outcome measures (worst case), are compared with respect to the kind of PST, the results further converge. With response rates of 57.8% in the heroin group and 44.3% in the methadone group under the

conditions of PsE/drug counselling and of 56.8% among heroin patients and 45.3% among methadone patients under the conditions of case management/MI, there is no significant difference of effect between the two forms of psychosocial treatment (Mantel-Haenszel-Chi^2=15.3, p<0.001). The overall odds ratio is 1.65 (p<0.001) and corresponds to that of the primary analysis (cf. paragraph 7.4.1).

7.4.3.3 Gender differences for the primary outcome measures

Does heroin treatment (compared to methadone maintenance) act differently for men and women? The answer to this question must take into account that the proportion of women in the model project is not very high with only 20.1% and the overall result is therefore mainly based upon the results of the male participants.[24]

Response rates (worst case) of the two primary outcome measures show that differences between experimental and control group are greater among men than among women. For the POM *health*, the overall response rate of men is 77.5%: 81.1% among heroin patients and 73.9% among methadone patients. Among female patients, the overall response rate is 75.0%. There are only slight differences between the heroin (75.7%) and the methadone group (74.3%). However, the Mantel-Haenszel test shows that, despite this obvious difference, the significant difference persists across the genders (Mantel-Haenszel-Chi^2=4.8, p=0.028; overall OR=1.41, p=0.024).

For the POM *drug use*, the response rate of men is 64.5% and of women 53.4%. Thus, improvement of user behaviour tends to be greater among men than among women under study medication. A comparison between the groups shows that this is mainly due to the effects of heroin treatment: Male heroin patients have response rate of 72.8%, methadone patients of 55.9%. In women, the difference between the response rates of heroin patients (54.4%) and methadone patients (52.5%) is only slight. The Mantel-Haenszel test shows again that the significant difference between the experimental and control group persists, taking into account the gender distribution (Mantel-Haenszel-Chi^2=21.1, p<0.001; overall OR=1.82, p<0.001). However, the Breslow-Day statistics (Chi^2=4.5, p<0.034) indicates significant deviances from the homogeneity of the odds ratio (between genders), and the difference between heroin and methadone group for the POM drug use is mainly based upon the results (positive in terms of the initial hypothesis) of the male study participants.

7.4.3.4 Analysis of secondary target criteria

Other changes under study medication are considered hereafter. In addition to the secondary target criteria described in the study protocol (Krausz et al. 2001), the treatment groups are compared with respect to the *ASI-Composite Scores*. The Composite Scores (CS) explore the extent of problems in the areas of life recorded by the EuropASI on a scale from 0-1; higher scores correspond to higher strains, i.e. greater need of treatment (McGahan 1986, Gsellhofer et al. 1999). The changes between baseline (T_{-1}) and T_{12} are presented for each treatment group; the strata MTF and NR are combined because of their similarities (cf. paragraph 7.2).

[24] This report treats gender differences only marginally. They will be treated in separate analyses and will be – in an extensive form – part of the 2-year final report.

All composite scores indicate an improvement of patients' life situation. Table 7.9 shows that, in general, this positive change occurs in both treatment groups. The covariance analysis at T_{12} indicates significant differences in the areas alcohol (ALC) and drug use (DRU2), legal situation (LEG) as well as family (FAM) and social relations (OTH), indicating that heroin patients benefit more from study treatment than methadone patients. The physical and mental conditions recorded by the medical investigators' examinations (mainly OTI-HSS and SCL-90-R) are not confirmed by the composite scores. The physical (MED) and mental (PSY) state of heroin patients markedly improved, but the differences to methadone patients at T_{12} are not statistically significant.

Table 7.9
ASI Composite Scores at T_{-1} and T_{12} according to treatment groups. Mean values and covariance analysis under consideration of the baseline value

ASI-CS[a)]		**Heroin**	**Methadone**	**Total**	**Significance ANCOVA at T12**
MED	T-1	0.42 (0.33)	0.42 (0.35)	0.42 (0.34)	F=2.1, df=1, p=0.143
	T12	0.33 (0.33)	0.36 (0.34)	0.34 (0.33)	
ECON	T-1	0.91 (0.24)	0.93 (0.21)	0.92 (0.23)	F=0.1, df=1, p=0.814
	T12	0.85 (0.30)	0.86 (0.29)	0.85 (0.30)	
SAT	T-1	0.39 (0.34)	0.35 (0.34)	0.37 (0.34)	F=0.1, df=1, p=0.755
	T12	0.16 (0.28)	0.16 (0.26)	0.16 (0.27)	
ALC	T-1	0.12 (0.18)	0.12 (0.19)	0.12 (0.19)	F=12.0, df=1, p=0.001
	T12	0.10 (0.18)	0.13 (0.21)	0.11 (0.19)	
DRU2	T-1	0.52 (0.14)	0.53 (0.13)	0.53 (0.14)	F=100.0, df=1, p<0.001
	T12	0.21 (0.17)	0.33 (0.18)	0.27 (0.19)	
LEG	T-1	0.42 (0.27)	0.40 (0.27)	0.41 (0.27)	F=42.7, df=1, p<0.001
	T12	0.18 (0.23)	0.28 (0.26)	0.23 (0.25)	
FAM	T-1	0.27 (0.21)	0.27 (0.20)	0.27 (0.20)	F=5.6, df=1, p=0.018
	T12	0.09 (0.16)	0.11 (0.17)	0.10 (0.16)	
OTH	T-1	0.26 (0.22)	0.28 (0.22)	0.27 (0.22)	F=4.4, df=1, p=0.036
	T12	0.10 (0.16)	0.12 (0.17)	0.11 (0.17)	
PSY	T-1	0.24 (0.21)	0.24 (0.22)	0.24 (0.22)	F=2.2, df=1, p=0.139
	T12	0.18 (0.21)	0.21 (0.22)	0.19 (0.21)	

[a)] EuropASI Composite Scores: MED(ical): physical health, ECON(nomic situation), SAT(isfaction): employment and upkeep situation, ALC(ohol): alcohol use, DRU(g)2: drug use (modified according to EuropASI), LEG(al): legal situation, FAM(ily), OTH(er): family and social relations, PSY(chiatric): mental health.

The different degrees of improvement expressed by the composite drug use score is probably mainly due to the greater decline of street heroin use in the experimental group. Cocaine use has also been shown to decline in both treatment groups, and for heroin patients, self-reports on the 30-day prevalence shows a significant decrease of cocaine use at T_{12} (cf. table 7.4). The composite scores also prove a decrease of alcohol use, again more marked among heroin patients. Alcohol use will be considered more closely, considering the amount taken in the

last 30 days in terms of consumption units. This will be followed by a description of changes that occurred in the consumption behaviour of other substances such as benzodiazepines, amphetamines, cannabis or hallucinogens.

The intensity of *alcohol use* also decreases during study treatment (see table 7.10). In general, the amount of drinking decreases more in heroin patients than in methadone patients. The average daily alcohol consumption (related to the last 30 days) among heroin patients declines from 6.6 to 4.1 consumption units; among methadone patients, the decrease is significantly lower, from 7.3 to 5.6.

Table 7.10
Drinking amount in consumption units (CU) at T_{-1} and T_{12} according to the treatment group. Mean values and covariance analysis under consideration of the baseline value

Units of consumption[a)]		**Heroin**	**Methadone**	**Total**	**Significance ANCOVA at T12**
Beer	T-1	4.5 (7.9)	4.4 (8.2)	4.5 (8.0)	F=2.0, df=1, p=0.159
	T12	3.1 (7.2)	3.7 (7.7)	3.4 (7.4)	
Wine	T-1	0.5 (2.5)	0.8 (3.8)	0.6 (3.2)	F=4.1, df=1, p=0.042
	T12	0.3 (2.0)	0.5 (3.0)	0.4 (2.5)	
Spirits	T-1	1.7 (6.5)	2.3 (9.2)	2.0 (7.9)	F=3.1, df=1, p=0.078
	T12	0.7 (4.9)	1.4 (6.6)	1.1 (5.8)	
Total	T-1	6.6 (12.0)	7.3 (14.0)	7.0 (13.0)	F=6.1, df=1, p=0.014
	T12	4.1 (9.6)	5.6 (11.4)	4.8 (10.5)	

[a)] Consumption unit beer: 0.5 l beer = 2.5 CU, 1 l beer = 5 CU.
Consumption unit wine: 0.2 l glass of wine = 2.5 CU, 0.7 l bottle of wine = 9 CU.
Consumption unit spirits: 0.02 l liquor or the like = 1 CU, double (0.04 l) = 2 CU, bottle (0.7 l) = 35 CU.

Focusing on the patients, who, according to self-reports, continue *using drugs*, a decrease is found in particular for street heroin and crack/cocaine as well as for benzodiazepines and cannabis. At T_{12}, the percentage of street heroin users of the control group is 54.5% and twice as high as in the experimental group (see table 7.11). At T_{12}, the proportion of heroin and methadone patients using cocaine is similar, but there is a significant difference concerning the frequency of use. Benzodiazepine use decreased in both treatment groups, but, with an average of 7 consumption days at T_{12}, these drugs (partly prescribed) play a rather important part.[25] The intensity of cannabis use does not change between baseline and the T_{12} examination, but a lower number of patients use cannabis. Amphetamine and hallucinogens played only a minor part prior to the study treatment and this did not change.

[25] Diazepam was prescribed to 80 heroin patients (15.5% of 515) and 72 methadone patients (14.4% of 500) at least once during the study treatment.

Table 7.11
Drug use in the last 30 days at T_{-1} and T_{12} according to the treatment group. Percentages and mean values (related to all patients), Chi^2 test and covariance analysis at T_{12} with consideration of the baseline value. Data from the external interview

Substance			**Heroin**	**Methadone**	**Total**	**Significance at T12**
Street heroin	Percentage	T-1	95.9%	95.6%	95.8%	Chi^2=71.3, df=1, p<0.001
		T12	27.1%	54.5%	40.4%	
	Number of days	T-1	21.5 (10.7)	21.2 (10.8)	21.3 (10.7)	F=72.7, df=1, p<0.001
		T12	2.2 (6.4)	7.0 (10.5)	4.5 (9.0)	
Cocaine/crack	Percentage	T-1	75.3%	70.1%	72.8%	Chi^2=0.0, df=1, p=0.866
		T12	51.7%	52.3%	52.0%	
	Number of days	T-1	11.1 (11.6)	10.7 (11.8)	10.9 (11.7)	F=4.6, df=1, p=0.033
		T12	4.5 (8.4)	5.5 (9.0)	5.0 (8.7)	
Benzodiazepines	Percentage	T-1	56.6%	56.8%	56.7%	Chi^2=0.3, df=1, p=0.596
		T12	41.7%	43.5%	42.6%	
	Number of days	T-1	9.2 (11.8)	9.4 (12.0)	9.3 (11.9)	F=0.3, df=1, p=0.854
		T12	7.0 (11.6)	6.9 (11.3)	7.0 (11.4)	
Amphetamines	Percentage	T-1	3.3%	5.7%	4.5%	Chi^2=0.1, df=1, p=0.715
		T12	4.9%	5.4%	5.1%	
	Number of days	T-1	0.1 (1.6)	0.3 (2.4)	0.2 (2.0)	F=0.5, df=1, p=0.461
		T12	0.2 (1.7)	0.2 (1.7)	0.2 (1.7)	
Cannabis	Percentage	T-1	59.0%	67.0%	63.0%	Chi^2=3.6, df=1, p=0.059
		T12	53.2%	59.4%	56.2%	
	Number of days	T-1	8.5 (11.3)	10.2 (12.1)	9.3 (11.7)	F=1.3, df=1, p=0.247
		T12	7.8 (11.3)	9.7 (12.2)	8.7 (11.8)	
Hallucinogens	Percentage	T-1	1.4%	1.2%	1.3%	Chi^2=0.3, df=1, p=0.585
		T12	1.3%	0.9%	1.1%	
	Number of days	T-1	0.2 (1.9)	0.1 (1.9)	0.1 (1.9)	F=0.0, df=1, p=0.840
		T12	0.0 (0.2)	0.0 (0.3)	0.0 (0.2)	

In addition to patients' self-reports regarding drug use within the last 30 days, the results of urinalyses at T_{-1}, T_6 and T_{12} are represented. They confirm the decrease of street heroin and cocaine use, more marked in the heroin groups (see table 7.12). But the cocaine related difference at T_{12} is not statistically significant. Based on the urinalyses, the decrease of benzodiazepines among heroin patients is slightly higher compared to methadone patients than based on the self-reports for the 30-day prevalence. Another finding concerns cannabis: The widespread assumption (also among GPs) that virtually all opioid addicts use cannabis more or less regularly seems to be refuted by the results of the urinalyses. In particular against the background that cannabis is traceable for a long time, it can be taken as certain that "only" about half of the study patients use cannabis frequently.

Table 7.12
Results of urinalyses at T_{-1}, T_6 and T_{12}[a)]

Substance		Heroin	Methadone	Total	Significance at T12
Street heroin	T-1 (n=972)	74.3%	73.8%	74.1%	Chi^2=34.6, df=1, p<0.001
	T6 (n=626)	16.0%	34.1%	23.3%	
	T12 (n=755)	14.9%	33.0%	23.0%	
Cocaine	T-1 (n=984)	56.1%	55.5%	55.8%	Chi^2=2.6, df=1, p=0.104
	T6 (n=607)	36.5%	40.4%	37.9%	
	T12 (n=806)	32.7%	38.2%	35.2%	
Benzodiazepi-nes	T-1 (n=984)	62.9%	61.6%	62.3%	Chi^2=3.8, df=1, p=0.051
	T6 (n=605)	50.3%	61.0%	54.2%	
	T12 (n=806)	43.1%	50.0%	46.3%	
Amphetamines	T-1 (n=984)	0.8%	1.9%	1.3%	Chi^2=0.0, df=1, p=0.895
	T6 (n=605)	0.8%	1.8%	1.2%	
	T12 (n=807)	2.0%	2.2%	2.1%	
Cannabis	T-1 (n=984)	54.7%	54.4%	50.0%	Chi^2=2.8, df=1, p=0.095
	T6 (n=605)	49.9%	55.0%	51.7%	
	T12 (n=805)	46.0%	51.9%	48.7%	

a) T_6: US for week 26, T_{12}: US for week 52.

Closely linked to illicit drug use is the issue of *risk behaviour* concerning the sharing of needles/syringes or injection equipment such as tins, spoons, filters and the like. In this respect, marked improvements occurred in both groups. 10.8% of the heroin patients and 7.3% of the methadone patients had shared needles "sometimes" or "often" in the last 6 months prior to the treatment. In the 6 months prior to the T_{12} examination, this still occurred in 2.3% of the heroin patients and 2.2% of the methadone patients.[26] The development is similar for the injection equipment: At baseline, 20.1% of the experimental group and 18.7% of the control group occasionally shared injection equipment with other drug users. One year later, the proportion had decreased to 3.6% in the heroin group and 3.3% in the methadone group.

Another objective of heroin treatment is the *separation from the context of the drug scene*. On the one hand, it is obvious that the treatment context permanently brings together people with severe addiction and addiction-related problems and that the process of separation can be disturbed by (less successful) treatment mates. On the other hand, scene contacts are often unavoidable depending on the location of the treatment unit and the continuity of contacts to drug counsellors. Nonetheless, the separation from old scene contacts, made superfluous because there is no necessity to use illicit heroin, remains a main concern for all types of maintenance treatment.

