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

Clinical study report

of the second 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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Hamburg, September 2006

Zentrum für Interdisziplinäre Suchtforschung der Universität Hamburg (ZIS)

Contents

Abbreviations

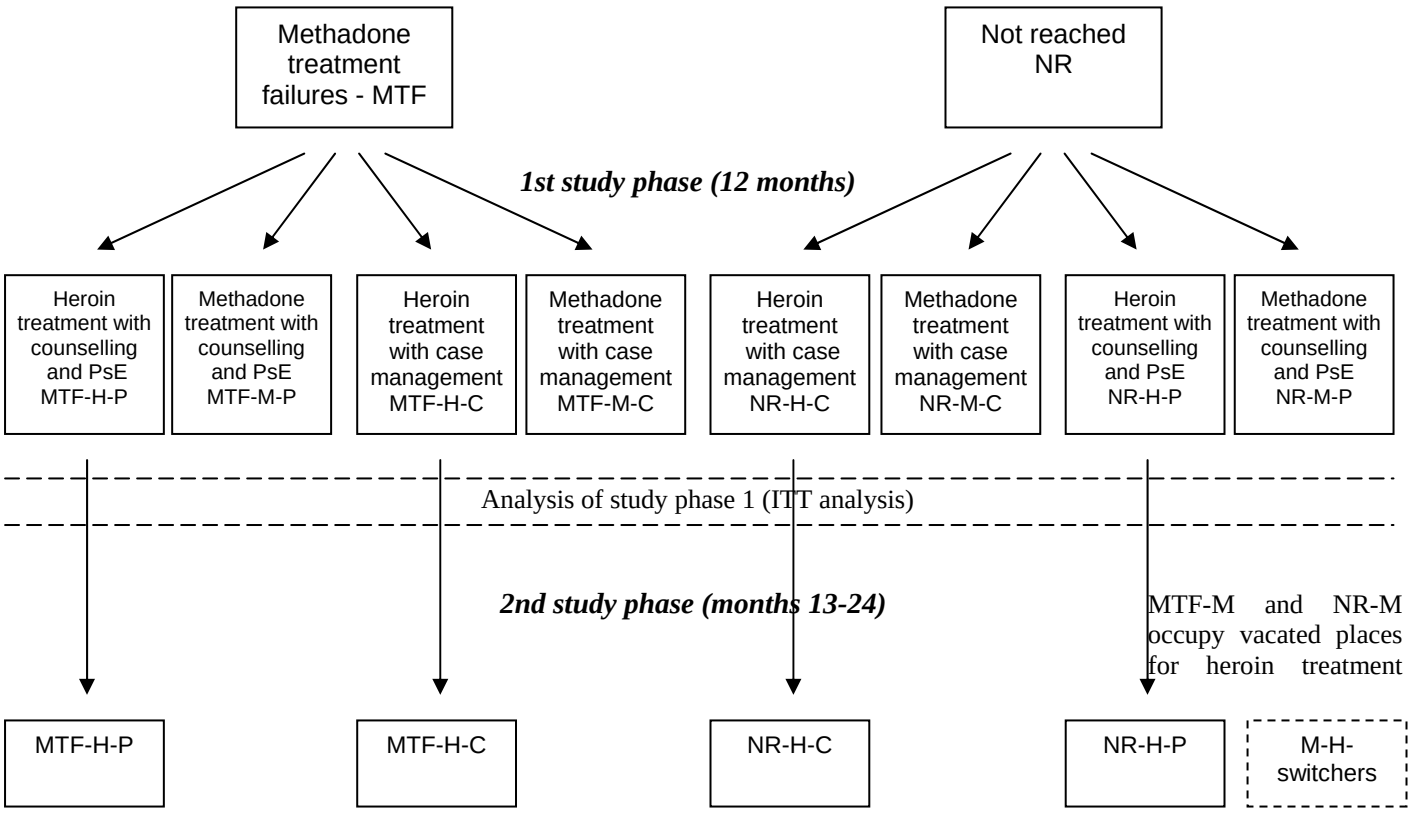
Aids: Acquired Immune Deficiency Syndrome
AMG: Arzneimittelgesetz
ASI: Addiction Severity Index
BfArM: Bundesinstitut für Arzneimittel und Medizinprodukte (regulatory authority)
BMI: Body-Mass-Index
BtMG: Betäubungsmittelgesetz
CGI: Clinical Global Impression
CIDI: Composite International Diagnostic Interview
CRF: Case Report Form
CS: Composite Scores
EKG: Electrocardiogramm
EuropASI: European Addiction Severity Index
GCP: Good Clinical Practice
GSI: Global Severity Index
HIV: Human Immunodeficiency Virus
ICD: International Classification of Diseases
ICH: International Conference on Harmonization
CI: confidence-interval
LOCF: Last Observation Carried Forward
LogReg: Logistic Regression
OR: Odds-Ratio
OTI-HSS: Opiate Treatment Index Health-Symptoms-Scale
P1: first study phase
P2: second study phase
POM: Primary Outcome Measure
SCL-90-R: Symptom-Check-List (revised)
SOP: Standard Operating Procedure
SOWS: Short Opiate Withdrawal Scale
WHO: World Health Organization

Résumé

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 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 benefitted 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 vs. control group: methadone) and psychosocial treatment (psychoeducation/drug counselling vs. case management/motivational interviewing). As a result, there were eight groups with 12 months of study treatment within the first study phase (see figure 0.1 below).

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



At the end of this period, patients, who had completed the entire programme of phase one, started the second study phase, also over a period of 12 months. Patients of the experimental group were able to continue heroin treatment, patients of the control group had the opportunity to occupy vacated heroin treatment places. Subsequent to the second study phase, heroin

assisted treatment could be continued in a follow-up phase of individual treatment. This follow-up phase will cease with the definite licence decision (and the establishment of the legal requirements).

A total of 434 patients started the second study phase, 344 continued heroin assisted treatment (79.3%) and 90 patients switched from methadone treatment (20.7%). According to the study design of the second phase (cf. figure 0.1), the 434 patients were distributed to four groups of about equal size: stratum MTF, heroin treatment with psychoeducation (27.2%); MTF, heroin treatment with case management (23.5%); NR, heroin treatment with psychoeducation (23.0%); NR, heroin treatment with case management (26.3%).

As expected, patients of the second study phase had a higher retention rate in the second year of treatment. Four fifths of them regularly concluded the study treatment of the second phase. Related to all the 515 patients ever randomised to the heroin stratum, 55% were still in treatment after 24 months. The retention rate was 10% higher among MTF patients than among NR patients.