[26] As questions related to the utilisation of syringes and injection equipment were not answered by all the patients (rather more by those who continued i.v. use), percentages are related to all n=924 patients, who participated in an external interview at T_{12}. At T_{-1}; the data are based on n=999 patients.

While more than 90% of the drug users visited the drug scene more or less regularly prior to the study treatment (at T_{-1}) – on average (related to all patients) on 19 days within the last month – this proportion had drastically decreased at T_{12} (see table 7.13). Half of the heroin patients versus 60% of the methadone patients still visit the drug scene after one year. Heroin patients (again related to all patients) are on the drug scene on 6 days on average, methadone patients on almost 9 days. Thus, the separation from the context of the drug scene was more successful in heroin patients than in methadone patients. It is explained by the reasons that patients give for visiting the drug scene. As expected, the first reason is heroin patients' reduced need to procure drugs. Money procuring for drugs as well as the necessity to offer "services" (in drug dealing or other activities) is, for heroin patients, less often a reason to visit the scene than for methadone patients. It is conspicuous that still 43% of the patients of both treatment groups state that they visit the scene out of boredom. The problem of increasing loneliness (Uchtenhagen et al. 1997) and the phenomenon of "redoubled" marginalisation with respect to old scene contacts as well as societal integration processes (Raschke 1994) might play a role, mainly in older drugs addicts. The establishment of new drugfree contacts and the integration into non-drug related contexts proves to be a difficult task for many of the addicts, who have been dependent for many years (some of them more than 20 years).

This corresponds to the fact that at $T_{12,}$ still one third of the study participants (heroin: 30.9%, methadone: 32.9%) spend most of their leisure time with relatives or friends or acquaintances, who have drug or alcohol problems themselves. Compared to the time prior to the treatment (heroin patients: 40.2%, methadone patients: 38.8%), this is a slight improvement but underlines the problems of re-orientation in a drugfree context.

Table 7.13
Scene visits within the last 30 days and reasons for the visits at T_{-1} and T_{12} according to treatment groups

Characteristic		Heroin	Methadone	Total	Significance at T12
Scene visits, proportion	T-1	90.6%	90.3%	90.5%	Chi^2: χ=9.1, df=1, p=0.003
	T12	49.6%	59.5%	54.4%	
Scene visits, duration in days	T-1	19.0 (12.1)	19.1 (11.8)	19.1 (12.0)	ANCOVA: F=14.1, df=1, p<0.001
	T12	6.0 (9.8)	8.6 (11.9)	7.2 (10.9)	
Reason: procuring drugs	T-1	84.3%	82.9%	83.7%	Chi^2: χ=7.4, df=1, p=0.007
	T12	55.9%	67.4%	61.9%	
Reason: using drugs	T-1	60.0%	62.9%	61.4%	Chi^2: χ=0.1, df=1, p=0.709
	T12	37.5%	39.1%	38.4%	
Reason: meeting people	T-1	59.0%	62.3%	60.6%	Chi^2: χ=0.3, df=1, p=0.555
	T12	56.5%	59.1%	57.8%	
Reason: procuring money	T-1	55.1%	55.5%	55.3%	Chi^2: χ=6.2, df=1, p=0.013
	T12	23.3%	33.1%	28.4%	
Reason: boredom	T-1	46.9%	48.5%	47.7%	Chi^2: χ=0.0, df=1, p=0.921
	T12	42.7%	43.1%	42.9%	
Reason: offering services	T-1	30.1%	35.6%	32.8%	Chi^2: χ=8.0, df=1, p=0.005
	T12	11.9%	21.0%	16.6%	
Rn.: establishing new contacts	T-1	25.2%	29.3%	27.2%	Chi^2: χ=3.0, df=1, p=0.082
	T12	15.8%	21.7%	18.9%	
Reason: prostitution	T-1	4.4%	3.5%	3.9%	Chi^2: χ=0.2, df=1, p=0.669
	T12	4.0%	3.3%	3.6%	
Reason: finding lodgings	T-1	7.9%	8.4%	8.1%	Chi^2: χ=1.7, df=1, p=0.187
	T12	4.0%	6.5%	5.3%	

This raises the question (parallel to the separation from the drug context) whether patients were at all able to establish new social contacts and to reorganise their leisure time under study treatment. No less than 41.7% of the study participants (heroin: 41.2%, methadone: 42.2%) succeeded in meeting new friends and acquaintances during the 12-month study phase. But since many patients still spend their spare time with drug users (see above), it must be assumed that many of the new acquaintances are also from the so-called drug milieu or are acquaintances of other patients.
The number of hobbies and leisure occupations slightly increased during treatment. Slightly more than two thirds of the patients (67.9%, heroin: 69.2%, methadone: 66.6%) report leisure activities at T_{12}, compared to 58.6% prior to the treatment (heroin: 59.5%, methadone: 57.6%). Typical leisure activities are playing music, listening to music, computer, bicycling, sports such as swimming, table tennis, jogging or football, reading and painting or drawing.

No great changes of the *social situation* can be expected within 12 months; developments of the housing, work and income situation of the study participants will be described hereafter. If the categories “own apartment”, “partner’s apartment”, “with parents/relatives” and „flat

sharing/room“ are combined to “stable” housing situation, almost three quarters of the heroin patients (72.2%) versus 67.6% of the methadone patients live in stable housing conditions at T_{12} (Chi^2=2.3, df=1, p=0.129). At the beginning of treatment, this was the case in 69.0% of the heroin patients and 69.7% of the methadone patients. One year after the treatment initiation (T_{12}), 47.3% of the heroin patients and 43.0% of the methadone patients are satisfied with their housing situation. The low degree of satisfaction in methadone patients might be due to the fact that 33.7% of them still share their lodgings with a drug user (prior to treatment: 35.7%). In heroin patients, this is true for only 28.7% (compared to 32.1% prior to treatment).
Prior to the treatment, 33.0% of the study patients (heroin: 33.7%, methadone: 32.3%) lived in a stable partnership. This proportion slightly increased to 35.0% after one year; there were no relevant differences between heroin patients (35.8%) and methadone patients (34.2%). Satisfaction with the partnership had increased: At baseline, the proportion was 37.4% (heroin: 37.5%, methadone: 37.3%), at T_{12}, it was 48.3% (heroin: 48.2%, methadone: 48.4%).
At baseline, 39.2% of the heroin patients and 36.1% of the methadone patients had own children. At that time, i.e. prior to treatment, only 14.8% of the parents in the heroin group and 14.3% in the methadone group lived with their children. In most cases, children lived with the other parent (48.5%), with adoptive or foster parents (12.9%) or with grandparents or other relatives (10.5%). This situation hardly changed during study treatment: The proportion of patients with children (heroin: 40.6%, methadone: 35.9%) as well as the residence of the children nearly remained constant at T_{12}. After one year, 11.5% of the parents participating in the study lived with their children (heroin: 13.7%, methadone: 8.9%). The children of the majority of parents (51.4%) still lived with the other parent, children of 10.9% lived with adoptive or foster parents, of 10.6% with grandparents or other relatives.[27]

The overall difficult labour market situation is even a greater challenge for long-term drug addicts, who try to find a way back to regular employment. Prior to the study, only 13.0% (within the last 30 days) are *employed* (heroin: 13.6%, methadone: 12.3%), the majority of patients are unemployed. The development is positive during study treatment: One fourth of the patients (25.3%) have a steady job after one year. This positive effect occurs both in heroin and methadone patients (heroin: 26.0%, methadone: 24.6%). Accordingly, employment as main income source increased from 4.4% (heroin: 5.1%, methadone: 3.8%) prior to treatment to 10.6% (heroin: 11.4%, methadone: 9.8%) after 12 months (see table 7.14). The number of patients living on welfare also markedly increased. Almost half of the patients state that it is their main source of income. This effect of an increase of social welfare payments, already observed in the Swiss study, is due to the fact that illicit sources of income are drastically reduced under study treatment and new, legal income sources were found. After 12 months, the increase of patients drawing unemployment benefits is slight, but as many as one fifth state that this is their main income source. Apart from a decrease of dealing

[27] At T_{-1}, there are rather more female than male patients with children with overall 45.3% (T_{12}: 45.4%) (male: 35.7%, T_{12}: 36.6%). Accordingly, women are more affected by problems related to the accommodation and care for children. At T_{12}, 21.0% of the women live with their children compared to 11.6% of the men.

and illicit "business activities", more marked in the heroin group, there are no other relevant differences of the income situation between the experimental and control group.

Table 7.14
Main income source at T_{-1} and T_{12} according to the treatment group

Characteristic		**Heroin**	**Methadone**	**Total**
Employment	T-1	5.1%	3.8%	4.4%
	T12	11.4%	9.8%	10.6%
Unemployment benefit	T-1	19.1%	17.6%	18.4%
	T12	21.9%	19.6%	20.8%
Welfare	T-1	32.3%	32.1%	32.2%
	T12	50.8%	46.7%	48.8%
Pension, sickness benefit	T-1	5.1%	6.2%	5.6%
	T12	5.9%	5.1%	5.5%
Partner, relatives, friends	T-1	3.7%	4.2%	3.9%
	T12	2.3%	2.2%	2.3%
Dealing	T-1	14.8%	16.2%	15.5%
	T12	2.5%	6.0%	4.2%
Other illicit income	T-1	7.4%	7.4%	7.4%
	T12	0.6%	2.0%	1.3%
Prostitution, pimping	T-1	4.9%	4.8%	4.8%
	T12	1.1%	2.9%	2.0%
Loan, savings	T-1	1.2%	1.6%	1.4%
	T12	0.2%	0.7%	0.4%
Begging	T-1	3.1%	3.0%	3.1%
	T12	0.6%	0.7%	0.7%
Other	T-1	3.5%	3.0%	3.3%
	T12	2.5%	4.2%	3.4%

The results of the ASI Composite Score with respect to the *legal situation* (see above) already indicated that delinquent behaviour and the judicial situation markedly improved under study treatment. There are marked differences between the study groups; legal behaviour of heroin patients developed more positively than that of methadone patients. A detailed description of the development related to delinquency in the course of the study and the biographic backgrounds and potential causal relationships are the objective of the criminological special studies. Therefore, patients' law-related behaviour will only be outlined here, based on the variables of the EuropASI.

Almost all patients have been convicted at least once. During study treatment, related to the last 12 months prior to T_{12}, it still occurred in 57.5% of the study participants (see table 7.15), with a marked difference between heroin and methadone patients (Chi^2=20.4, df=1, p<0.001). Also with respect to imprisonments during treatment, the results are in favour of the heroin group. The percentage of heroin patients with imprisonments is, with 13.8%, significantly lower than in the methadone group with 23.6% (Chi^2=12.2, df=1, p<0.001). Involvement in

illegal activities (for profit) or "illicit transactions" also clearly declined. Related to the last 30 days prior to the respective examination, the proportion of patients with illegal activities decreased in the heroin group from 73.3% to one third at T_6 and only 27.4% at T_{12} (see table 7.15). In the methadone group, the decline is less marked. In both follow-up examinations, the differences between experimental and control groups are statistically significant (T_6: Chi^2=19.6, df=1, p<0.001; T_{12}: Chi^2=16.8, df=1, p<0.001).

Table 7.15
Convictions and imprisonments at T_{-1} (lifetime) und T_{12} (within the last 12 months) and illicit activities according to the groups

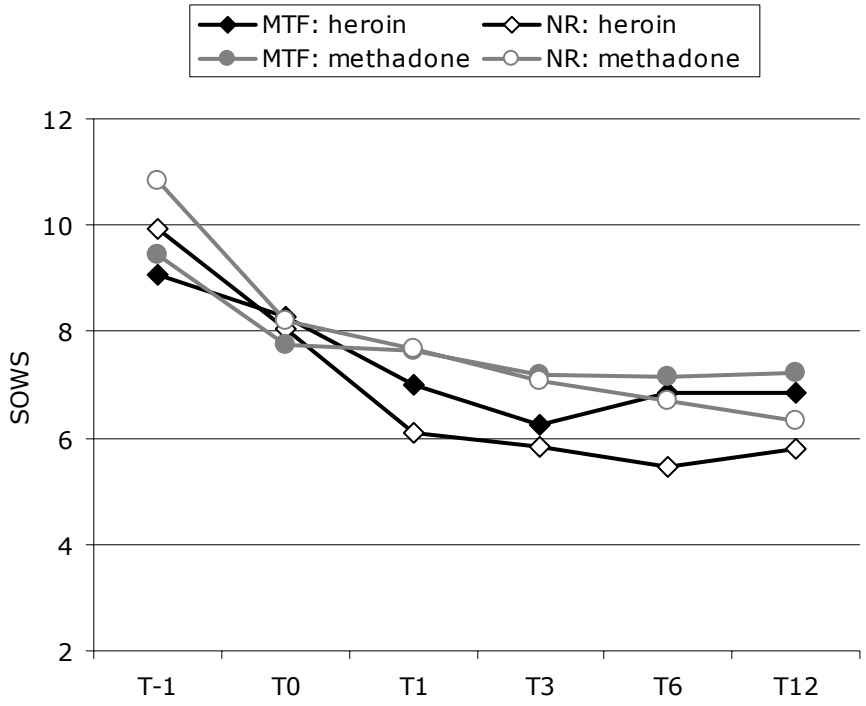
		Heroin	**Methadone**	**Total**
Convictions	T-1: lifetime	96.8%	95.7%	96.3%
	T12: last 12 months	49.7%	65.9%	57.5%
Custody or imprisonment	T-1: lifetime	73.9%	75.1%	74.5%
	T12: last 12 months	13.8%	23.6%	18.3%
Involvement in illegal last 30 days	T-1	73.3%	72.3%	73.8%
	T6	32.3%	48.3%	39.3%
	T12	27.4%	40.2%	33.6%

To conclude, it should be mentioned that *quality of life* also improved under study treatment, in heroin patients clearly more than in methadone patients. While the average LQ sum score (following Pukrop et al. 1999) was 3.28 points at treatment initiation (heroin: 3.34, methadone: 3.22), it improved to 4.05 points in the heroin group and 3.89 points in the methadone group. This difference, cleared by the baseline value at T_{-1}, is statistically significant (ANCOVA: F=4.5, df=1, p=0.035).

7.4.3.5 Withdrawal symptoms and direct effects of the study medication

At each examination, the medical investigators recorded the direct effects of the study medication and opioid related withdrawal symptoms using the SOWS (Gossop 1990). The course of withdrawal symptoms is presented in figure 7.13. Because MTF patients have been treated with methadone immediately before the study treatment, it is reasonable to represent the course of symptoms separated according to stratum. It can be seen that withdrawal symptoms decline under treatment in all the patient groups. If baseline values are included, the decline of symptoms is more marked in the NR stratum, the NR heroin group has the lowest degree of withdrawal symptoms. The effect of symptom decrease prior to treatment inititation (T_0), already observed for physical symptoms (according to OTI-HSS) is evident here, too. Withdrawal symptoms already clearly decline in the phase of preparations and indication examinations at T_{-1}, also under the influence of transitional treatment. Heroin patients tend to have less withdrawal symptoms than methadone patients.

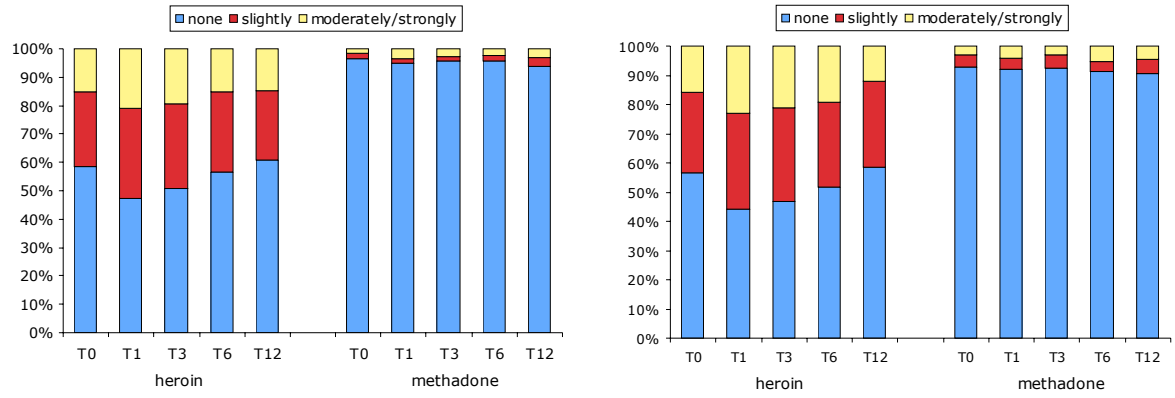
Figure 7.13
Change of withdrawal symptoms (SOWS) according to group and stratum



When contemplating the direct (so-called euphoric) effects of the study medication such as the rapid „kick“ or the longer lasting euphoria, the expected differences between heroin and methadone are apparent. The feeling of a “kick” caused by the rapid flooding of heroin is reported by 41.3% of the heroin patients compared to only 3.5% of the methadone patients at the beginning of treatment (see figure 7.14). It can also be seen that this direct effect of heroin – after a temporary increase at T_1 – decreases in the course of treatment (T_{12}: 39.2%). The average duration of the heroin kick is 5-6 minutes at all times of examination. Methadone patients report a duration between 8 and 30 minutes; however, only 10 to 26 patients made any statements.

Statements related to the feeling of euphoria are almost identical. The course is similar in heroin patients: After initially 43.4% at T_{-1}, there is an increase after one month (55.8%), followed by a decrease to 41.4% in the further course. 7.4% to 9.3% of the methadone patients report a feeling of euphoria (slightly increasing in the course). Regarding the duration of euphoria, there are marked differences between the study groups: While the duration is 46 to 54 minutes in heroin patients, methadone patients (again only few of them) report effects between 80 and 160 minutes. In both patient groups, a tendency regarding the duration of euphoria cannot be recognised in the course of treatment.

Figure 7.14
Euphoric effects: „kick/flash“ immediately after taking the study medication (left-hand) and feelings of euphoria (right-hand) in the course according to the study group



7.4.3.6 Comparison between responders and non-responders

In order to obtain possible predictors of treatment success, responders and non-responders are compared with respect to selected variables. For the sake of clarity, this is based on patients with a response (according to worst case) in *both* primary outcome measures. A comparative representation for each POM would be too confused and would contain overlap effects preventing clear conclusions. Therefore, the comparison includes n=519 (corresponding to 51.1%) responders (heroin: n=295, 57.3%, methadone: n=224, 44.8%) and n=496 (corresponding to 48.9%) non-responders (heroin: n=220, 42.7%, methadone: n=276, 55.2%).
The rate of concluders, i.e. the proportion of patients, who regularly concluded the first study phase, is higher in responders, with 57.6% (heroin: 74.6%, methadone: 35.3%), than in non-responders, with 49.8% (heroin: 57.3%, methadone: 43.8%) (comparison responders vs. non-responders: Chi^2=6.2, df=1, p=0.013). This corresponds to the expectation that treatment conclusion and positive effects are closely related. However, this is apparently only true for the heroin treatment: It is conspicuous that among methadone patients, the rate of concluders is higher among non-responders than among responders. Thus, treatment success and regular conclusion apparently do not correlate (in the expected direction) in the control group.
First of all, the two groups are described according to the individual variables at the base of the primary outcome measures in order to show the extent of changes under study treatment. As expected, non-responders have worse outcomes for all criteria across the two study groups after one year, though they also improved – if less markedly – under the treatment (see table 7.16). Non-responders tend to have a negative development (increase of consumption) only with respect to the intensity of cocaine use, detected through hair analyses. It is conspicuous that in almost all variables of responders and non-responders, methadone patients have a worse outcome at T_{12} than heroin patients. That means that, independent of patients' success (according to the definition of the POM), methadone patients make less progress under study treatment. At baseline at T_{-1}, there is no great difference between responders and non-responders with respect to these characteristics. The mental situation of non-responders tends

to be somewhat better, a fact that can hardly be found to make sense in relation to the treatment failure.

Table 7.16
Change of health state according to the OTI health scale and GSI of the SCL-90-R and of the use of street heroin and cocaine between T_{-1} and T_{12}[a)]. Mean values of responders compared to non-responders for each group

Target criterion		Responders			Non-responders		
		Heroin	Methadon	Total	Heroin	Methadon	Total
OTI-HSS	T-1	18.8 (4.8)	19.9 (5.4)	19.2 (5.1)	18.7 (5.7)	18.5 (5.3)	18.6 (5.4)
	T12	7.0 (5.0)	8.6 (5.2)	7.6 (5.1)	9.9 (6.4)	12.0 (6.9)	11.1 (6.7)
GSI, SCL-90-R	T-1	1.17 (0.63)	1.33 (0.69)	1.24 (0.66)	1.07 (0.64)	1.09 (0.61)	1.08 (0.62)
	T12	0.56 (0.49)	0.68 (0.48)	0.61 (0.49)	0.86 (0.63)	0.92 (0.68)	0.89 (0.66)
Heroin, Number of days	T-1	22.4 (10.0)	21.2 (10.4)	21.9 (10.2)	22.8 (9.9)	23.2 (9.7)	23.0 (9.8)
	T12	0.7 (2.5)	2.0 (5.2)	1.2 (3.9)	5.1 (9.6)	11.7 (12.0)	8.9 (11.5)
Cocaine, number of days	T-1	10.4 (10.9)	11.6 (11.8)	10.9 (11.3)	10.7 (11.4)	10.0 (11.2)	10.3 (11.3)
	T12	2.3 (5.1)	2.5 (6.0)	2.4 (5.5)	7.0 (9.3)	8.5 (10.7)	7.9 (10.1)
Cocaine, HA, µg/g, mean	T-1	24.5 (41.5)	39.4 (121.4)	30.7 (84.5)	22.5 (48.2)	30.5 (71.9)	26.9 (62.4)
	T12	7.1 (21.3)	8.5 (34.1)	7.6 (26.6)	29.8 (59.6)	35.6 (84.4)	33.0 (74.3)
Cocaine, HA, µg/g, median	T-1	6.2	5.9	6.1	4.0	5.2	4.6
	T12	0.2	0.5	0.4	6.5	5.7	5.9

[a)] Missing data at T_{12} were completed, if possible by information obtained in the context of the external interview. For heroin and methadone use, data from medical investigators' examinations are presented, missing data are completed from information of the external interview. The values at T_{-1} include the hair analyses performed at T_0. Similarly, missing HA data at T_{12} are completed from examination results at T_6.

The initial situation of responders and non-responders prior to the study treatment (T_{-1}) does not present any relevant differences. As already known from the (secondary) analysis of the gender comparison (cf. paragraph 7.4.3.3), this (as if reversed) way of contemplation also reflects the greater treatment success of male heroin patients (see table 7.17). The only statistically significant differences are found for general health (Karnofsky index) and alcohol use. Non-responders were in a slightly worse general condition, but used less alcohol.
Since treatment conclusion and treatment success in methadone patients are not positively correlated (see above), this analysis does not reproduce the differences between regular concluders and dropouts (cf. paragraph 7.4.3.1). Both analyses have in common that previous experience of addiction treatment has no influence on the outcome – neither for regular conclusion nor response.

Table 7.17

Patient characteristics of responders (n=519) and non-responders (n=496) at baseline (T_{-1}). Standard deviation is given in brackets. The values marked in grey point to significant differences between responders and non-responders.

Characteristic	Responders			Non-responders		
	Heroin	Metha	Total	Heroin	Metha	Total
Gender, male proportion	85.1%	79.9%	**82.9%**	73.2%	79.7%	**76.8%**
Age, years	36.5 (6.6)	36.4 (7.1)	**36.5 (6.8)**	35.8 (6.8)	36.7 (6.5)	**36.3 (6.6)**
Social situation						
Stable housing situation	72.4%	65.8%	**69.6%**	64.4%	72.8%	**69.1%**
Stable partnership	30.8%	32.3%	**31.5%**	37.4%	32.2%	**34.5%**
Children	37.8%	35.0%	**36.6%**	41.1%	37.0%	**38.8%**
Employment last 30 days	16.7%	9.0%	**13.4%**	9.5%	14.9%	**12.5%**
Illegal activities (for profit) last 30 days	74.2%	74.0%	**74.1%**	72.0%	70.9%	**71.4%**
Health state [a)]						
Karnofsky index (0-100)	73.3 (12.0)	70.9 (12.9)	**72.3 (12.4)**	69.5 (13.3)	71.4 (13.3)	**70.5 (13.4)**
HIV positive	6.8%	9.5%	**8.0%**	11.1%	9.5%	**10.2%**
HCV positive	79.5%	87.0%	**82.8%**	81.9%	77.7%	**79.6%**
Skin abscesses	6.8%	5.9%	**6.4%**	5.1%	8.7%	**7.1%**
Echocardiography pathol. finding [b)]	14.6%	13.4%	**14.1%**	18.6%	17.0%	**17.7%**
ECG pathol. finding [b)]	21.4%	17.0%	**19.5%**	15.0%	18.5%	**16.9%**
Abdominal sonogr. pathol. finding [b)]	60.0%	53.6%	**57.2%**	55.0%	52.2%	**53.4%**
Thorax x-ray pathol. finding [b)]	3.7%	1.8%	**2.9%**	0.5%	1.4%	**1.0%**
GAFS (0-100)	53.8 (11.2)	53.3 (11.8)	**53.6 (11.4)**	53.7 (11.7)	53.5 (11.8)	**53.6 (11.7)**
Global clinical impression (CGI, 0-7)	4.6 (0.9)	4.7 (1.0)	**4.6 (1.0)**	4.5 (1.1)	4.6 (1.0)	**4.6 (1.0)**
Drug use [a)]						
Beginning regular heroin use, age	19.9 (5.0)	20.2 (5.4)	**20.0 (5.2)**	20.1 (5.8)	20.4 (5.1)	**20.3 (5.4)**
Beginning regular cocaine use, age	22.6 (7.4)	22.5 (7.5)	**22.6 (7.5)**	22.0 (7.8)	23.1 (6.6)	**22.6 (7.2)**
Years of regular heroin use	13.7 (6.2)	13.6 (6.3)	**13.6 (6.2)**	13.6 (6.5)	13.6 (6.4)	**13.6 (6.4)**
Years of regular cocaine use	5.6 (6.7)	5.9 (6.4)	**5.7 (6.5)**	5.3 (6.7)	5.4 (6.3)	**5.4 (6.5)**
Heroin use last 30 days	95.9%	95.5%	**95.7%**	95.9%	95.7%	**95.8%**
Cocaine use last 30 days	73.6%	69.8%	**72.0%**	77.7%	70.3%	**73.6%**
Benzodiazepine use last 30 days	53.6%	61.3%	**56.9%**	60.7%	53.3%	**56.6%**
Alcohol use (harmful) last 30 days	17.6%	12.6%	**15.5%**	10.0%	11.2%	**10.7%**
Multiple use last 30 days	86.0%	92.7%	**88.9%**	88.8%	90.9%	**90.0%**
Intravenous use last 30 days	96.9%	95.0%	**96.1%**	96.3%	95.6%	**95.9%**
Drug overdose up to now	68.6%	74.0%	**70.9%**	75.0%	62.3%	**67.9%**
Money spent on drugs last 30 days, Euro	1,096 (1,583)	979 (1,130)	**1,046 (1,406)**	1,108 (1,486)	1,114 (1,647)	**1,112 (1,576)**
Money spent on alcohol last 30 d., Euro	28 (53)	32 (69)	**29 (60)**	32 (73)	29 (73)	**30 (73)**
Needle sharing	8.5%	8.2%	**8.4%**	14.0%	6.6%	**9.9%**
Sharing of injection equipment	17.7%	19.1%	**18.3%**	23.3%	8.5%	**20.6%**
Addiction treatment						
Outpatient detoxification up to now	33.5%	33.3%	**33.4%**	28.4%	35.6%	**32.5%**
Inpatient detoxification up to now	85.2%	84.0%	**84.7%**	84.8%	86.4%	**85.7%**
Maintenance treatment up to now	87.1%	93.2%	**89.7%**	90.4%	87.9%	**89.0%**
Psychosocial treatment up to now	49.1%	56.6%	**52.3%**	50.0%	53.4%	**51.9%**
Outp. abstinence treatment up to now	9.1%	13.0%	**10.8%**	11.7%	11.6%	**11.7%**
Inpat. abstinence treatment up to now	62.1%	55.8%	**59.4%**	53.3%	57.8%	**55.9%**
Therap. living community up to now	27.7%	26.1%	**27.0%**	22.0%	26.8%	**24.7%**
Non of these treatments up to now	2.0%	1.3%	**1.7%**	1.4%	1.8%	**1.6%**

[a)] The individual criteria, already listed in table 7.16 as characteristics of the corresponding POM, are not considered here.

[b)] Percentages related to all patients (examinations performed: echocardiography: n=890, ECG: n=940, sonography: n=935, x-ray: n=78).

7.4.4 Statistical analyses

The statistical procedures used in the primary analysis are described in detail in the study protocol no. ZIS-HV9-0701 (Krausz et al. 2001) and in the statistical analysis plan (Verthein et al. 2005). These documents, attached to this report, also describe the handling of missing data or dropouts and the consideration of covariates.

7.4.5 Individual response data

Annex II includes lists of all 1,015 study patients with data related to the outcome of the primary outcome measures (A) and (B) and the underlying individual variables in OTI-HSS, SCL-90-R (GSI), number of positive urinalyses, hair analyses and data on the 30-day prevalence for street heroin and cocaine.