A comparison between switchers from methadone to heroin after the first study phase with patients, who received heroin for the entire 2-year period, shows that the switchers succeed in catching up with the 2-year heroin patients in the second year of treatment (under heroin medication). In contrast to the results after 12 months, no significant differences could be detected between the 2-year heroin patients and the methadone-heroin switchers with respect to the outcome criteria health improvement and reduction of illicit drug use after 24 months. The analysis of the “switcher group” thus provides independent scientific-methodological evidence of the superiority of heroin treatment over methadone treatment. Both groups achieved more, statistically significant improvements or stabilisation of the existing changes during the second year of treatment. Risk behaviour related to intravenous drug use (sharing of needles and injection equipment) is completely dropped.

The second study phase focuses on the effects of the 2-year heroin treatment. The average daily dose of diacetylmorphine is 452 mg during the entire 2-year period. Additionally, 7 mg of methadone were prescribed on average relating to all the days of heroin dispensing. The heroin dose continuously decreases during the 24 months, while the average dose of methadone slightly increases. Not only the health situation of heroin patients stabilises or improves during the second study phase but also their social situation continues to take a positive course. Their housing situation stabilises, social contacts slightly increase and leisure occupations develop positively. But the problem of loneliness stays with many heroin patients. Two thirds have no steady partner and one tenth no reliable friends. This indicates that the process of social integration outside the drug context is a slow one.

The professional situation develops in a remarkable extent. Against the background of a difficult labour market situation, the increase of patients in regular jobs by 11%, attaining 27% after 2 years of heroin treatment, is a genuine success. Among the patients assessed as “fit for work”, the proportion of wage earners even increased from 25% to 43%. This demonstrates that heroin treatment in connection with psychosocial treatment has a direct and indirect (through health improvement and restoration of fitness for work) positive effect on the working situation.

The two types of psychosocial treatment – psychoeducation and drug counselling; case management and motivational interviewing – are intensively utilised by the heroin patients. Treatment satisfaction is slightly higher in patients who received case management. During the first study phase, no differences in the primary outcome criteria were found between the types of psychosocial treatment, but after 24 months, the situation is different. Treatment success is greater in patients, who received drug counselling and participated in psychoeducative groups. This result is independent of centre effects and raises questions regarding the optimisation of psychosocial treatment offers.
With respect to the safety of medication, (severe) adverse events generally declined during the second study phase. Switching from methadone to heroin hardly involves new complications for the patient. The reason could be effects of habituation both in patients and in treatment personnel (concerning the handling of patients and of medication) as well as selection effects, since patients prone to complications are more likely to have dropped out earlier. The mortality rate of the second study phase is also 1%, no death was found to have a causal relationship with the study medication.

The results of the second study phase confirm and substantiate the findings of the comparative study of the first phase in an impressive way. Heroin-assisted treatment proves to be decidedly successful in the treatment of the most severely dependent heroin users. With the introduction of heroin-assisted treatment as an approved treatment option, the “selection mechanism” related to study conditions will no longer exist and examinations will be less elaborate so that acceptance of this type of treatment is likely to increase even more. The inclusion criteria and quality standards of heroin-assisted treatment proved to be effective and should be maintained in regular treatment – until more recent findings suggest modifications.
Meanwhile, several studies found scientific evidence of the positive effects of heroin treatment; therefore, the necessary health policy steps towards creating the legal pre-conditions for the implementation should be initiated without delay. Delays lead to a vague situation – especially for patients and professionals of the treatment units – so that it becomes difficult to carry on treatment and support in an ethically responsible way. In accord with the assessments and requirements of numerous internal and international experts and the representatives of doctors, treatment institutions and addiction associations, the evaluation of the positive results of both study phases of the German model project leads to the explicit recommendation to include this type of treatment into the treatment catalogue for heroin-dependent patients.

1. Introduction

After the positive vote of the Ethics Committee in Hamburg in Summer 2001 and the authorisation by the BfArM to conduct the model project of heroin assisted treatment in accordance with the submitted study protocol (Krausz et al. 2001) and according to § 3 section 2 of the BtMG, administrative and practical preparations were intensified in the participating centres. Within a short time, the recruiting phase started with the screening of potentially qualified heroin users. In March 2002, heroin assisted treatment was initiated in the first patient in Bonn. The study partners in Karlsruhe, Munich, Hanover, Cologne and Hamburg successively opened their treatment centres in the summer of 2002. The 7th study centre opened in Frankfurt in February 2003. The recruiting phase was completed at the end of 2003. A total of 1,032 study participants were randomised. At the end of 2004, all patients had run through their first year of treatment. With the compilation of the clinical study report in the summer of 2005 (and the revision in January 2006), the first study phase with the control group comparison between heroin and methadone treatment was closed (Naber & Haasen 2006). It established evidence of the superiority of heroin-assisted treatment over methadone treatment with respect to health improvement and reduction of illicit drug use. This report was a component part of the licence application submitted by the drug company to the BfArM. Based on the results of the first study phase, the BfArM concluded the expert examination with a positive assessment. Since at present, trafficking and application of this medication would violate § 25 section 2 Nr. 7 AMG (because the necessary legal amendments are pending), the licence application is suspended for the time being.
All patients included in the second study phase (with exclusively heroin-assisted treatment) concluded their second year of treatment at the end of 2005. The results of the 2-year course of all the 434 patients, who started the treatment of the second study phase, constitute the main content of the present report. It focuses on the long-term effects of heroin-assisted treatment in terms of health and psychosocial stabilisation and reduction of co-use and on the comparison between patients treated with diacetylmorphine for 24 months and patients, who switched from methadone to heroin after the first study phase. The study was conducted according to the guidelines of “Good Clinical Practice” (GCP) (ICH 1996).
All study patients, who remained in the heroin-assisted treatment, are presently in the follow-up phase, which, based on a study protocol amendment, continues until December 31, 2006.

The successful conduction of the two phases of the German heroin project was only possible because of the great commitment of many actors, to whom we gratefully give our thanks. First of all, we want to draw attention to the patients, who took upon themselves a randomisation procedure often experienced as “threatening” in order to participate in the study, which many of them concluded. Many of them did not shy away from the numerous scientific examinations and interviews, even prior to the study treatment, and thus considerably contributed to the success of the model project.
The implementation process of the study protocol required great commitment of the medical investigators and the staff at the treatment centres. They were the backbone of the study be-

cause they supported their patients' cause all through the treatment implementation, the elaborate recruiting process and normal everyday treatment; moreover, they performed a major part of the evaluation work. We also greatly appreciated the monitors' part, whose important work for the study's quality assurance was not always easy considering the great amount of study documents.
The sponsor of the project, the DLR, particularly contributed to the success of the model project. Their competent managing supported the work of the scientific study coordinators and helped to successfully cope with the overall coordination and difficult processes of policy mediation.
The members of the international advisory board were also of great importance to the overall success. They offered their scientific advice during the design and implementation process of the study and assisted in overcoming occasional methodological-conceptional obstacles.
And last not least, we should mention the authorities that supported the project financially – 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 regional and federal representatives of these institutions and the representatives of the special departments of the federal states and local authorities not only achieved the decisions and provided the funds, but also showed great personal involvement in the model project and championed the continuation of heroin-assisted treatment.