7.4.6 Dosage and treatment response

According to the study protocol, the heroin and methadone dose could be individually adapted. The upper limit for heroin was 400 mg for single doses and 1,000 mg for daily doses. Additional methadone doses (for the night) should not exceed 60 mg. In the control group, the methadone dose was not specified (cf. study protocol, Krausz et al. 2001).
The average daily heroin dose across all patients and all study centres during the first study phase (365 days) is 442 mg. It is markedly lower than in the Dutch study, where the average dose was 548 mg (van den Brink et al. 2003)[28]. The mean daily dose of additionally prescribed methadone in the heroin group is 39 mg with respect to all really issued methadone doses, which is also markedly below the additional methadone dose in the Dutch study (injection study: 60 mg, inhalation study: 57 mg). However, not all heroin patients received additional methadone. Related to all 515 heroin patients (including those, who did not start treatment), 82.7% of the heroin group received additional methadone at least once during the study treatment. Therefore, it is more meaningful to consider the average amount of additionally prescribed methadone related to all heroin doses, i.e. take into account methadone not issued (or not claimed). Then, the average dose of methadone additionally prescribed to heroin patients decreases to 7.7 mg per day.
Methadone patients were treated with an average daily dose of 99 mg, which is clearly above the mean dose of the control group of the injection trial of the Dutch study (71 mg). Insufficient efficacy had been attributed to the supposedly too low dose of methadone in the Dutch control group;[29] this difficulty has thus been avoided in the German study.
Contemplations of the course are more meaningful than mean total doses. Figure 7.15 presents the average daily doses for the 1st, 3rd, 6th and 12th month of treatment.[30] An increase of the heroin dose from 406 to 476 mg can be discerned within the first 3 months (the initial updosing was concluded already after a few days). In the 6th month, heroin patients also

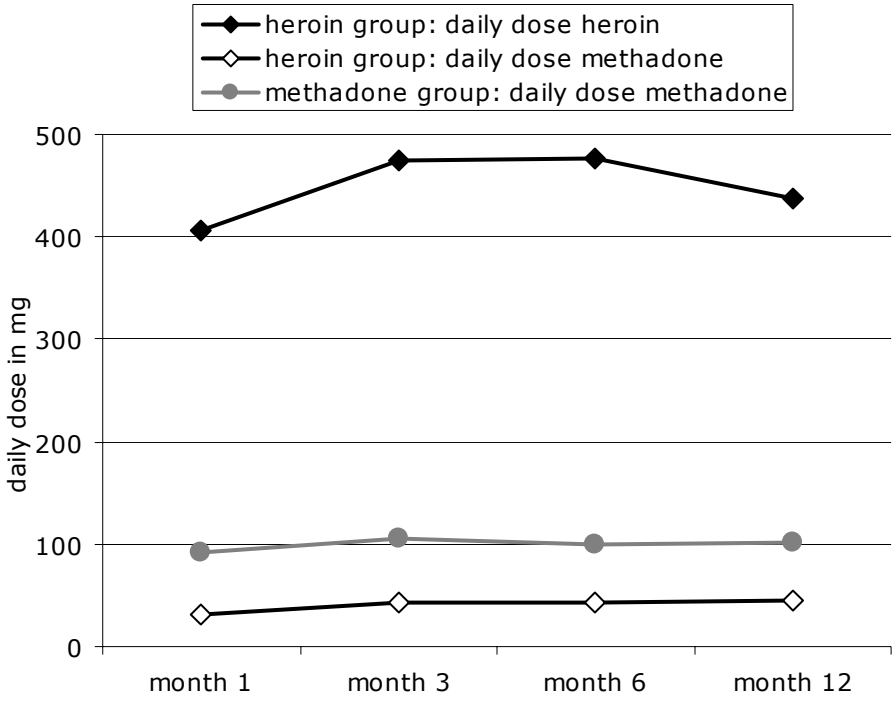
[28] This refers to the mean daily dose of heroin in both Dutch trials, the injection and the inhalation study.

[29] Cf. the reactions to the study by van den Brink et al. (2003) published on the internet at http://bmj.bmjjournals.com/cgi/eletters/327/7410/310.

[30] These average values only include doses really given out, i.e. interruptions (or „zero-dosages“) are not counted.

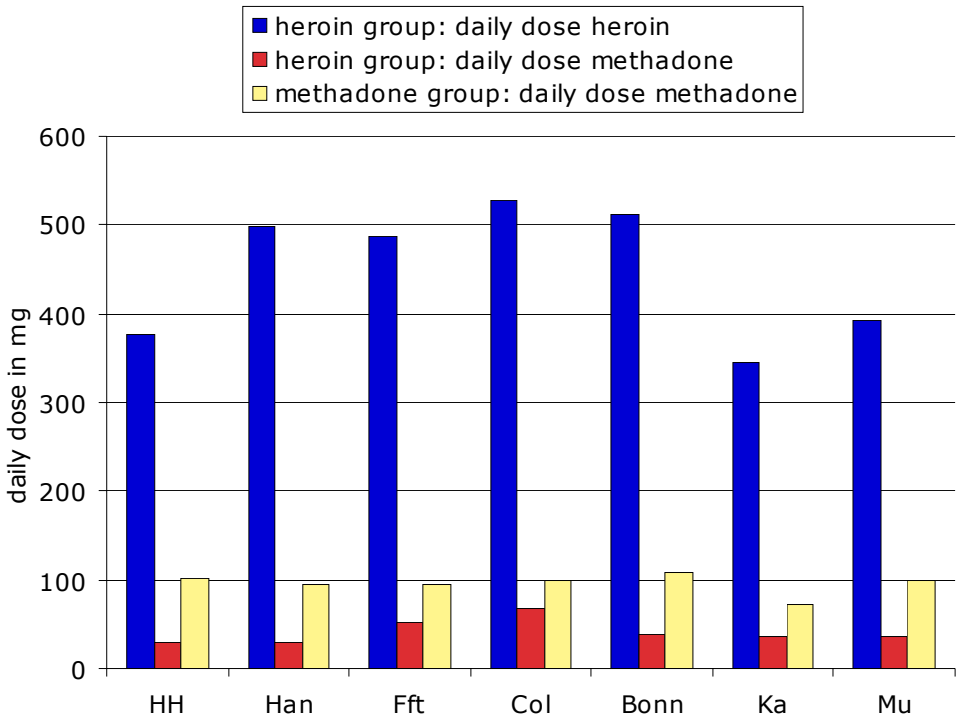
receive an average of 476 mg of diamorphine, at the end of the first study phase in the 12th month, the dose decreases again to 439 mg daily. The average amount of additionally prescribed methadone is 32 mg in the first month and stabilises to values between 42 and 45 mg. In the control group, the average dose of methadone was 91 mg in the 1st month, 106 mg in the 3rd month and 102 mg in the 12th month.

Figure 7.15
Average daily dose of study medication (in mg) in month 1, 3, 6 and 12 according to the study group



For the comparison of heroin and methadone dosage at the different study centres, the overall average doses are considered (for reasons of clarity). It is conspicuous that in Hamburg (377 mg), Karlsruhe (344 mg) and Munich (393 mg), heroin doses are generally lower than in the other centres, where the average daily dose is around 500 mg (see figure 7.16). If methadone is additionally prescribed, most study centres give out an average of 29-39 mg, in Frankfurt und Cologne, however, 51 mg and 67 mg respectively. With the exception of Karlsruhe, where the control group, too, receives less methadone on average (73 mg), methadone patients are treated in all centres with a mean daily dose between 94 and 107 mg.

Figure 7.16
Average daily dose of study medication (in mg) during the total period of the first study phase (365 days) according to study group and study centre



Except for maximum doses, study medication is not subject to rigid dosage regimens, which allows the treatment staff to adapt the individual dose to the patient's condition or his "need" at any time. Accordingly, a definite interrelation between dosage and response (or a difference between responders and non-responders) cannot be expected. Table 7.18 shows that, in general, differences between responders and non-responders are only slight. None of the criteria shows a statistically significant relationship. There is a slight tendency that responders of the heroin group, irrespective of the POM, receive a somewhat higher dose; but against the background of time differences (see above) and individual dosage adaptation, this should not be overrated. In the methadone group, even contrary differences can be observed for the two POM: Responders of the POM health receive a lower average dose, responders of the POM drug use receive a higher dose of methadone.

Table 7.18
Average daily dose of study medication (in mg) over the entire period of the first study phase according to study group and treatment response for each POM (standard deviation in brackets)

Patient group		**Response in the POM health**		**Response in the POM drug use**		**Response in both POM**	
		yes	**no**	**yes**	**no**	**yes**	**no**
Heroin	Heroin dose	446 (191)	425 (206)	449 (191)	424 (199)	444 (187)	438 (203)
	Methadone dose	39 (24)	41 (28)	39 (24)	40 (27)	39 (24)	40 (27)
Methadone	Methadone dose	97 (50)	104 (46)	103 (49)	93 (48)	100 (48)	98 (49)

7.5 Efficacy conclusions

The feasibility of heroin-assisted treatment of opioid dependent patients has already been proved by the Swiss study as well as by the Dutch study with respect to the co-prescription of methadone. The German study was partly based on these experiences; it was possible to focus on aspects of efficacy, in general as well as under consideration of specific groups of patients and treatment settings.
The present report includes the interim evaluation of the German model project of heroin-assisted treatment and focuses on the comparison of heroin and methadone treatment. This randomised, controlled survey conducted in the first study phase serves a.o. the purpose of applying for the licensing of heroin as a medical drug for the treatment of opioid dependent patients in Germany.
Before discussing the central result and the different efficacy aspects of the study treatment, it should be emphasised that the retention rate of heroin treatment is considerably higher than the retention rate of methadone treatment. Obviously, it was difficult to motivate patients, who had been randomised to the control group, for the one-year participation in the study treatment. Due to many patients' negative previous experience of methadone treatment – in particular in the MTF sample that consisted of possible candidates for the heroin treatment because of unsatisfactory results of the methadone maintenance treatment -, it had to be expected that patients were disappointed at the "wrong" randomisation result and would, therefore, drop out of treatment or not even show up for treatment. The incentive to occupy vacated heroin treatment places was obviously not strong enough, as no guarantees of subsequent heroin treatment could be given. A closer examination shows that the lower rate of concluders is mostly due to the high proportion of patients, who did not start methadone treatment. Therefore, the experimental and the control groups differ rather in their outreach than in their treatment commitment. This is a central difference to the Dutch study, where the rate of concluders was somewhat higher among methadone patients then in the experimental group (CCBH 2002). The Dutch model project took care, however, that conditions of the control group remained as unchanged as possible compared to baseline, while the experimental group received additional interventions along with heroin treatment, which, in some patients, apparently contributed to their decision to leave the heroin-methadone

treatment prematurely. Moreover, the clients of the Dutch study were subjected to a longer, multistage selection process; towards the end of this process more patients, whose treatment perseverance was more probably, consented to the study participation.[31] The result of the German study is more in line with the first randomised survey, the study by Hartnoll et al. (1980), where the retention rate among patients treated with heroin was also higher than in the methadone group. Moreover, the added value of the German study consists in the fact that it is orientated towards the realistic conditions of ordinary treatment, where patients (of a certain target group) are compared, who *newly* enter one of the treatment settings and are not – like in the Dutch project – continuously treated with methadone with or without additional heroin. This corresponds to the objective that, in Germany, the model project should reach the group of addicts "not reached". The switching of MTF patients from their former (not very successful) maintenance treatment to an outpatient unit that carried out the study treatment, apparently did not hold sufficient positive aspects or treatment advantages for many patients to motivate them to stay in the new methadone treatment for the one-year study period. It must be considered, however, that a major part of those, who dropped out of study treatment, took up (again) maintenance treatment outside the study.
The average daily dose of heroin over the entire period of the first study phase (365 days) was 442 mg. The mean daily dose of methadone additionally prescribed to heroin patients is 39 mg, related to all really delivered methadone doses. Methadone patients were treated with an average daily dose of 99 mg, which corresponds to a therapeutically effective dose (Strain et al. 1999). Compared to the Dutch study, the average dose of heroin is thus considerably lower, the dose of the methadone control group in contrast clearly higher (cf. van den Brink et al. 2003). Thus, the low methadone dosage of the Dutch control group, which had been criticised repeatedly as being too low and was partly made responsible for the low degree of treatment success, does not prevail in the German study.

The central result of the German model project shows a significant superiority of heroin over methadone treatment for *both* primary outcome measures. Heroin treatment has significantly higher response rates both in the field of health and the reduction of illicit drug use. *According to the study protocol, evidence of the greater efficacy of heroin treatment compared to methadone maintenance treatment has thus been produced.* Heroin treatment is also clearly superior to methadone treatment when focusing on patients, who fulfil the two primary outcome measures.
The effects for the criterion drug use are within the expected frame; for the health criterion, the difference of effect is lower, though statistically significant. Not only the overall remarkably high proportion of responders is impressive, but also the difference between experimental and control group of only 6% indicates that the methadone treatment, conducted according to the conditions of the model project, obviously achieved great effects also in the field of health. The positive results also indicate that methadone treatment was conducted on a

[31] This is all too often typical for randomised controlled studies with the result that many patients, who would be eligible for the study treatment, cannot take part. A prominent example is the project MATCH, where finally less than 40% of the persons eligible for the study were included (Project MATCH Research Group 1997).

high-quality level, which was certainly also due to the general conditions of the study (e.g. financial and personnel provisions and treatment conditions). Though it is widely known that methadone treatment successfully contributes to the health stabilisation of heroin addicts (e.g. Ball & Ross 1991; Gossop et al. 2001; 2003; Verthein et al. 1998; Ward et al. 1998), the extent of positive effects is still astonishing, as the retention rate in the control group was, with less than 40%, very low after 12 months. Therefore, it can be assumed that conditions outside or subsequent to the (discontinued) study treatment also played a part in the achieved changes, particularly as one third of the control patients did not even start methadone treatment. Here, the subsequent treatments (or alternative treatments) deserve particular attention, as they were utilised to a great extent (44%) particularly by dropouts of the control group. However, the comparison among patients, who regularly concluded the 12-month study treatment, the per-protocol analysis, confirms the superiority of heroin over methadone treatment for both target criteria. As expected, this analysis yields overall higher response rates; regular concluders are more successful than dropouts.

From a methodological point of view, the big leap in health improvement was also due to the fact that, at baseline, patients' health was definitely bad with an average of 19 points on the OTI health scale and 69 points on the SCL-90-R.[32] The structured setting of the heroin and methadone treatments contributed to a distinctly positive development already during the first weeks. Physical improvements that occurred prior to the initiation of the study treatment can partly be explained by the positive effects of the admission procedure and the baseline examinations (during several appointments). Differences between groups increase in the further course of treatment, with greater health improvements among heroin patients than among methadone patients. A more strict definition of the POM, e.g. an improvement by 40% compared to baseline, would have resulted in overall lower response rates, the response difference between the heroin and methadone group would have slightly increased.

With respect to the POM illicit drug use, not only street heroin, but also cocaine use gradually decreased in the course of study treatment. The decrease of street heroin use is clearly in favour of heroin treatment, for cocaine use, differences between groups are only slight. The results of hair analyses have a tendency towards a slight, but not significant advantage of heroin treatment. Based on the patients' reports on the 30-day prevalence (which had proved reliable in the context of the study), patients treated with heroin benefit significantly more than methadone patients. A slight decrease of cocaine use could be expected based on the Swiss experiences and the Dutch results. In the German study, the difference between experimental and control groups is, however, more marked. Therefore, it is justified to conclude at least in tendency that heroin treatment is also more effective than methadone treatment with respect to the decrease of cocaine use. This effect is understandable against the background of a greater separation from the context of the drug scene (and illegal activities) in heroin patients.

[32] Comparative values on the OTI health scale in other user groups are mainly available from Australia. In the mentioned study by Darke et al. (1991), study participants, mostly in methadone treatment, had a mean score of 12.6 points. Spooner et al. (2000) examined adolescent drug users (14-18 years) waiting for an inpatient treatment place, and they found an average of 17 symptoms on the OTI health scale. Among heroin users, the score was even 19.2 points. In the Hamburg study among homeless drug users by Prinzleve (2000), the average symptom score was 17.3 points (personal communication by the author).

When evaluating the study results, the conservative, robust analysis strategy must be kept in mind. Part of the responders in the control group (5.4% in the POM health, 4.4% in the POM drug use) must be put down to the asymmetric coding of missing data in study dropouts. This procedure, resulting from the open character of the study, minimises potential methodological reservations, but the alternative (though lower-ranking) kind of analysis rating study dropouts in both groups as non-responders, appears more realistic, as there is a greater probability that treatment dropouts and "treatment refusers" are non-successful patients. Therefore, the results of the primary analysis can be seen as "minimum effects" resulting from the comparison between heroin and methadone treatment.
Finally, it should be mentioned that heroin treatment proves to be superior over methadone treatment even if only individual improvement in *both* primary outcome measures were counted as study success. This consideration allows a direct comparison with the results of the Dutch study, where, combined in one (single) multiple target criterion, health development and user behaviour (as well as social contacts) were in the focus of the efficacy analysis (CCBH 2002). If the response rates of the worst case analysis (heroin: 55.3%, methadone: 39.8%) are considered, the response rates of the German study are slightly higher both in the heroin group (57.3%) and in the methadone group (44.8%).

An important added value of the German study consists in the systematic consideration of two target groups: patients currently in methadone treatment, who did not sufficiently benefit from their treatment (MTF stratum), and heroin users currently not reached by the addiction services (NR stratum). First of all, it must be emphasised that the investigators succeeded in recruiting a sufficient number of patients from the two groups, which, regarding health condition, pattern of consumption, judicial background and current life situation, must be counted among the "most severely dependent patients".[33] This could not be taken for granted, since, on the one hand, due to the meanwhile well-established and widespread methadone treatment in Germany, it was difficult to estimate the need for treatment in the group of the so-called not reached. On the other hand, potential oppositions and reservations had to be expected from doctors or treatment units involved in maintenance treatment with respect to the heroin treatment that was to be tested. A lot of on-site informational work was required to explain the importance and goals of the model project, which was successfully carried out due to the great commitment of the persons regionally in charge.
It is a first result that both target groups are virtually not different with respect to their baseline situation and their drug related background. With the exception of currently more frequent (intravenous) heroin use in the group of those "not reached" and the related greater involvement in the illicit (scene) context and a more instable housing situation, no indications can be found that that these opioid addicts are in a worse situation than those currently in maintenance treatment, whose treatment did not have a satisfactory course. The latter used more benzodiazepines, which is often observed in unsatisfactory maintenance treatment, and they had more previous experience of addiction treatment. One reason for the similarities of

[33] Contrary to initial doubts of some therapists and scientists concerning the complexity of the study design, is was possible to recruit – in the process of randomisation – eight groups of about similar size differentiated according to stratum, target group and medication.

the target groups might consist in the fact that heroin addicts, who, no doubt, are among the severely ill, marginalised drug users with (from the therapeutic point of view) an unfavourable prognosis, are reached at different stages of their individual drug and treatment careers. The second – more important – result is related to the effects of the study treatment: In both primary outcome measures, the target group affiliation has no influence on the overall result. Neither is there an effect modulation in the sense of an interaction between stratum affiliation and group affiliation, which was separately controlled for each POM. The similarity of the target groups (or sample strata) are reflected by the effects of the study treatment; the superiority of heroin treatment over methadone maintenance treatment is valid for both target groups. It can be concluded that heroin treatment is promising both for methadone non-responders and for heroin addicts with no contacts to treatment services.

In multicentre studies, the homogeneity of results in the individual study centres is usually checked statistically – in this case in the framework of the multivariate primary analysis. For the POM health, no influence by the factor study centre could be detected, however, there was a significant relationship for the criterion drug use.
It is conspicuous that in Hanover, Cologne and Munich, methadone patients had slightly higher response rates for the health criterion than heroin patients. In Hanover, this might be partly due to slightly lower numbers of control patients reached again for follow-up, who were counted as responders according to the worst case procedure.[34] In the centres Cologne and Munich, methadone treatment delivered in the context of the study, apparently had definitely positive effects also among this target group of severely dependent patients. In Cologne, the higher proportion of patients "not reached" (70% of recruits), might explain that the methadone study medication (compared to other programmes) particularly appeals to this group of patients. As for Munich, the specific study on treatment research might discover whether methadone treatment of the control group delivered in Munich is any different (positively) from maintenance treatment usually offered in this region.
For the criterion drug use, only the centre in Hanover deviates from the superiority of heroin treatment. At least, the tendency is uniform for both target criteria in this centre (negative in terms of the study result). But it is difficult to explain the deviations of the response rates within the groups between health criterion and drug use criterion in Cologne and Munich. In general, it is assumed that a positive development of user behaviour is reflected by health improvement. In Cologne and Munich, where the response difference between heroin and methadone groups for the POM drug use is particularly in favour of heroin, these effects obviously develop independently from each other. It is possible, however, that there is an influence of time and that health improvement as consequence of changed user behaviour is delayed. This development can be further investigated during the second study phase.

[34] The proportion of patients of the control group not reached for the T_{12} examination is highest in Hanover with 11.5% (Hamburg: 8.6%, Frankfurt: 6.5%, Cologne: 6.1%, Karlsruhe: 4.2%, Munich: 0%, Bonn: 0%). The difference for non-reached control patients at T_6 is even higher, with Hamburg ranging highest: Hamburg: 55.3%, Hanover: 52.5%, Frankfurt: 41.3%, Karlsruhe: 33.3%, Munich: 22.2%, Bonn: 10.0%, Cologne: 6.1%. All data are based on the ITT sample (n=1,015).

The kind of psychosocial concomitant treatment has no (statistically identifiable) influence on the treatment effect. Both treatment types – psychoeducation with individual drug counselling and case management with motivational interviewing – yield similar response rates and comparable effect differences between heroin and methadone treatment. This is a decisive step closer to answering the important question (formulated after the results of the Swiss study), whether the positive results of heroin treatment are due to the medical (pharmacological) setting or to the psychosocial treatment. Although the detailed analysis of the utilisation behaviour is still pending – it is part of the specific study on treatment evaluation –, the superiority of heroin over methadone treatment for both kinds of PST points to an overall result independent of the psychosocial treatment setting. The exact degree of contribution of concomitant interventions to the treatment success can still not be exactly defined; this would require a study design where at least one study branch would not receive any PST. In any case, it is a positive result that different kinds of treatment (in the context of an integrated treatment concept) can have comparable effects. Thus, therapists and the staff of regional addiction services would be able to offer heroin treatment in different settings according to the patients' individual needs.

Gender differences with respect to the effects of heroin and methadone treatment are remarkable. Although the superiority of heroin treatment can be shown in men for both primary outcome measures, this is not true for women. They have lower response rates in the heroin group, only slightly above those of the methadone group. The momentous statement that, in women, heroin-assisted treatment has no advantages compared to methadone maintenance treatment cannot be made on the basis of these results, as gender-specific effects were not the focus of the present study (nor of the methodological design). Further explorative analyses might find explanations for this difference. Future studies should focus more on potential gender-specific effects.

The main focus of the model project are the effects of heroin treatment in the fields of health and user behaviour. These criteria were explored confirmatorily according to the requirements of the statistical analysis plan. According to the broader goals of the study, treatment success can be detected also in other areas (by secondary analyses).
Changes concerning the use of other drugs are rather slight. Cannabis and benzodiazepine use slightly decreases, but there are no significant differences between heroin and methadone patients. This concerns both self-reports and the results of urinalyses, although the latter point to somewhat clearer differences between experimental and control groups. The decrease of alcohol use, related to the amount of drinking is also clearly in favour of heroin patients. The effects of heroin treatment (as well as methadone maintenance treatment) first of all concern the use of street heroin – according to the original treatment goal. Cocaine use, which also clearly decreases, is often related to heroin, on the one hand indirectly through scene contacts and procuring, on the other hand consciously used for complementary effects. This development goes hand in hand with the separation from the context of the drug scene, where heroin patients succeeded better than methadone patients. This is mainly due to the fact that heroin patients are less in need to procure illicit drugs or the money to procure them. The

separation from the drug scene is not tantamount to building new, drugfree contacts. Two fifths of the patients from both groups report having made new acquaintances and friends during the treatment, but it is doubtful whether these are drugfree persons, as many patients still spend most of their leisure time with relatives or friends, who have a drug or alcohol problem. However, the comparatively short treatment period of 12 months must be taken into account. Building new contacts needs time, particularly in a situation, where the need to settle own (health and social) problems and conflicts is particularly great.
The mentioned restrictions also concern the patients' social situation, in particular possibilities to work. The housing situation of heroin patients became more stable; there are no great changes in the methadone group. The proportion of patients living in a stable partnership hardly changed in both groups, but the satisfaction with the partnership markedly increased in both groups. Gainful employment of the study patients developed positively. Only 13% were employed immediately before the treatment, after 12 months, the number had doubled to one fourth of the patients. The increase within one year is remarkable, and heroin and methadone patients benefit to the same degree. It is similar to the increase found in the Swiss heroin trial (Uchtenhagen et al. 2000); so far, no other German studies found this kind of positive development among methadone patients (Verthein et al. 1998). The second study phase will show whether the positive trend will continue.
Study treatment has a particularly positive effect on the development of the delinquency situation. These effects are investigated by two special studies and are explored in more detail both qualitatively and quantitatively based on external police and court data. The available data show already a distinct effect in favour of heroin treatment. Illicit activities drastically decreased and, with 27%, are clearly below the level of methadone treatment (40%) after 12 months. This corresponds to a decrease of convictions and arrests – also more marked in heroin-treated patients. Thus, a major advantage of heroin treatment concerns delinquency, related to the separation from the illegal context of the drug scene. It suggests economic benefits of heroin treatment. This will also be investigated by a special study, whose results will be presented by the end of 2005.

The German model project for heroin-assisted treatment of opioid dependent patients is so far the largest randomised control group study that investigated the effects of heroin treatment. This fact alone lends particular importance to the results in the (meanwhile worldwide) discussion of effects and benefits of heroin treatment. For the group of so-called most severely dependent patients, heroin treatment proves to be superior to the goals of methadone maintenance based on pharmacological maintenance treatment. This result should not be left without consequences. In accordance with the research results from other countries, it has to be investigated to what extent heroin-assisted treatment can be integrated into the regular treatment offers for severely ill i.v. opioid addicts.

8. Safety analyses

The following reports adverse events (AEs) (paragraph 8.1) and severe adverse events (SAEs) (paragraph 8.2) that occurred during the first study phase. The events are combined to categories. A listing of the individual events is attached in annex II paragraph 2.

8.1 Adverse events (AEs)

8.1.1 Recording of AE reports

Adverse events (AEs) occurring during the study period were recorded for each person at the participating centres. The documentation of AEs during the first year of the study provided four CRF pages (D1 to D4) for each participant. Nine AEs could be described on each page. In order to allow complete and comprehensive documentation of the AEs, it was moreover possible to list further AEs on copies of these pages. This became necessary in five participants due to the frequency of AEs.
According to the guidelines of GCP, the recording of following data was standardised, in addition to the description of the AE:

- Date of beginning and end
- Recording whether the AE is ongoing
- Time of beginning and end
- Degree of severity
- Measures concerning study medication
- Causal relationship with study medication
- Consequences/outcome
- Assessment whether AE is severe or not.

Documentation of AEs by the medical investigators was very conscientious, therefore, the data record at the base of the analysis has a very high degree of completeness. Only the category recording the times of beginning and end of the AEs has major gaps, so that an analysis related to these times was relinquished. Neither has the relationship between AE and dose of study medication been calculated. The reason is, on the one hand, that due to the documentation design, there are no exact data on the amount of dose for each day. On the other hand, the date of beginning of the AE is often indicated vaguely (often only month and year), which prevents dates of doses to be clearly attributable.
The coding in ICD-10 diagnoses was done by qualified personnel (doctors) of the team of the principal investigator in Hamburg using the programme „ICD-10-Navigator Medizin, ORIS Version 4.0“. Therefore, it is possible to categorise and evaluate AEs in relation to diagnoses as well as in relation to symptoms.

8.1.2 Description of adverse events (AEs)

A total of 9,238 AEs were described during the first year of the study. In 61 patients, it was stated that no AEs were recorded. As a rule, these are patients, who did not start the study

treatment or who dropped out very early. The distribution of these patients is as follows: 30 in Hamburg, 14 each in Frankfurt and Hanover, 2 in Cologne, one in Munich.
The safety analysis is limited to AEs that occurred after treatment initiation (T_0) and during the first study phase. This reduces the number of AEs to be analysed to 7,069 (see table 8.1). This is due to the fact that, on the one hand, medical investigators had already started documentation prior to the treatment initiation (from T_{-1}onwards) and, on the other hand, that events that occurred in the second study year had been described on the sheets for the first year. The present report only considers AEs that occurred between the actual treatment initiation (with heroin or methadone) and the end of the first study year or treatment discontinuation. The analysis of AEs of the second study phase already recorded will be part of the final report of the model project.

Table 8.1
Number of documented adverse events (AEs)

Adverse events			
Prior to treatment	After 1st study phase	Between T0 and T12	Total
688	1,481	**7,069**	9,238

The documentation of adverse events requires, for each AE, an evaluation of the degree of severity, the causal relationship with the study medication, measures taken with respect to the study medication and the outcome of the AE. The results of these assessments are presented in tables 8.2 to 8.5.
During the first year of the study, 4,189 AEs were reported in the heroin group and only 2,880 AEs in the methadone group. However, it must be taken into account that data on heroin patients are based on 465 participants and data on methadone patients on 355 study participants. The duration of treatment also differs between the two groups. The mean treatment duration of heroin patients (with documented AEs) is 290 days, of methadone patients 195 days. If all individual treatment days are added up, an AE occurs every 35.7 treatment days in the heroin group and every 33.9 treatment days in the methadone group. Patients of the heroin group have an average of 8.99 AEs and patients of the methadone group 8.11 AEs.
Overall, only 6.2% of all recorded AEs are assessed as “severe” (see table 8.2). The difference between heroin and methadone group is 0.5%. Related to the treatment days, a “severe” AE was recorded on average every 558.7 treatment days in the heroin group and every 598.3 treatment days in the methadone group. The assessment of an AE as “severe” is not equivalent to the assessment of an AE as a severe adverse event (SAE) according to the definition. SAEs are described separately in paragraph 8.2.

Table 8.2
Indications of the degree of severity of AEs

Degreee of severity of AEs	Heroin		Methadone		Total	
	Number	%	Number	%	Number	%
Minor	2,357	56.4	1,396	50.5	3,753	54.1
Medium	1,520	36.4	1,201	43.4	2,721	39.2
Severe	267	6.4	163	5.9	430	6.2
Not applicable	32	0.8	6	0.2	38	0.5
Total	**4,176**	**100.0**	**2,766**	**100.0**	**6,942**	**100.0**

In more than 50% of all AEs, there is no causal relationship with the study medication, neither in the heroin nor in the methadone group (see table 8.3). A potential to certain relationship was found in 21.3% of all AEs (heroin: 24.2%; methadone: 17.3%). In the heroin group, an AE with causal relationship with the study medication occurred every 147.8 days, in the methadone group only every 198.6 days. The differences between the two study groups will be addressed more closely in paragraph 8.1.2.2.

Table 8.3
Causal relationship between AEs and study medication

Causal relationship with study medication	Heroin		Methadone		Total	
	Number	%	Number	%	Number	%
None	2,303	55.3	1,698	59.6	4,001	57.1
Unlikely	853	20.5	659	23.1	1,512	21.6
Possible	670	16.1	413	14.5	1,083	15.4
Likely	263	6.3	70	2.5	333	4.7
Certain	76	1.8	8	0.3	84	1.2
Total	**4,165**	**100.0**	**2,348**	**100.0**	**7,013**	**100.0**

A very high proportion of the AEs (91%) did not require any change of the medication neither for the study medication heroin nor for methadone (see table 8.4).