1.1 Background and state of knowledge on heroin-assisted treatment – recent results and developments

In addition to the findings from the United Kingdom, Switzerland and the Netherlands, more recent experiences concerning the prescription of heroin to opioid dependent patients are now available, e.g. various results of the first phase of the German model project (Naber & Haasen 2006), results of collateral studies of this project and the results of the Spanish study now published (March et al. 2006). As for the Canadian study that started in 2005, information on implementation and feasibility of the study protocol are available but not yet patient related results. A compilation of the reviews on experiences with heroin treatment presented in the study protocol (Krausz et al. 2001), the report of the first study phase (Naber & Haasen 2006) and more recent results will be presented hereafter.
The results of the first 12-month study phase of the German model project for heroin-assisted treatment in opioid-dependent patients, so far the largest randomised control group study including 1,032 patients, compare the effects of heroin treatment with methadone maintenance treatment. The first study phase investigated the central question whether the prescription of pharmacologically pure heroin in a structured treatment setting in heroin dependent patients, who did not sufficiently benefit from methadone treatment, or those, who are not reached by the treatment system, would have greater effects in terms of health stabilisation and reduction of illicit drug use than methadone treatment. The central result of the German model project provides evidence of the superiority of heroin treatment over methadone treatment in both primary target criteria. Heroin treatment had significantly higher response rates both with re-

spect to health (heroin: 80.0%, methadone: 74.0%) and the reduction of illicit drug use (heroin: 69.1%, methadone: 55.2%).

The retention rate of heroin treatment after 12 months was 67% and slightly lower than in the Dutch and Swiss studies. Only 39% of the patients of the methadone group conclude their study treatment; however, it should be kept in mind that 39% of the heroin dropouts and 44% of the methadone dropouts were in maintenance treatment outside the study or in some other addiction treatment at T_{12}. Moreover, heroin patients apparently were better able to disengage themselves from the drug scene. After 12 months, half of the heroin patients no longer visited the drug scene, 60% of the methadone patients still had contacts to the drug scene (Naber & Haasen 2006).

An in-depth comparison between heroin and methadone treatment (Löbmann 2006) explored the development of self-reported delinquency during the first year of treatment. A marked decline of various offences was found for both treatment groups: Compared to the preceding year, slightly less than two thirds of the persons committed frauds, robbed other persons or dealt with hard or soft drugs. They were less involved by about 50% in assaults, shoplifting or thefts from private persons. Overall, 80% of the test persons committed offences in the year preceding treatment; during the first year of treatment, their number declined to 46% in the heroin group, and 63% in the methadone group. The number of offences also markedly declined: In the previous year, participants of the heroin group committed on average a total of 77 offences; the number dropped to 27 in the first year of treatment. In contrast, the average number of offences in methadone patients declined from 80 to 50. Overall, both the number of regular and of occasional offenders declined. Thus, the decline of delinquency was more marked in patients, who received heroin-assisted treatment than in the methadone control group (Löbmann 2006). These results of the (quantitative) dark field analysis on the decline of delinquency under study treatment were confirmed for the German model project by a qualitative study. 92% of the qualitative interviews were assessed as authentic. For most participants, a marked decline of delinquency could be assumed (Köllisch & Kreuzer 2006).

A differentiated examination of the psychosocial concomitant treatment (Kuhn et al. 2006) showed the influence of psychosocial treatment (PST) on treatment results; the different settings of psychosocial treatment – psychoeducation with drug counselling (PE/DC) or case management with motivational interviewing (CM/MI) – proved to have no relevance for the overall treatment success. Patients, who were randomised to the heroin group, were more willing to utilise the offers of psychosocial treatment than patients of the methadone group. This correlates with the utilisation of medical treatment. A total of 23% of the patients did not utilise the treatment with PE/DC and 20% the CM/MI treatment. The overall retention rate of PST was 43% in the first year of treatment. While the retention rate of the heroin branch did not significantly differ between PE/DC and CM/MI, there was a difference in the methadone branch between the two types of psychosocial treatment: Methadone patients, who received case management and motivational interviewing stayed on average longer in psychosocial concomitant treatment (Kuhn et al. 2006).

Moreover, in the context of the first study phase, cost effectiveness of the heroin and methadone treatment was investigated from a societal perspective. Both types of treatment were found to be cost-effective due to the increase of health related quality of life (v. d. Schulen-

burg & Claes 2006). For those, who remained in treatment for 12 months, the average annual costs under study conditions were 18,060 Euro for each participant of the heroin treatment and 6,147 Euro for each participant of the methadone treatment. Compared to these costs, savings in the heroin group related to health, delinquency, incarceration and court costs amounted to a total of 6,017 Euro per annum. On the other hand, the methadone group caused additional costs of 2,347 Euro a year. Unlike e.g. the Dutch project (Dijkgraaf et al. 2005), the German model project could not demonstrate that the higher treatment costs for heroin-assisted treatment are directly overcompensated by economies related to police and justice and by less damage to victims. Nonetheless, from a societal perspective, the health-economical investigation expects a medium-term economy from the introduction of heroin-assisted treatment into the catalogue of standard treatment (v. d. Schulenburg & Claes 2006). If, in the context of the cost-benefit analysis, the quality of life gained through treatment (measured by an index instrument unrelated to a specific illness and preference-based, the EQ-5D) is related to the costs incurred, it appears that through the additional treatment costs of heroin-assisted treatment, a higher level of health related quality of life could be attained. The cost-benefit relations show that in the heroin-assisted treatment, fewer funds were necessary to reach an increase by one quality-adjusted life-year (QALY) than in methadone maintenance treatment (heroin: 153,934 Euro per QALY; methadone: 178,672 Euro per QALY) (v. d. Schulenburg & Claes 2006).

Overall, available results of concomitant studies of the first study phase of the German model project confirm the superiority of heroin treatment for a group of heroin addicts with considerable health and social burdens and previous treatment failures.

In Andalusia (Spain), a randomised control group study investigating the effects of heroin-assisted treatment compared to methadone treatment was concluded at the end of 2004 (March et al. 2006). The results have now been published. The recruitment of 240 heroin addicts in two treatment centres (Granada and La Linea), as planned in the original design, could not be realised because of the noticeable decline of intravenous drug use in the region. 176 users were recruited for the screening procedure outside the treatment centres “on the street”. Most of them could not be included in the study (one third because of the inclusion criteria requiring evidence of two previous methadone treatments, and another third dropped out in the course of the lengthy recruiting process). Finally, 62 patients were included in the study and randomised to the two study branches. 31 patients were allotted to the experimental group (i.v. diamorphine twice a day and optional oral methadone) and 31 patients to the control treatment (oral methadone once a day). The medication was dispensed during 9 months. 50 of the 62 patients were followed-up (experimental group n=27; control group n=23). The central areas of investigation were health, quality of life, drug related problems, use of street heroin, risk behaviour (HIV, HCV) and the mental, familial and social situation. Following the Dutch study, a dichotomous, multidimensional target criterion was construed: Response was defined as a 20% improvement of the ASI composite scores in the fields of health or mental or familial level of functioning (with no simultaneous deterioration by 20% in one of these areas).

The analysis of the Andalusian model project shows that both groups improved in the central areas of investigation. However, in the experimental group, the health situation improved

more significantly and risk behaviour decreased more markedly than in the control group. Moreover, street heroin use declined more significantly in the experimental group (from 25 to 8 days per month), and heroin patients clearly experienced fewer days with drug related problems during the last month. Concerning delinquency, there was a (statistically not significant) trend towards the superiority of the experimental group (reduction by 12 days to less than one day per month) compared to the methadone group (reduction from 8 to 4 days per month). The experimental group included a greater proportion of responders (70.4% vs. 60.9%) with respect to the primary dichotomous target criterion, but this difference is not statistically significant, a.o. because of the small sample size strongly divergent from the methodologically planned number of cases. Although the Spanish study did not meet the primary target criterion, its individual results are additional evidence of the feasibility and safety of heroin-assisted treatment for the group of most severely dependent patients.

More recent analyses of the Dutch study results confirm the superiority of heroin-assisted treatment for a special group of patients. The study by Blanken et al. (2005) combined the two randomised control group studies with injectable and inhalable heroin. This resulted in n=174 patients, who received heroin and methadone (experimental group) and n=256, who received only methadone (control group). The treatment response was defined in accordance with the individual studies in a dichotomous, multidimensional target criterion in terms of improvement of the physical, mental or social state of health by (at least) 40% compared to baseline (without simultaneous deterioration by 40% in one of these areas and without increase of cocaine use). After 12 months, the number of responders in the experimental group was significantly higher: 51% vs. 28% in the control group. The physical and mental health of the responders treated with heroin reached, after 12 months, a level that is comparable to the general health situation of the Dutch population. The proportion of patients, who improved to such a degree that they did no longer meet the health related inclusion criteria, was by 18% higher in the heroin group than in the methadone group. Even in the worst-case scenario, where all heroin patients not reached for the 12-month examination were considered as non-responders and all methadone patients not reached as responders, the heroin group (51%) was still significantly superior to the methadone group (35%).

The present report of the second study phase focuses on the long-term effects of heroin-assisted treatment. A reference point is the 6-year follow-up study by Güttinger et al. (2002; 2003) on the long-term effects of heroin-assisted treatment in Switzerland. In this study, out of the 366 patients, who initiated treatment between January 1994 and March 1995, 148 (40.4%) were still in heroin-assisted treatment after 6 years. 175 (47.8%) had meanwhile left the treatment, 43 (11.7%) patients died in the observation period (5 of them participated in the heroin programme at the time of their death). Almost 83% of the patients could be interviewed again, on average 6.3 years after their (first) treatment initiation. With respect to the long-term goals of heroin treatment, it is of particular importance that a relevant proportion of the persons, who had concluded heroin treatment, took up abstinence-orientated treatment (24.3%) and another 21.6% switched to methadone maintenance treatment. A general finding of this long-term study is that patients succeeded in stabilising the positive effects that occurred after 12-18 months over a longer period of time (Rehm et al. 2001). It should be particularly emphasised that patients, who had left the heroin treatment (after an average treat-

ment duration of 2.4 years), showed positive developments in their life situation and the reduction of illicit drug use comparable to those of patients, who were still in treatment after 6 years. It is true that the proportion of daily users of (additional) street heroin was, with 18.9%, significantly higher in the group of concluders than in the group of treatment participants (3.8%). But in both study groups, a drastic decline occurred compared to baseline (concluders: 76.1%, participants: 84.7%). No significant differences were found for regular cocaine use at follow-up. In both groups, there was a marked decline of drug use (concluders: from 27.5% to 5.3%, participants: from 30.8% to 9.8%). The development of the social situation is even more strikingly similar. In almost all areas – homelessness, unemployment, illicit gains, court procedures, social contacts – there were parallel, mostly positive developments which showed that patients, who had abandoned heroin treatment, were in a life situation comparable to the situation of patients still in heroin-assisted treatment. This shows that many patients can succeed in stabilising their life situation within two to three years to an extent that allows them to leave the heroin treatment. On the other hand, it appears that for a group of patients, it is necessary to offer longer periods of treatment so that they can achieve long-term benefits.
A recent study on the development of the incidence of heroin use in Zurich (Nordt & Stohler 2006) contains important information on indirect long-term effects of maintenance treatment in general and heroin-assisted treatment in particular. Based on the record of maintenance treatment of the city of Zurich related to the years 1991 to 2005 and its case related information on drug careers (time difference between problematic use and first initiation of maintenance treatment, different phases of maintenance treatment and of leaving the treatment) as well as on estimations regarding untreated heroin users, incidence rates were calculated for each year. According to this record, the incidence of heroin users steeply increased from 80 persons in 1975 to 850 persons in 1990 and then continuously declined to 150 new users in 2002. The authors interpret this development, for which no parallel was found in other countries, a.o. as the result of a policy of harm reduction and consistent medicinalisation of the heroin problem, which, in Zurich, included heroin prescription already at an early date. Contrary to the expectations of many sceptics, this did not entail an increasing number of users and a prolonged dependency, but demystified the image of heroin. Heroin increasingly acquired the image of a “looser drug” and became unattractive for young people.

2. Objectives, study plan, methods

The implementation of the model project for heroin-assisted treatment is based upon a previously established study protocol (Krausz et al. 2001), which describes in detail the two study phases – randomised comparative study (part B) and 2-year progressive study (part C): the implementation requirements, the schedule, the methods of investigation and data collection and the statistical analyses. In addition, several amendments are concerned with specifications and corrections (cf. paragraph 5.9 of the Clinical Study Report, Naber & Haasen 2006).

2.1 Study objective, hypotheses

The objective of the second study phase is to explore whether medically prescribed diacetylmorphine dispensed at an integrated treatment setting (medical treatment combined with psychosocial treatment) is able to stabilise or even further enhance improvements attained in the first year of treatment, focusing on following issues: integration into addiction services, reduction of illicit use and related problems, health, mental and social improvement and stabilisation, controlling and overcoming the dependency.