Table 8.4
Initiated actions related to the study medication

Actions	Heroin		Methadone		Total	
	Number	%	Number	%	Number	%
No change	3,752	90.0	2,637	92.5	6,389	91.0
Reduced	169	4.1	40	1.4	209	3.0
Increased	30	0.7	13	0.5	43	0.6
Temporarily discontinued	112	2.7	17	0.6	129	1.8
Discontinued	12	0.3	5	0.2	17	0.2
Not applicable	96	2.3	139	4.9	235	3.3
Total	**4,171**	**100.0**	**2,851**	**100.0**	**7,022**	**100.0**

A very low percentage of all adverse events (3%) resulted in lasting consequences for the patient's health (see table 8.5). They include e.g. consequences of accidents or operations on the locomotor apparatus. Data on deaths do not correspond with the actual deaths within the study period. A detailed documentation is presented in paragraph 8.2.4 on severe adverse events (SAEs).

Table 8.5
Outcome of the adverse event

Outcome of AEs	Heroin		Methadone		Total	
	Number	%	Number	%	Number	%
Restored	3,252	78.0	1,822	63.5	5,074	72.1
Restored with consequences	76	1.8	132	4.6	208	3.0
Continuing	817	19.6	867	30.2	1,684	23.9
Patient died	2	0.0	1	0.0	3	0.0
Not known	20	0.5	47	1.6	67	1.0
Total	**4,167**	**100.0**	**2,869**	**100.0**	**7,036**	**100.0**

8.1.2.1 Adverse events classified according to ICD-10

Each described AE was coded using (up to three) ICD-10 diagnoses. Only seven AEs could not be attributed to an ICD-10 diagnosis (see table 8.6). 7,062 first diagnoses were attributed; a second diagnosis was attributed in 712 AEs and a third diagnosis in 97 AEs. The following analysis only considers the first diagnoses, as they classify the main symptom. Annex II includes a detailed table listing all adverse events for each patients with ICD-10 diagnoses and their assessments.

Table 8.6
Adverse events with no ICD-10 diagnosis

Random no.	**Description of AE**
10006	Development of heat
40042	Removal of external fixation
40154	Left cardiac catheter + PTCA
60006	Blind biopsy of liver, elective hospitalisation
60020	Withdrawal treatment
70036	Burning
80015	„Thoughts revolving around study and crass people“

The ICD-10 diagnoses were combined to higher categories, according to their content, and analysed with respect to the frequency of their occurrence. Table 8.7 presents the detailed list of the higher categories.

Table 8.7
List of the higher ICD-10 categories

Category	Designation of category	ICD-10
1	Infectious intestinal diseases	A09
2	Bacterial diseases, infections through sexual intercourse	A4 - A6
3	Viral infection (skin lesions, mucosal lesions)	B0
4	Viral hepatitis	B1
5	HIV disease	B2
6	Mycotic infections	B3
7	Pediculosis and other infectious diseases	B8 - B9
8	Benign neoplasms	D7.9, D2 - D4
9	Diseases of the blood and of hematogenic organs	D5 - D7
10	Endocrinal, nutritional and metabolic dieseases	E
11	Organic mental disorders	F0, F6, F8. F9
12	Psychological and behavioural disorders by psychotropic substances	F1
13	Schizophrenia, schizotypal and delusional disorders	F2
14	Affective disorders	F3
15	Neurotic, stress and somatoform disorders	F4
16	Behavioural abnormities	F5
17	Extrapyramidal diseases and motor disturbances	G2
18	Episodic and paroxysmal diseases of the nervous system	G4
19	Diseases of nerves and other diseases of the nervous system, paralytic syndromes	G5, G83.4, G91.1
20	Diseases of the eye and the ocular adnexa (except for 21)	H0 - H4, H50, H51, H52, H55, H57
21	Visual disturbances and blindness	H53, H54
22	Diseases of the ear	H6, H9
23	Diseases of the circulatory system	I
24	Infections of the upper respiratory tracts	J0, J3
25	Influenza and pneumonia	J1
26	Infections of the lower respiratory tracts	J2
27	Other diseases of the respiratory tracts	J4, J8, J9
28	Diseases of the oral cavity, the salivary glands and the maxillaries	K0, K1
29	Diseases of the stomach, the appendix, hernias	K2, K3, K4
30	Non infectious enteritis and colitis	K52
31	Other diseases of the intestine, the peritoneum, the liver, the bile and the pancreas	K56, K57, K59, K6, K7, K8, K9
32	Diseases of the skin and the subcutis	L
33	Arthropathies	M0, M1, M2
34	Diseases of the spine and the back	M4, M5
35	Diseases of the soft tissues	M6, M7, M8
36	Diseases of the urogenital tract	N
37	Pregnancy, birth, childbed	O
38	Symptoms of the circulatory system and the respiratory system	R0
39	Symptoms of the digestive system and the abdomen	R1
40	Symptoms skin and the soft tissue	R20, R21, R22, R23
41	Symptoms of the nervous system and the muscle and skeletal system	R25, R27, R29
42	Symptoms of the urinary system	R3

43	Symptoms of the recognition and perception system, of speech and voice	R4
44	General symptoms	R5
45	Abnormal laboratory findings	R7, R8, R9
46	Injuries by external causes	S, T0, T1, T2, T3
47	Poisenings	T4, T5, T62, T63
48	Other damages caused by external causes (e.g. complications in surgical interventions)	T67, T7, T8
49	External causes of morbidity and mortality	V, W, X, Y, Z

The following table 8.8 informs about the frequency of adverse events for each higher ICD-10 category, separated according to heroin and methadone groups.

Table 8.8
Frequency of AEs in the higher ICD-10 categories according to groups

Category	Heroin		Methadone		Total	
	Number	%	Number	%	Number	%
1	81	1.9	26	0.9	107	1.5
2	26	0.6	13	0.5	39	0.6
3	36	0.9	39	1.4	75	1.1
4	10	0.2	7	0.2	17	0.2
5	2	0.0	2	0.1	4	0.1
6	27	0.6	20	0.7	47	0.7
7	13	0.3	7	0.2	20	0.3
8	8	0.2	3	0.1	11	0.2
9	27	0.6	30	1.0	57	0.8
10	16	0.4	14	0.5	30	0.4
11	10	0.2	3	0.1	13	0.2
12	120	2.9	49	1.7	169	2.4
13	13	0.3	11	0.4	24	0.3
14	54	1.3	43	1.5	97	1.4
15	20	0.5	11	0.4	31	0.4
16	49	1.2	62	2.2	111	1.6
17	14	0.3	4	0.1	18	0.3
18	169	4.0	78	2.7	247	3.5
19	19	0.5	8	0.3	27	0.4
20	41	1.0	15	0.5	56	0.8
21	47	1.1	46	1.6	93	1.3
22	45	1.1	40	1.4	85	1.2
23	130	3.1	107	3.7	237	3.4
24	274	6.6	187	6.5	461	6.5
25	24	0.6	14	0.5	38	0.5
26	47	1.1	46	1.6	93	1.3
27	89	2.1	58	2.0	147	2.1
28	184	4.4	107	3.7	291	4.1
29	29	0.7	18	0.6	47	0.7
30	128	3.1	87	3.0	215	3.0
31	107	2.6	64	2.2	171	2.4
32	307	7.3	229	8.0	536	7.6
33	64	1.5	47	1.6	111	1.6
34	50	1.2	29	1.0	79	1.1
35	62	1.5	42	1.5	104	1.5
36	69	1.6	40	1.4	109	1.5
37	2	0.0	3	0.1	5	0.1
38	196	4.7	166	5.8	362	5.1
39	287	6.9	164	5.7	451	6.4
40	99	2.4	68	2.4	167	2.4
41	64	1.5	43	1.5	107	1.5
42	20	0.5	27	0.9	47	0.7
43	114	2.7	75	2.6	189	2.7

44	572	13.7	459	15.9	1031	14.6
45	43	1.0	29	1.0	72	1.0
46	218	5.2	178	6.2	396	5.6
47	60	1.4	37	1.3	97	1.4
48	71	1.7	8	0.3	79	1.1
49	26	0.6	16	0.6	42	0.6
Total	**4,183**	**100.0**	**2,879**	**100.0**	**7,062**	**100.0**

The only higher ICD-10 category, whose frequency of occurrence is above 10% (heroin: 13.7%; methadone: 15.9%), includes only one ICD-10 diagnosis (R5). This diagnosis, however, subsumes a great variety of symptoms and diseases under the umbrella term "general symptoms". It includes headache, edemas, bouts of fever, weak conditions, loss of appetite and swollen lymph glands.
Infections of the upper respiratory tract (category 24) are, with 6.5%, the second most frequently documented AEs (heroin: 6.6%; methadone: 6.5%), followed by symptoms of the digestive system and the abdomen (category 39) with 6.4% (heroin: 6.9%; methadone: 5.7%). Only injuries through external causes (5.6%; heroin: 5.2%; methadone: 6.2%) and symptoms of the circulatory and the respiratory systems (5.1%; heroin: 4.7%; methadone: 5.8%) had also a frequency of more than 5% (see table 8.9).

Table 8.9
ICD-10 categories combined according to the frequency of occurrence

	ICD-10 categories	**%**
Individual cases / very rare (less than 0.1%)	-	-
Rare (less than 1%)	2, 4, 5, 6, 7, 8, 9, 10, 11, 13, 15, 17, 19, 20, 25, 29, 37, 42, 49	38.7
Occasionally (1%-10%)	1, 3, 12, 14, 16, 18, 21, 22, 23, 24, 26, 27, 28, 30, 31, 32, 33, 24, 35, 36, 38, 39, 40, 41, 43, 45, 46, 47, 48	59.2
Often (more than 10%)	44	2.0

Table 8.10 presents an overview of the higher ICD-10 categories with respect to the degree of severity of the AEs and the assumed causal relationship with the study medication. The heading "relationship" subsumes all AEs, where the medical investigators saw a possible, probable or certain relationship with the heroin or methadone medication. AEs with no or improbable relationship with the study medication are presented under the heading "no relationship".

Table 8.10
Number of higher ICD-10 categories according to the relationship with the study medication and the degree of severity of the recorded AEs

ICD-10 category	Heroin						Methadone					
	Relationship			No relationship			Relationship			No relationship		
	low	med.	severe	low	med.	severe	low	med.	severe	low	med.	severe
1	18	21	-	23	15	3	4	3	-	9	10	-
2	-	1	-	10	12	3	-	-	-	3	7	2
3	-	-	-	30	6	-	1	-	-	25	12	-
4	-	-	-	3	5	1	-	-	-	1	4	2
5	-	-	-	-	-	2	-	-	-	-	1	1
6	-	-	-	23	3	1	-	-	-	9	10	-
7	-	-	-	7	5	1	-	-	-	6	1	-
8	-	-	-	5	2	1	1	-	-	1	-	-
9	1	1	-	16	7	2	1	2	-	16	10	1
10	-	-	-	11	4	-	-	3	-	4	6	-
11	6	-	-	1	3	-	-	-	-	-	3	-
12	17	33	**12**	9	18	9	2	9	**4**	6	14	8
13	-	1	-	-	9	3	-	-	**1**	-	5	5
14	2	2	-	7	35	8	2	3	**1**	8	18	11
15	-	-	**1**	3	11	4	-	-	**1**	2	6	2
16	19	15	**1**	4	7	3	23	18	-	6	10	-
17	5	5	-	3	1	-	1	-	-	1	2	-
18	20	37	**27**	38	33	10	12	10	**2**	18	29	3
19	-	-	**1**	7	9	2	-	-	-	2	4	2
20	5	1	-	18	14	3	1	-	-	9	4	-
21	21	3	-	19	4	-	16	2	-	17	8	-
22	3	-	-	31	9	-	6	1	-	18	11	1
23	15	10	**4**	50	41	6	12	4	-	37	34	14
24	1	2	**1**	119	139	11	1	1	-	93	81	4
25	-	-	-	4	13	6	-	-	-	1	6	7
26	-	-	-	20	23	4	-	3	-	7	29	7
27	5	11	**3**	24	35	11	2	1	-	22	22	5
28	3	3	-	94	75	6	-	-	-	44	54	2
29	2	3	-	10	11	-	2	1	-	5	9	1
30	9	9	**1**	74	31	3	7	3	**1**	35	37	2
31	54	18	**6**	12	11	6	27	7	**2**	13	8	2
32	53	30	**1**	147	65	10	-	2	**1**	88	105	16
33	2	2	-	42	16	2	1	1	-	34	9	1
34	1	5	-	15	25	4	-	-	-	12	15	2
35	5	1	-	39	16	1	1	6	-	18	16	1
36	6	-	-	32	27	1	6	2	**1**	21	5	2
37	-	-	-	1	1	-	-	-	-	-	2	1
38	10	11	**7**	122	43	3	11	1	-	91	55	-
39	67	31	**2**	116	66	4	25	25	-	53	54	4
40	12	11	**2**	66	6	2	4	3	-	38	19	-
41	18	8	-	31	7	-	7	1	-	24	10	-

42	3	2	**-**	10	4	-	1	1	**-**	18	6	-
43	27	17	**5**	49	15	1	16	3	**1**	33	15	3
44	77	43	**9**	306	113	15	78	37	**4**	184	107	12
45	1	2	**-**	19	18	3	-	9	**-**	5	14	1
46	2	6	**3**	107	90	6	6	10	**2**	50	95	11
47	16	17	**3**	14	7	3	4	3	**-**	14	11	1
48	15	17	**6**	18	13	1	-	-	**-**	1	6	1
49	1	1	**2**	9	8	3	-	1	**-**	3	8	3

A relationship between severe AEs and the study medication is rather rare related to the total number of all reported AEs. 97 AEs (9.6%) of the heroin group and only 21 AEs (4.4%) of the methadone group belong to this category (see table 8.11). A more detailed description of these AEs according to the symptoms will be presented in paragraph 8.1.2.2.

Table 8.11
Number of AEs according to their relationship with the study medication and the degree of severity

		Low		**Medium**		**Severe**		**Not applicable**		**Total**
		Number	**%**	**Number**	**%**	**Number**	**%**	**Number**	**%**	
Heroin	No relationship	1818	57.8	1134	36.0	169	5.4	25	0.8	3146
	Relationship	522	51.9	381	37.9	**97**	9.6	6	0.6	1006
Methadone	No relationship	1105	48.9	1007	44.6	141	6.2	6	0.3	2259
	Relationship	281	58.8	176	36.8	**21**	4.4	-	-	478

8.1.2.2 Symptom analysis of AEs

The Swiss trials, among others, discovered that the injection of heroin might produce cerebral convulsions (Seidenberg & Honegger 1998). The heroin and methadone groups differ with respect to the occurrence of convulsions. Heroin patients suffered more often from convulsions under study conditions (see table 8.12). In the heroin group, a total of 63 convulsions were reported as AEs related to the study medication; 26 of them were assessed as “severe”. In the methadone group, only one severe convulsion occurred in connection with the study medication. In addition, there were convulsions, reported as severe adverse events (SAE) (see paragraph 8.2).

Table 8.12
Frequency of cerebral convulsions in the heroin and methadone group according to the degree of severity of the AEs

		Low		Medium		Severe		Not applicable		Total
		Number	%	Number	%	Number	%	Number	%	
Heroin	No relationship	2	16.7	2	16.7	8	66.7	-	-	12
	Relationship	6	9.5	29	46.0	26	41.3	2	3.2	63
Methadone	No relationship	1	10.0	6	60.0	3	30.0	-	-	10
	Relationship	-	-	-	-	1	100.0	-	-	1

As already stated, only 21 AEs of the methadone group were assessed as “severe” as well as connected with methadone. In the heroin group, this applied to 98 AEs; one AE could not be assigned to an ICD-10 diagnosis. The 98 AEs of the heroin group were observed in a total of 65 patients, the 21 AEs of the methadone group in 17 patients.
With the exception of the convulsions described above, the 72 AEs of the heroin group and the 20 AEs of the methadone group are described according to their symptoms in table 8.13. It is conspicuous that respiratory depression, respiratory insufficiency and dazed states occurred more often in the heroin group, most often immediately (a few minutes) after the intravenous application of heroin.