According to the overall hypothesis of the study, heroin-assisted treatment is a therapeutically effective supplement of drug services in the treatment of heroin addicts, who were not reached in a therapeutically effective way by existing offers of addiction services or who did not benefit sufficiently by previous methadone maintenance treatment. The results of the first study phase revealed a statistically significant superiority of heroin-assisted treatment over methadone treatment with respect to physical and/or mental health and reduction of illicit drug use. Beyond these two primary outcome measures, additional positive effects such as separation from the drug scene or decline of delinquency were found to a greater extent in the heroin group than in the control group treated with methadone (Naber & Haasen 2006).

The second study phase is concerned with changes between the state reached during the first study phase and the situation at the end of the second study phase after a total of 24 months with respect to following criteria:

- improvement or stabilisation of the improved physical and/or mental health,
- reduction of the use of street heroin, cocaine, benzodiazepines, amphetamines, alcohol,
- fewer contacts with the drug scene,
- decline of delinquent behaviour,
- stabilisation of the housing situation,
- establishment of new social contacts,
- integration into professional work/training,
- improvement of the quality of life,
- regular conclusion of heroin treatment or switching to abstinence treatments.

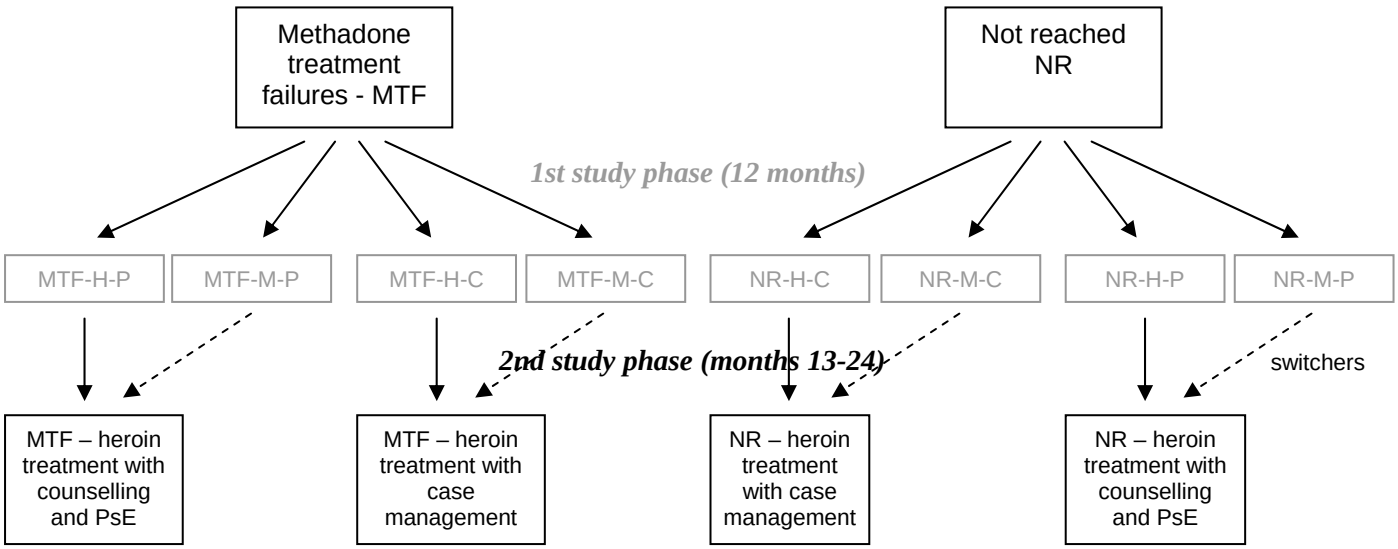
Moreover, the effects of switching to heroin-assisted treatment after one year of methadone maintenance are analysed (within the specific target groups of the study). Significant health improvements under heroin treatment are expected in switchers, as well as (further) decline of illicit drug use during the second study phase.

To conclude, safety issues related to the medication (adverse events) and side effects of diacetylmorphine are addressed again. Safety data of a 2-year period are now available for analysis. Deaths occurring during the second study phase are described and analysed with respect to a possible relationship with the study medication.

2.2 Description of the study design

The second phase of the German model project for heroin-assisted treatment combines the eight study groups of the first phase into four groups (or 2 x 2 groups in terms of strata): *former experimental groups (MTF-H-C) and (NR-H-C):* heroin treatment with concomitant case management, *former experimental groups (MTF-H-P) and (NR-H-P):* heroin treatment with concomitant psychoeducation/drug counselling. The switchers from the *former control groups (MTF-M and NR-M)* were distributed to the four groups according to their randomisation state (see figure 2.1). As vacated heroin treatment places were filled again, about 500 patients were expected to initiate the second study phase, about 125 in each group.

Figure 2.1
Study groups of the second phase of the model project for heroin-assisted treatment of opioid-dependent patients



The study treatment of the second phase consists in the daily administration of intravenously applicable heroin, concomitant medical examinations and regular psychosocial treatment consisting of case management or psychoeducation/drug counselling. Heroin is dispensed up to three times a day (morning, noon, night), with an additional optional methadone dose for the night. The outpatient drug units implemented for the model project continue to deliver the heroin-assisted treatment.

2.2.1 Recruitment of patients, randomisation of the switchers

Patients of the second study phase are exclusively recruited from regular concluders of the first phase of the model project, which limits the number of available heroin treatment places. A total of 515 treatment places were available for the second study phase.

If the number of control group patients, who regularly concluded the first study phase, exceeded the number of vacated heroin places, the places were distributed according to a re-randomisation plan. Methadone patients of the four control groups, eligible for switching, were reported to the principal investigator, and were assigned randomly to vacated places. They were assigned block by block according to a consecutive list (compiled separately for each study centre by the leading centre). In the sequence of this list, patients were asked individually whether they wanted to occupy the heroin-assisted treatment place. Switching was only possible to places vacated by *patients, who had initiated heroin treatment within the same space of time indicated by the block size*. Thus the problem was avoided that control group patients, who were the first to conclude the first study phase, would occupy most of the available heroin places, i.e. all those so far vacated.[1] If the patient declined, the consecutive list was run through until the corresponding heroin places were filled. If not all the heroin places were filled in one randomisation block, it was resorted to patients of former blocks, who had not been able to get a heroin treatment place. In that case, the block nearest in time was always considered first. Places were assigned first within the sample strata (e.g. control patients MTF-M-C switched to MTF-H-C). Only if, within one control group, no participant was available across all available blocks, it was possible to switch within the same concomitant treatment according to the above described step-by-step procedure (e.g. NR-M-C switch to MTF-H-C). If heroin places were then still available, it was possible to switch irrespective of the concomitant treatment as described.[2]

Remaining control group patients dropped out of the study treatment after the first study phase and continued methadone treatment in the framework of the normal treatment system or followed a methadone withdrawal treatment.

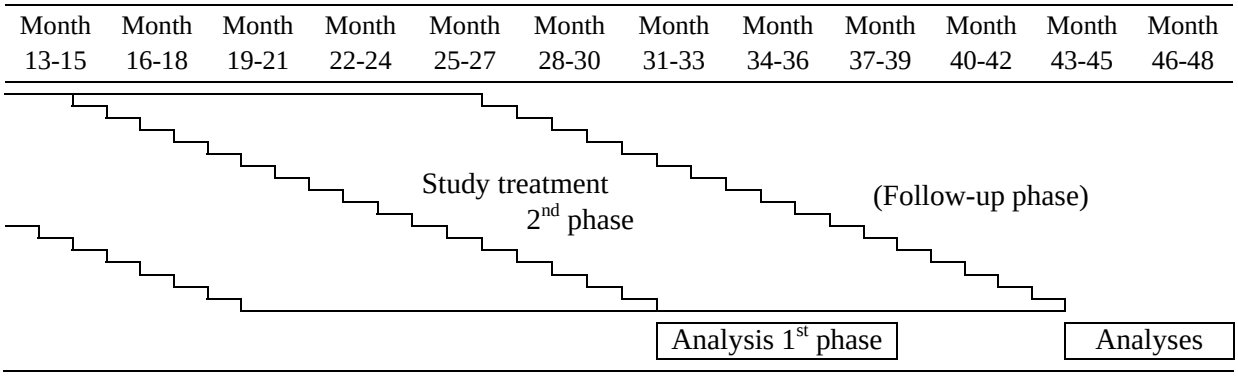
2.2.2 Duration and course of the study

The duration of the second study phase was 12 months. Due to delayed recruitment, its organisational duration extended over a period of about 30 months (see figure 2.2). The first patient (in Bonn) initiated the second phase in March 2003, the last patient (in Hamburg) at the end of December 2004.

[1] Therefore, not all vacated heroin places could be filled at once, but the space of time defined by the block size had to be awaited.

[2] In smaller study centres, which offered only one form of concomitant treatment, not all the switching combinations were possible.

Figure 2.2
Organisational course of the second study phase of the model project for heroin-assisted treatment for opioid-dependent patients within an overall period of 30 months



The last data of the second study phase were transmitted to the principal investigator at the end of March 2006, the last queries were addressed and concluded in May. Verification of the safety data (adverse events) required another five weeks so that the final set of data of the second study phase (and the entire 2-year treatment period) was available in July 2006.

2.2.3 Documentation and examinations

Data collection and documentation of the course of treatment were done, analogous to the first study phase, on three planes: documentation of the medical examinations, laboratory results and prescriptions (A, "med-CRF"), documentation of the psychosocial concomitant treatment (B), PST utilisation data being transferred to the "med-CRF", external scientific survey based on interviews and questionnaires (C, "ext-CRF"). The examination schedule of the second study phase is represented in figure 2.3. In terms of (descriptive) case control, the T_{12} examination at the end of the first study phase is the baseline for the second study phase.
All external interviews (ext-CRF) were face-to-face interviews; confidentiality was assured even vis-à-vis the treatment unit. In the context of these interviews, patient filled-in questionnaires were also checked for completeness by the interviewer so that missing data could be added in accordance with the patient. The interviewers had previously been trained in interview technique and investigation instruments. They were not part of the staff of any of the treatment units.
Test stripes were used at the treatment centre to test the weekly urine samples for drug use. Local laboratory associations were involved in the serological analyses of blood and urine samples.

Figure 2.3
Schedule of examinations and surveys of the second study phase. T_{18} = survey time 18 months after treatment initiation, T_{24} = end of second study phase

	T_{18}	**T_{24}**
Application for treatment continuation[a)]		X
Patient's information, consent[a)]		X
A. Medical examinations/laboratory:		
Case history general, specific	X	X
Physical examination	X	X
OTI health scale	X	X
Mental state	X	X
SCL-90-R	X	X
SOWS	X	X
Smear in case of skin infections	X	X
Blood count	X	X
Hepatitis B, C, HIV, syphilis		X
Tine test		X[b)]
Echocardiography		X
EKG	X	X
Thorax x-ray		X
Urine analyses	weekly	
MSLQ	X	X
B. PST:		
Documentation (activities, contents)	Concomitant to PST	
Specific surveys of the course	Concomitant to PST	
C. External survey:		
EuropASI (completed)	X	X
Social support, SOZU	X	X
Readiness to change, VSS-K	X	X
Self-esteem, mental condition	X	X
Coping, delayed reward	X	X
Abstinence confidence , HEISA	X	X
Survey of economic situation		X
Delinquency (quantitative interview)		X
Analysis of police data („light field")		X[c)]

a) Patients still in heroin treatment at the end of the second study phase were able to continue their individual treatment (follow-up phase) based on a study plan amendment agreed with the ethics committee and the BfArM. Patients' information and consent were again required.

b) The Tine test at T_{24} was only carried out in case of negative results of the preceding examination.

c) The analysis of police data was performed retrospectively for 3 years for all the patients included in the study.

2.3 Selection of the study sample

Heroin-assisted treatment is targeted at opioid-dependent patients with many years of i.v. use, who were not reached by the treatment system of drug services or who did not sufficiently benefit from previous treatments. The second study phase included only patients, who had regularly concluded the first phase of the model project.

2.3.1 Inclusion criteria

In order to explore long-term effects of heroin-assisted treatment, patients, who fulfilled following criteria, were included in the second phase of the study:

- Main diagnosis of opioid dependency according to the ICD-10 criteria
- Participation in and regular conclusion of the first study phase
- Voluntariness and ability to comply with the treatment conditions
- For methadone patients (control group): re-randomisation to vacated heroin treatment places.

2.3.2 Exclusion of patients from study treatment

Study participation was voluntary, i.e. patients could withdraw their treatment consent (and further study participation) at any time. Patients, who fulfilled at least one of the following criteria, were excluded from the study treatment:

- Patients with severe somatic complication in connection with the heroin or methadone treatment, when medical investigators and safety board assessed treatment continuation to be irresponsible
- Patients with abnormal changes in 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 for reasons caused by themselves or without giving a reason and who had interrupted the intake of the study medication
- Patients taken into custody or going to prison for 1 month or longer
- Patients whose treatment was interrupted for more than 3 months due to hospitalisations or other specific treatment regimens
- Patients, who, according to the medical investigator, were 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 discontinued heroin treatment, i.e. were excluded, broke off, changed to another treatment form or regularly concluded treatment by withdrawal or “tapering” were offered or mediated to alternative treatment options on request (e.g. methadone maintenance, buprenorphine treatment, mediation to outpatient or inpatient detoxification treatment with the option of subsequent outpatient or inpatient abstinence treatment).