Table 8.13
Frequency of severe symptoms related to the study medication

	Heroin	Methadone
Respiratory depression / resp. insufficiency / dazed state	23	1
Allergic reaction (skin)	7	-
Arterial application	2	-
Weight loss or weight gain	2	1
Abdominal pain / obstipation	6	3
Mixed intoxication / withdrawal	7	4
Fall / accident	3	3
Diarrhea	1	1
Grippal infection	1	-
Hepatitic episode / icterus	2	-
Infection of a cardiac valve	1	-
Headache	5	1
Tingling	1	-
Fit of perspiration	3	-
Sleep disturbances	2	1
Edemas	1	2
Development of heat	1	-
Depression / anxiety / psychosis / agitation	4	3

The rather frequent occurrence of cerebral convulsions as well as of respiratory depression, respiratory insufficiency and dazed states are not unexpected due to the intravenous form of application. They most often occurred in connection with non-reported co-use of benzodiazepines (respiratory depression, respiratory insufficiency and dizziness) and alcohol and/or cocaine (convulsions). As patients were obliged to stay on the site for 30 minutes after the application of heroin, and as these adverse events occurred immediately (only a few minutes) after the application, they were easily clinically treated. Neither the medical investigators nor the principal investigator considered this to be a major safety risk for the study participants, as these events were not assessed as unexpected. This view was explicitly confirmed by the Safety Board in a meeting on 21.10.2003 (Minutes of the meeting of the Safety Board on 21.10.2003).

8.2 Severe adverse events (SAEs)

All severe adverse events (SAEs) were recorded and reported in the course of the study according to the legal provisions (law on drugs §§ 40 and 41) and guidelines (GCP/ICH and EG-GCP, ICH 1996). The ensuing necessary actions were specified and put down in a study-specific SOP.
The currently valid definition of a SAE in this study precisely states that a *planned hospitalisation for the treatment of a chronic condition* is not a SAE.
The report and the follow-up of SAEs occurs on a specially developed form with the assessment of the causal relationship as *certain, probable, possible, improbable* or *none* and the outcome of the SAEs as *worse, restored, permanent damage, not yet restored, fatal outcome* or *unknown*.
The safety manager reported notifiable SAEs to the appropriate authorities as well as to the safety board established for this study. As convened with the BfArM, those SAEs were reported to the BfArM (within 7 days), where a causal relationship with the study medication was assumed to be possible, probable or certain. The safety board received a copy of all the reported SAEs.

8.2.1 Safety Board

The Safety Board inspects and assesses all the AEs/SAEs at regular intervals. This concerns checking the compliance with notifying obligations, assessment of the classification as severe or not severe and the assessment of a relationship with the study medication. The safety boward meets twice a year. Each member of the safety board may convene a special meeting, e.g. if the occurrence of an SAE leads to the assumption that the safety of the study participants is at risk.

Members of the Safety Board:

- Prof. Dr. Rainer Böger
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Further (optional) members of the Safety Board:

- *Members of the study group of the ZIS, Universitätsklinikum Hamburg-Eppendorf:* Prof. Dr. Michael Krausz, LKP; after September 1, 2003, Prof. Dr. Dieter Naber; PD Dr. Christian Haasen, safety manager; Dr. Peter Degkwitz, study coordinator
- *Main monitors:* Dr. Andreas Kolt, Nora Wolf

8.2.2 Description of the severe adverse events (SAEs)

A total of 381 SAEs were described in the first study phase, 199 in 134 patients of the heroin group and 182 in 118 patients of the methadone group. Of the 381 SAEs, 42 SAEs occurred in patients, who had not started the study treatment (i.e. during the observation period T_{-1} to T_0). Of the remaining 339 SAEs, 24 SAEs were reported for patients, who had started the treatment, but whose SAE occurred *prior* to the actual initiation of treatment (observation period T_{-1} to T_0). The following describes the remaining 315 SAEs (177 of them in 124 patients of the heroin group and 138 in 88 patients of the methadone group) observed in the period T_0 to T_{12}, irrespective of the patients dropping out of the study treatment prematurely.
In contrast, *all* the deaths that occurred between T_{-1} and T_{12} are described, irrespective of the initation of treatment (see paragraph 8.2.4).

Table 8.14 shows that there were slightly more SAEs in the heroin group than in the methadone group. A causal relationship (possible, probable or certain) between SAE and the study medication was assumed more often in the heroin group than in the methadone group: in 58 cases in the heroin group and in 15 cases in the methadone group (ratio 3.87:1). If these cases are brought in relation to the individual treatment days (cumulatively), a SAE related to the study medication occurred every 2,572 treatment days in the heroin group and every 6,501 days in the methadone group (ratio 1:2.53). Thus, a SAE with causal relationship occurred about 2.5 times more often in the heroin group than in the methadone group. All the 73 SAEs with a (possible, probable or certain) causal relationship with the study medication were reported to the BfArM.

Table 8.14
Causal relationship between SAEs and study medication for n=313 SAEs[a)]

Causal relationship with the study medication	Heroin		Methadone		Total	
	Number	%	Number	%	Number	%
None	81	45.8	97	71.3	178	56.9
Improbable	38	21.5	24	17.6	62	19.8
Possible	34	19.2	8	5.9	42	13.4
Probable	11	6.2	5	3.7	16	5.1
Certain	13	7.3	2	1.5	15	4.8
Total	**177**	**100.0**	**136**	**100.0**	**313**	**100.0**

a) For 2 SAEs of the methadone group of the total of 315 SAEs, no data on the relationship are available. In both cases, the SAE occurred after the end of treatment, so that no relationship exists.

The listing of initiated measures (see table 8.15) shows that SAEs led to a reduction or discontinuation of the study medication more often in the heroin group than in the methadone group.

Table 8.15
Measures related to the study medication for n=307[a)]

Measures	Heroin		Methadone		Total	
	Number	%	Number	%	Number	%
No change	30	17.1	67	50.8	97	31.6
Reduced	36	20.6	9	6.8	45	14.7
Increased	0	0.0	5	3.8	5	1.6
Temporarily discontin'd	71	40.6	12	9.1	83	27.0
Discontinued	6	3.4	2	1.5	8	2.6
Not applicable	32	18.3	37	28.0	69	22.5
Total	**175**	**100.0**	**132**	**100.0**	**307**	**100.0**

a) For eight (6 in the methadone group and 2 in the heroin group) of the total of 315 SAEs, no data on measures related to the study medication are available.

As to the outcome of the SAEs, table 8.16 shows that the condition prior to the SAE could be restored in a great proportion of cases in both treatment groups. In a smaller proportion, the initial condition could be restored with consequences.

Table 8.16
Outcome of the severe adverse event for n=315

Outcome of the SAEs	Heroin		Methadone		Total	
	Number	%	Number	%	Number	%
Restored	140	79.1	93	67.4	233	74.0
Restored with consequences	27	15.3	36	26.1	63	20.0
Ongoing	4	2.3	3	2.2	7	2.2
Patient died	5	2.8	3	2.2	8	2.5
Unknown	1	0.6	3	2.2	4	1.3
Total	**177**	**100.0**	**138**	**100.0**	**315**	**100.0**

8.2.3 Severe adverse events (SAEs) classified according to ICD-10

The SAEs were coded, analogous to the AEs, according the the ICD-10 (cf. table 8.7). The ICD-10 diagnoses were categorised according to the ICD-10 categories described in paragraph 8.1.2.1 and the frequency of their occurrence (see tables 8.17 and 8.18).

Table 8.17
Frequency of the SAEs according to the higher ICD-10 categories for n=315 (cf. paragraph 8.1.2.1, table 8.7)

Category	Heroin		Methadone		Total	
	Number	%	Number	%	Number	%
2	6	3.4	6	4.3	12	3.8
3	-	-	1	0.7	1	0.3
4	1	0.6	-	-	1	0.3
5	-	-	1	0.7	1	0.3
7	2	1.1	-	-	2	0.6
8	2	1.1	-	-	2	0.6
9	1	0.6	-	-	1	0.3
10	-	-	1	0.7	1	0.3
11	-	-	1	0.7	1	0.3
12	42	23.7	26	18.8	68	21.6
13	1	0.6	8	5.8	9	2.9
14	14	7.9	10	7.2	24	7.6
15	4	2.3	2	1.4	6	1.9
18	11	6.2	5	3.6	16	5.1
19	2	1.1	-	-	2	0.6
20	2	1.1	2	1.4	4	1.3
23	18	10.2	12	8.7	30	9.5
24	1	0.6	-	-	1	0.3
25	9	5.1	9	6.5	18	5.7
26	2	1.1	-	-	2	0.6
27	4	2.3	4	2.9	8	2.5
29	3	1.7	3	2.2	6	1.9
30	-	-	1	0.7	1	0.3
31	4	2.3	10	7.2	14	4.4
32	12	6.8	7	5.1	19	6.0
33	3	1.7	1	0.7	4	1.3
34	1	0.6	1	0.7	2	0.6
35	1	0.6	5	3.6	6	1.9
36	1	0.6	1	0.7	2	0.6
37	1	0.6	-	-	1	0.3
38	2	1.1	1	0.7	3	1.0
39	3	1.7	1	0.7	4	1.3
40	-	-	1	0.7	1	0.3
43	2	1.1	-	-	2	0.6
44	3	1.7	-	-	3	1.0
45	3	1.7	2	1.4	5	1.6
46	13	7.3	12	8.7	25	7.9
47	-	-	1	0.7	1	0.3
48	1	0.6	-	-	1	0.3
49	2	1.1	3	2.2	5	1.6
Total	**177**	**100.0**	**138**	**100.0**	**315**	**100.0**

Table 8.18

Frrequency of the SAEs according to the higher ICD-10 categories with respect to their connection[a)] with the study medication for n=313

Category	Heroin		Methadone		Total	
	No connection	Connection	No connection	Connection	No connection	Connection
2	6	-	6	-	12	
3	-	-	-	1	-	1
4	-	1	-	-	-	1
5	-	-	1	-	-	1
7	2	-	-	-	2	-
8	2	-	-	-	2	-
9	1	-	-	-	1	-
10	-	-	1	-	1	-
11	-	-	1	-	1	-
12	11	31	19	6	30	37
13	1	-	7	1	8	1
14	14	-	8	2	22	2
15	4	-	2	-	6	0
18	1	10	4	1	5	11
19	2	-	-	-	2	-
20	2	-	2	-	4	-
23	14	4	12	-	26	4
24	1	-	-	-	1	-
25	9	-	8	1	17	1
26	2	-	-	-	2	-
27	3	1	4	-	7	1
28	-	-	-	-	-	-
29	3	-	3	-	6	-
30	-	-	1	-	1	-
31	3	1	8	2	11	3
32	10	2	7	-	17	2
33	3	-	1	-	4	-
34	1	-	1	-	2	-
35	1	-	5	-	6	-
36	1	-	1	-	2	-
37	1	-	-	-	1	-
38	-	2	1	-	1	2
39	2	1	-	1	2	2
43	-	2	-	-	-	2
44	3	-	-	-	3	-
45	3	-	2	-	5	-
46	10	3	12	-	22	3
47	-	-	1	-	1	-
48	1	-	-	-	1	-
49	2	-	3	-	5	-
Total	**119**	**58**	**121**	**15**	**240**	**73**

a) „No connection“ describes the assessment categories: no or improbable relationship. „Connection“ describes the assessment categories: possible, probable or certain relationship.

Table 8.18 (see also list of patients under 2.2.1 in Annex II) shows that the most frequent SAEs with a causal relationship can be put down to an intoxication related to the basic disease (opioid dependency) – in 31 out of 58 cases (53%) in the heroin group and in 6 out of 15 cases (40%) in the methadone group. In the SAE reports, mainly respiratory depressions after intravenous heroin application with unclear co-use are described for the heroin group. In each case, the outcome of the SAE was described as "restored".
Another frequent cause for SAEs with causal relationship in the heroin group (10 of the 58 cases, 17%) are cerebral convulsions after i.v. heroin application, also often in connection with unclear co-use. In all the cases, the outcome of the SAE was described as "restored".
Both the respiratory depression and the cerebral convulsions after i.v. heroin application could be well treated by the physicians present at the outpatient centre; this was due to the stipulated dispensing order (controlled dispensing of heroin, supervised self-application by patient, obligation to stay at the site for 30 minutes after the application). The Safety Board dealt with the frequency of these two SAEs in the heroin group and came to the conclusion that there was no reason for terminating the study – these effects of medication were not unexpected and as patients were obliged to stay at the unit for half an hour after i.v. application, the SAEs could be medically adequately treated (Minutes of the Safety Board meeting on 21.10.2003).

8.2.4. Deaths

The following describes the 12 deaths (5 in the heroin group, 7 in the methadone group) that occurred during the first study phase. Seven of the 12 deaths (2 of the heroin group, 5 of the methadone group) occurred *after* discontinuation of study treatment or after randomisation *without* treatment initiation. The remaining 5 deaths (3 in the heroin group, 2 in the methadone group) occurred during the treatment period. Thus, a case of death occurred every 49,720 treatment days in the heroin group and every 48,757 days in the methadone group. A causal relationship with the study medication was excluded in 7 cases and considered improbable in 5 cases.
Four autopsies were performed, in three cases, there were no results going beyond the presumption diagnosis (see individual description in paragraph 8.2.4.1). Four expert opinions were procured in the case of the 44-year old woman with the randomisation no. 40046. All the death reports, including postmortem reports and expert opinions, were reported to the BfArM.
The distribution of deaths according to gender and medication is presented in table 8.19.

Table 8.19
Deaths during the first study phase according to gender and study medication

Study medication	**Women**	**Men**	**Total**
Heroin	1	4	5
Methadone	1	6	7
Total	**2**	**10**	**12**

The classification of the causes of death shows that in the majority of patients, the cause of their death is not known (see table 8.20). The reasons are that patients were either found dead

in their apartment and the public prosecutor did not order an autopsy, or the patients died after dropping out of the study and there are no further information.
The three deaths with mixed intoxication occurred outside of the current dispensing process. In one case, the patient injected non-prescribed methadone and died of methadone intoxication. Another case occurred after discontinuation of a long-term treatment and prior to the planned re-admission to the heroin study. The last case occurred in a female patient, who had never started the study treatment.
The deaths due to cardio-vascular failure were either attributable to the basic disease (coronary heart disease) or were the consequence of a severe grippal infection.

Table 8.20
Causes of death during the first study phase (n=12)

Cause of death	Number	Not in treatment	In treatment
Mixed intoxication	3	2	1
Accident	1	-	1
Complication of basic disease	2	1	1
Not known	6	4	2

Overall, there are no significant differences in the mortality rate between the heroin and the methadone group.