2.4 Study treatment

Similar to the first study phase, heroin treatment was delivered in special outpatient units, as required on the one hand by the standards of a clinical trial according to the study protocol, on the other hand the safety and economic requirements of the units. For reasons of practicability, economic efficiency and general study conditions, the units had to have an appropriate size to accommodate a relevant number of patients. Equipment and training of the (responsible) staff members correspond to the specifications of §§ 5 and 6 of the BtMG. The treatment centres provide adequate space for the concomitant case management and the psychoeducative treatment/drug counselling. Psychosocial treatment continues to be provided by staff members of the treatment unit or in other institutions experienced in outpatient drug treatment.

2.4.1 Description of medical treatment

Also in the second study phase, the setting of medical treatment required a minimum of weekly contacts between patient and treating doctor. Comprehensive physical examinations and blood counts (10 ml per sampling) occurred after 18 and 24 months, the 12-month examination of the first phase being the baseline examination of the second phase. Moreover, the course of treatment was controlled by weekly urine analyses (qualitative evidence).
Problematic (co-)use, e.g. of benzodiazepines was expected to decline under heroin treatment with the aim to completely withdraw these substances. The heroin dose could be refused to patients under the influence of alcohol, barbiturates or benzodiazepines. If excessive alcohol use was suspected (smell of alcohol), a breath control was performed. According to § 5 (1) BtMG, (principal) medical investigators are responsible for assuring that the law on narcotics is observed.
Patients, who switched from the control group to heroin-assisted treatment, were stabilised to heroin according to their last methadone dose (cf. paragraph 5.5.6, Naber & Haasen 2006; Seidenberg & Honegger 1998).

2.4.2 Description of psychosocial treatment

The setting of psychosocial treatment (PST) involved regular contacts 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 patient's overall psychosocial situation and his perception of the treatment offers were documented at treatment initiation and then at regular intervals.
In the second year of treatment, there were also 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" (cf. Wendt 1997; Oliva et al. 2001; Miller & Rollnick 1999).
- *Drug counselling with psychoeducation*. Continuation of established drug counselling with additional psychoeducational programme consisting of 12 weekly group sessions and sub-

sequent refreshing sessions based on a manualised treatment programme (cf. Kieserg & Hornung 1996; Farnbacher et al. 2002).

These two distinct settings are continued under comparable medical treatment conditions. Intensity and utilisation of case management and counselling/ psychoeducation might differ, which is taken into account in the analyses of the special study concerning Psychosocial Treatment.

The care ratio of case management/MI and psychoeducation/drug counselling is 1 : 25.

2.4.3 Study medication

Experimental study medication is the DIAPHIN injectable solution of the drug company DiaMo GmbH & Co KG with 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. A comparison substance was not issued in the second study phase as the control group was not continued.

2.4.4 Dosage of study mediation

In the first study phase, it was important to stabilise patients – after an initial phase of one to two weeks – to a stable maintenance dose of i.v. heroin for the entire study period. From the start, an additional medication of d,l methadone was offered for the night. Also in the second study phase, heroin was dispensed up to 3 times a day during the opening hours of the 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 was 1,000 mg, the individual maximum dose 400 mg. The average daily dose of heroin for the entire period of the first study phase was 442 mg. If methadone is claimed for the night, it can be taken on the premises during the evening opening hours or 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. Related to all heroin treatment days, the daily dose of additional methadone was 8 mg during the first year of the study (Naber & Haasen 2006).

The following dosage regimen is a guideline for the process of switching from d,l methadone to i.v. heroin. Most patients of the second study phase continued heroin treatment with, as a rule, a stable maintenance dose. For the group of patients, who switched from d,l methadone to heroin, the daily dose is based upon the last daily dose of methadone. Determination of the dose is again based upon a methadone daily equivalence dose (MTQ), where a certain daily dose of d,l methadone corresponds to about three times the amount of heroin distributed over

the day. The basic rule of the dosage regimen states that the i.v. 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 & Honegger 1998; Bundesamt für Gesundheit 2000).
Switching from oral methadone to i.v. heroin is orientated towards the methadone dose of the previous day. Figure 2.4 presents an example for the transition 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 2.4
Increase of i.v. heroin dosing starting from a low dose of methadone

	Oral methadone	i.v. heroin	MTQ (i.v. heroin	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 additional d,1 methadone p.o. for the night, 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).

2.4.5 Concomitant treatments

The study did 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).

2.5 Variables

Efficacy and safety variables were continuously documented in the course of the second study phase. 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) were documented by appropriate statistical categories.

2.5.1 Efficacy variables

The survey of efficacy variables in the course of the second study phase is represented in figure 2.5. They focus on health related (somatic and mental) and consumption parameters (drugs and alcohol). The course of the social situation was investigated in the context of the external interviews (EuropASI, Kokkevi & Hartgers 1995) based on variables related to housing, employment and income and to social contacts and leisure behaviour.

Figure 2.5
Schedule of examinations and surveys related to efficacy variables in the second study phase

Examinations/variables	**T_{18}**	**T_{24}**
Health: OTI-HSS, physical results	X	X
Health: SCL-90-R, mental state	X	X
Withdrawal symptoms: SOWS	X	X
Drug use: urinalyses	weekly	
Quality of life: MSLQ	X	X
Life situation: EuropASI (supplemented)	X	X
Drug use: EuropASI	X	X
Readiness to change: VSS-K	X	X
Treatment satisfaction: TPQ	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 were calculated by the medical investigator and recorded on the CRF. The urinalyses were assessed as positive or negative based on qualitative or semi-quantitative evidence on site. All other scales (e.g. SOWS), instruments (e.g. MSLQ) or questionnaire scores (e.g. ASI-Composite Scores) were analysed centrally under the responsibility of the principal investigator.

2.5.2 Safety variables

In the second study phase, adverse events (AEs) and severe adverse events (SAEs) and side effects were also consistently recorded in terms of safety variables. Side effects – similar to main effects – were measured quantitatively. At each scheduled examination, following effects and side effects of 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 consciousness, hypotension.

Blood counts, performed in the context of the study, were checked for deviations from the norm (safety lab). Such deviations were recorded on the CRF and counted as adverse events (AE) and, if applicable, as adverse effects of the medical drugs (ADE). Moreover, the examinations described in figure 2.6 included the collection of safety-relevant data, which, as the case may be, were recorded as adverse events, but were also analysed separately. The degree of severity of AEs and SAEs and their relationship with the study medication were assessed by the medical investigators. Moreover, severe adverse events were discussed with the safety board.