8.2.4.1. Individual description of the cases of death

Random. no.:	**10061**
Gender:	male
Age:	46 years
Treatment initiation:	07.01.2003 (heroin group)
Daily dose:	Not applicable (treatment dropped on 08.01.2003)
Date of event:	23.04.2003
Study medication immediately before event:	Not applicable
Symptoms, course, final condition:	Patient was admitted to hospital with abdominal trouble, died in hospital on the same day
Presumption diagnosis:	Complication of the basic disease
Emergency measures, treatment:	Operation
Causal relationship with study medication:	None
Relevant examination results:	Pseudomonas aeruginosa sepsis with multiple organic failure with ascending, purulent cholecystitis with cholecystolithiasis
Simultaneously administered medication:	None
Comments:	None

Random. no.:	**10129**
Gender:	Male

Age:	34 years
Treatment initiation:	Randomisation to the methadone group on 26.05.2003, patient died between randomisation and treatment initiation, did not receive any study medication
Daily dose:	Not applicable
Date of event:	On 09.06.2003 found dead in own apartment
Study medication immediately before event:	Not applicable
Symptoms, course, final condition:	Not known
Presumption diagnosis:	Not known
Emergency measures, treatment:	Not applicable
Causal relationship with study medication:	None
Relevant examination results:	None
Simultaneously administered medication:	None
Comments:	Information about death by mother

Random. no.:	**10133**
Gender:	Male
Age:	36 years
Treatment initiation:	10.06.2003 (methadone group)
Daily dose:	150 mg methadone, last medication on 13.01.2004
Date of event:	Found dead in own apartment on 05.02.2004
Study medication immediately before event:	Not applicable
Symptoms, course, final condition:	Not known
Presumption diagnosis:	Not known
Emergency measures, treatment:	Not applicable
Causal relationship with study medication:	Improbable
Relevant examination results:	None
Simultaneously administered medication:	Chlorprothixen, zoplicon
Comments:	None

Random. no.:	**30025**
Gender:	Male
Age:	45 years
Treatment initiation:	26.09.2002 (methadone group)
Daily dose:	Not applicable (excluded from study on 7.04.2003)
Date of event:	03.10.2003
Study medication immediately before event:	Not applicable
Symptoms, course, final condition:	Not known
Presumption diagnosis:	Not known
Emergency measures, treatment:	Not known
Causal relationship with study medication:	None
Relevant examination results:	None
Simultaneously administered medication:	Not known
Comments:	Patient was excluded from the study on 07.04.2003 for stealing from a member of the

	unit staff

Random. no.:	**30067**
Gender:	Male
Age:	41 years
Treatment initiation:	26.09.2002 (heroin group)
Daily dose:	1000 mg i.v. heroin
Date of event:	14.12.2002
Study medication immediately before event:	Not applicable, last dose on 11.12.2002 (600 mg)
Symptoms, course, final condition:	Not known
Presumption diagnosis:	Not known
Emergency measures, treatment:	Not known
Causal relationship with study medication:	Improbable
Relevant examination results:	According to the postmortem report, patient suffered from myocarditis and pneumonia, which can be considered to be the cause of death.
Simultaneously administered medication:	Berodual
Comments:	Patient was found dead by mother in own apartment

Random. no.:	**30087**
Gender:	Male
Age:	35 years
Treatment initiation:	No external interview at T_{-1}, did not show up again after randomisation to methadone group on 31.10.2002, excluded from analysis
Daily dose:	Not applicable
Date of event:	06.07.2003
Study medication immediately before event:	Not applicable
Symptoms, course, final condition:	Not known
Presumption diagnosis:	Not known
Emergency measures, treatment:	Not known
Causal relationship with study medication:	Not applicable
Relevant examination results:	None
Simultaneously administered medication:	Not known
Comments:	A staff member of a drug counselling service reported patient's death

Random. no.:	**40046**
Gender:	Female
Age:	44 years
Treatment initiation:	13.06.2003 (heroin group)
Daily dose:	460 mg i.v. heroin
Date of event:	15.08.2003
Study medication immediately before event:	230 mg i.v. heroin (12:20 h)

Symptoms, course, final condition:	Fall on underground rails around 13 h, died in hospital at 14:28 h
Presumption diagnosis:	Hepatic cirrhosis, distinctly enlarged spleen, swelling and hemorrhage over central and left backward body parts just above pelvis, splenic rupture and fragmentation, rupture in left kidney, 1.5 l blood in abdominal cavity with distinct anemia in tissues [main diagnoses]
Emergency measures, treatment:	Dose of naloxone, flumazenil, etomidate, midazolam, dopamine, epinephrine
Causal relationship with study medication:	Improbable (assessment of medical investigator)
Relevant examination results:	When leaving heroin outpatient unit 40 minutes afer heroin application, no sign of intoxication (clinical assessment of medical investigator)
Simultaneously administered medication:	Zerit, epivir, ziagem, cotrim forte, dominal
Comments:	Several expert opinions were procured for this death case:

1. Postmortem report of the institute for forensic medicine of the Johann Wolfgang Goethe University (Institut für forensische Medizin im Klinikum der Johann Wolfgang Goethe Universität), Frankfurt/Main, Prof. Dr. med. Hansjürgen Bratzke:
1.5 l of liquid blood was found in the abdominal cavity, which was caused by rupture and partial fragmentation of the spleen. The left kidney also haemorrhaged in its capsule and ruptured. The fall on rails could be suited to cause this picture of injuries. Whether there was an immediate connection between the administration of drugs and the fall will have to be cleared by a chemico-toxicological expert survey.

2. Chemico-toxicological expert survey of the institute for forensic toxicology, department of forensic medicine of the Johann Wolfgang Goethe university (Institut für Forensische Toxikologie, Zentrum für Rechtsmedizin, Klinikum der Johann Wolfgang Goethe Universität), Frankfurt am Main, Prof. Dr. med. G. Kauert:
An extremely high concentration of free morphine was ascertained in the blood, which could have led to the clouding of consciousness resulting in the fall, so that the intoxication was seen as the cause for the death by the expert. The significance of the interaction between diamorphine and the benzodiazepines also taken was emphasised. A determination of free morphine values was performed in ten comparable probands of the heroin group, but no unusual values of free morphine were found (result only orally communicated to the heroin outpatient service, Dr. Zokai, by Prof. Kauert).

3. Report by DiaMo Narcotics GmbH, Dr. Markert:
An expert statement does not see a causal influence of the last diamorphine application on the death.

4. Chemico-toxicological second expert opinion (recommended by the Safety and Advisory Boards) by the university hospital Zurich, Dept. for internal medicine, PD. Dr. med. Karin Fattinger:
Due to the contradiction between the clinical assessment (there was no intoxication when leaving the heroin outpatient unit 40 minutes after the heroin application) and the chemico-toxicological assessment (death caused by clouding of consciousness due to intoxication, leading to the fall), and on recommendation by the Safety & Advisory Board, the sponsor commissioned a second chemico-toxicological expert report. This report comes to the conclusion that a connection between the administration of diamorphine and the fall is not probable and that acute drug intoxication did not exist. The extremely high concentration of free morphine is most likely attributable to a postmortal deglucuronidation of morphine-3 glucoronide. The high value of free morphine could not be explained by the diamorphine dose, even in case of hepatic cirrhosis.

Random. no.:	**40076**
Gender:	Male
Age:	35 years
Treatment initiation:	Randomisation to the methadone group on 18.09.2003, did not show up for treatment
Daily dose:	Not applicable
Date of event:	Found dead in own apartment on 23.08.2004
Study medication immediately before event:	Not applicable
Symptoms, course, final condition:	Not known
Presumption diagnosis:	Not known
Emergency measures, treatment:	Not applicable
Causal relationship with study medication:	None
Relevant examination results:	None
Simultaneously administered medication:	Not known
Comments:	None

Random. no.:	**50065**
Gender:	Male
Age:	31 years
Treatment initiation:	07.10.2002 (heroin group)
Daily dose:	560 mg i.v. heroin, last on 13.05.2003
Date of event:	Found dead in own apartment on 13.11.2003
Study medication immediately before event:	Not applicable
Symptoms, course, final condition:	Not known
Presumption diagnosis:	Intoxication
Emergency measures, treatment:	Not applicable
Causal relationship with study medication:	None
Relevant examination results:	None
Simultaneously administered medication:	Not known
Comments:	Patient received heroin up to 13.05.2003, from 14.05-21.05.03 he received methadone daily. From 21.05.-23.06.03 detoxification

	followed by withdrawal treatment from 23.06.-08.11.03, which he discontinued prematurely

Random. no.:	**50077**
Gender:	Male
Age:	38 years
Treatment initiation:	11.11.2002 (methadone group)
Daily dose:	110 mg methadone
Date of event:	21.10.2003
Study medication immediately before event:	110 mg methadone
Symptoms, course, final condition:	Cardiac trouble, admission to hospital, died there
Presumption diagnosis:	Complication of basic disease (rupture of aortic dissection with subsequent pericardial tamponade)
Emergency measures, treatment:	Emergency treatment with resuscitation attempt
Causal relationship with study medication:	Improbable
Relevant examination results:	Pericardial tamponade
Simultaneously administered medication:	None
Comments:	Postmortem performed on 30.10.2003 by the institute for forensic medicine of the university of Cologne, there were no secondary findings

Random. no.:	**60099**
Gender:	Male
Age:	38 years
Treatment initiation:	28.03.2003 (heroin group)
Daily dose:	70 mg i.v. heroin (updosing phase)
Date of event:	Found dead on 30.03.2003 at 9:40 h
Study medication immediately before event:	25 mg i.v. heroin on the night of 29.03.2003
Symptoms, course, final condition:	Found dead in hostel for the homeless
Presumption diagnosis:	Mixed intoxication due to additionally taken methadone
Emergency measures, treatment:	Not applicable
Causal relationship with study medication:	Not probable
Relevant examination results:	Oxigen saturation (SPO2) after last heroin application 96%, no indication of intoxication by study medication
Simultaneously administered medication:	Doxepine at night
Comments:	Postmortem on 10.04.2003 by the institute for forensic medicine of the Rheinische Friedrich-Wilhelms-Universität, no further findings beyond the presumption diagnosis

Random. no.:	**80057**
Gender:	Female
Age:	40 years
Treatment initiation:	Randomisation to the methadone group on 20.01.2003, treatment not initiated, revocation, no external interview at T_{-1}, excluded from analysis
Daily dose:	Not applicable
Date of event:	11.02.2003
Study medication immediately before event:	Not applicable
Symptoms, course, final condition:	Found dead in public washroom
Presumption diagnosis:	Intoxication
Emergency measures, treatment:	Rescucitation attempt by emergency doctor
Causal relationship with study medication:	None
Relevant examination results:	Narcotic intoxication
Simultaneously administered medication:	Not known
Comments:	Postmortem on 20.02.2003 by the institute for forensic medicine of the university of Munich, no findings beyond the narcotic intoxication

8.2.5 Evaluation

During the first study phase, a greater number of severe adverse events (SAEs) occurred in the heroin group than in the methadone group. For the safety assessment of a medication, mainly those SAE have to be considered where a causal relationship with the medication is suspected. Overall, SAEs with causal relationship occurred about 4 times as often in the heroin group than in the methadone group. But since treatment periods in the methadone group were distinctly shorter on average, the number of SAEs with causal relationship has to be seen in relative terms. But even if individual treatment days are considered, SAEs with causal relationship occur about 2.5 times as often in the heroin group than in the methadone group. Cerebral convulsions and respiratory depressions immediately after i.v. heroin application are most often responsible for the SAEs; these are not unexpected medication effects of diamorphine that can occur mainly in case of not reported co-use of benzodiazepines (respiratory depression), alcohol or cocaine (convulsions); they can easily be clinically treated due to patients' obligation to stay at the outpatient heroin unit for 30 minutes after application.

Concerning mortality, there is no indication of a difference between heroin and methadone groups. Mortality is just above 1% and thus in the lower range of the estimated mortality between 1%-3% for opioid dependency and comparable to the mortality in heroin-assisted treatment in Switzerland (Rehm et al. 2005). This is of great significance because, based on the inclusion criteria, the sample of patients recruited for this study consists of severely ill opioid addicts, where higher mortality might have been expected. In particular it must be emphasised that no death occurred with causal relationship with the study medication.

8.3 Safety conclusions

The safety of the study medication can be easily represented in terms of the documented adverse events (AEs) and mainly the severe adverse events (SAEs). It must be stated first of all that the very high number of AEs and SAEs, in particular the high number of events with no causal relationship with the study medication, indicates that no so-called underreporting occurred. It can, therefore, be assumed that the documentation of the AEs/SAEs with a causal relationship is complete.

The number of AEs and SAEs shows that a higher number of (severe) adverse events occurred in the heroin group. But since the retention rate in the heroin group was slightly higher, the relationship between AEs and SAEs respectively in the heroin and methadone groups must be corrected. The frequency of AEs was about the same in both groups, but SAEs occurred more often in the heroin group.

For the evaluation of the safety of a study medication, the AEs and SAEs with a causal relationship with the study medication are of relevance. This included all AEs and SAEs where the medical investigator documented a possible, probable or certain relationship with the study medication. This was the case for 21.3% of the AEs and 23.2% of the SAEs. The events with a causal relationship with the study medication occurred more often in the heroin group than in the methadone group, for AEs 1.3 times as often and for SAEs 2.5 times as often. Based on the frequency of events, it can thus be stated that treatment with injectable heroin represents a higher safety risk compared to treatment with oral methadone.

A closer examination of the events with causal relationship reveals an accumulation of respiratory depressions and cerebral convulsions in the heroin group. These events occurred immediately, within a few minutes after the application of heroin in the outpatient study centres and are most often attributable to non-reported co-use of benzodiazepines (which can lead to respiratory depressions) or cocaine (which can produce cerebral convulsions). The relative withdrawal or short-term discontinuation of alcohol or benzodiazepines can also produce cerebral convulsions. Both kinds of events are effects of medical drugs, not unexpected in i.v. heroin application, and can be easily controlled by the medical investigator in attendance at the outpatient heroin treatment unit. It is, therefore, important that heroin patients stay on the premises for about 30 minutes after application. The (safety) risk can thus be medically controlled.

It should, however, be emphasised that the occurrence of events such as respiratory depression and cerebral convulsions is at least as frequent for street heroin. Due to the low (or uncertain) degree of purity of street heroin, these complications are probably much more frequent. As the patients included in the study all regularly injected street heroin prior to the study treatment (partly despite methadone treatment), the relative safety risk of the medical application of pure heroin has to be considered also under this aspect. In particular, methadone patients with additional i.v. use of street heroin probably experience rather often respiratory depression or a cerebral convulsion. At the best, convulsions are experienced without severe consequences due to their limited duration, and the initial condition is restored without any medical documentation.

Mortality rates are of major importance when assessing the safety of a study medication. The mortality rate of the present study was 1.2% in the first study phase, with 5 deaths in the heroin group and 7 deaths in the methadone group. In comparison, mortality rates among opioid addicts are in general between 1%-3%. Considering the very bad health condition of the study participants and their long drug career, the mortality rate within the study is rather low. In the course of treatment, 3 deaths occurred in the heroin group and 2 in the methadone group. As the total number of treatment days in the heroin group was higher by about 50%, this difference must be seen in relative terms. For the safety of the study medication, it is of major importance that no death was assessed as having a causal relationship with the study medication.

To conclude, it must be stated that heroin treatment involves a somewhat higher safety risk than methadone treatment. This is mainly due to the intravenous form of application. The rather frequently occurring respiratory depressions and cerebral convulsions are not unexpected and can easily be clinically controlled. Overall, the mortality rate was low during the first study phase, and no death occurred with a causal relationship with the study medication. Compared to much higher health risks related to the i.v. application of street heroin, the safety risk of medically controlled heroin prescription has to be considered as low.

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Annexes

- Annex II – Patient data
- Study protocol no. ZIS-HV9-0701
- Amendments no. ZIS-HA9/1 to ZIS-HA9/7, ZIS-HA9/9, ZIS-HA9/10, ZIS-HA9/13 and ZIS-HA9/14
- Statistical analysis plan, version 3
- Monitoring Conventions
- Self Evident Corrections (med-CRF, ext-CRF, special study criminology)