Figure 2.6
Schedule of safety-relevant examinations within the second study phase

Examinations	**T_{18}**	**T_{24}**
Medical history	X	X
Physical examination	X	X
OTI health scale	X	X
Swabs in case of skin infection	X	X
Diff. blood count	X	X
Clin. chemistry	X	X
EKG	X	X
Echocardiography		X
Effects of intoxication	X	X

The majority of the ascertained safety and efficacy variables have already been used in evaluation studies concerning addiction treatment and generally in clinical trials (cf. Krausz et al. 2001). All the recording instruments are standardised or at least structured procedures, with analyses performed either according to standardised patterns or – in case of categorical, qualitative data – as individual information. The only exception is 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.

2.5.3 Compliance

The compliance of study participants was recorded on the one hand by documenting the medical visits, on the other hand by their participation in psychosocial treatment. Medical investigators documented discontinuations or regular terminations of the second study phase on the CRF. In the external interviews (ext-CRF), patients were asked whether they were in any addiction treatment at the time of the interview (or in the last 6 months).
The retention rate of the study treatment is defined according to the proportion of patients still in treatment after 24 months, i.e. patients, who complied with the treatment conditions in the 24th month of treatment, compared to the total number of patients included in the study. A

difference is made between the 2-year retention rate related to all randomised patients (n=1,032) and the retention rate of the second study phase related to all patients, who initiated the second phase (n=434).

2.6 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), and the manual extensively describes the process of data collection. Examinations by medical investigators are also based on a comprehensive CRF manual; 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.

An independent monitoring was performed. The implementation and handling of CRF controlling (matching of source data, checking for completeness) are described in the monitoring conventions.

Data processing is subject to complex controls. For instance, based on the list of so called *crucial variables* (an element of the 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 and also recorded in a programme syntax. Data, which are not counted among the “crucial variables” such as lab data and data regarding medical apparatus examinations, were checked for missing or implausible values (“outliers”) and matched with the CRF data, but no queries to the study centres 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 as soon as possible. Data management by the principal investigator was audited separately in the spring of 2004, deficiencies were corrected within a short time in accord with the auditor. Both audit reports certified 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.

2.7 Statistical analyses

The report of the first study phase (Naber & Haasen 2006) and the statistical analysis plan (Verthein et al. 2005) extensively described the process of determining the sample size required for a randomised comparison of heroin and methadone treatment in the first study phase. A minimum sample size of n=964 was determined, and the recruiting process resulted in a sample of n=1,032. 17 of these patients had to be excluded from the analysis; thus, the ITT analysis of the first study phase referred to a sample of n=1,015 patients (cf. Naber & Haasen 2006). 515 patients were randomised to heroin-assisted treatment, which defined the total number of heroin treatment places available in the second study phase. Contrary to the expectation that all vacated heroin places of the first study phase would be filled by switchers at the beginning of the second phase, only 84.3% of all the heroin treatment places available according to the study design (see chapter 3) were filled (again), by 434 patients.
The second study phase no longer included a control group, since comparative effect measuring had been concluded in the first phase. The focus was now on long-term effects of heroin treatment, investigating whether improvements reached during the first year of treatment could be maintained and analysing the effects of direct switching from methadone to heroin treatment. Both issues are of major importance in view of a potential integration of heroin treatment into the catalogue of approved treatment options and the acceptance of this type of treatment.
Long-term effects of heroin treatment (stabilisation and change) are analysed after 24 months based on the four remaining study groups (see figure 2.7). On the one hand, the effect analysis of the second study phase is based on intraindividual changes. On the other hand, the efficacy of psychosocial concomitant treatment (case management with integrated motivational interviewing vs. counselling and psychoeducation) can also be analysed by group comparisons, in order to determine long-term, possibly differing effects of the various settings.

Figure 2.7
Study groups included in the analyses of the second study phase of the heroin-assisted treatment (after 24 months)

<table>
<tr><td colspan="3">MTF (target group “methadone treatment failures”)</td><td colspan="3">NR (target group “not reached”)</td></tr>
<tr><td colspan="2">Long-term analysis of the effect of psychosocial concomitant treatment in heroin treatment</td><td>Analysis of the long-term effects (stabilisation) of heroin treatment</td><td colspan="2">Long-term analysis of the effect of psychosocial concomitant treatment in heroin treatment</td><td>Analysis of the long-term effects (stabilisation) of heroin treatment</td></tr>
<tr><td>MTF-H-C</td><td>MTF-H-P</td><td>intraindividual:
MTF-H-C
MTF-H-P</td><td>NR-H-C</td><td>NR-H-P</td><td>intraindividual:
NR-H-C
NR-H-P</td></tr>
</table>

The group of methadone switchers, distributed to the four study branches, is analysed separately. In these patients, it is possible to analyse intraindividually potential changes in the treatment course caused by the switching.

First of all, the variables described in paragraph 2.5.1 are analysed to find out whether improvements are stable or increased after (18 and) 24 months. The main focus is on long-term goals such as rehabilitative steps in terms of reuptake of work or training, (drugfree) social contacts, long-term development of co-use and the retention power or transfers to further treatments. Due to similarities of sample characteristics at baseline and response rates of the primary outcome measures identified between the target groups (cf. Naber & Haasen 2006), the MTF and NR strata are predominantly analysed jointly. The analyses are carried out as "on treatment" analyses among all patients, who initiated the second study phase. The statistical analyses are carried out according to the scale levels of the variables or the generated indices, i.e. in the framework of bivariate or multivariate analyses. Fisher's Exact Test is applied in frequency comparisons, T test (if necessary after previous safeguarding of the normal distribution) and variance analyses in metric characteristics comparisons. Case analyses with dependent data are carried out by T tests (for dependent samples), repeated measurement models and for categorical data by McNemar and Cochrane test. The ascertained p-values are interpreted descriptively in terms of an explorative data analysis.

2.8 Ethical and legal aspects

2.8.1 Ethics committees

The study protocol (No. ZIS-HV9-0701, Krausz et al. 2001) and the amendments 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 (Naber & Haasen 2006).

2.8.2 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).

2.8.3 Patient information and consent

Prior to the study inclusion, each patient gave written consent of participation after receiving comprehensible oral and written information about the aims, method, extent and risks of the study. Prior to the transition to the second study phase, the required inclusion criteria were verified, but a renewed declaration of consent was not required, as patients had been informed about the two study phases (and the 24-month overall period) at the beginning of the study.

2.8.4 BtMG

Heroin was not a substance eligible for prescription in Germany at the time the study was conducted. According to § 3 (2) BtMG, the use of heroin was only allowed „in exceptional cases for scientific or other purposes of public interest“. In order to use heroin in the maintenance treatment of opioid addicts, it must be incorporated in Annex III of § 1 (1) BtMG (trafficable and prescribable narcotics). The Bundesopiumstelle (federal narcotics bureau) issued a BtM number to the leading medical investigators of each centre entitling them to drug trafficking within the limits of this study.

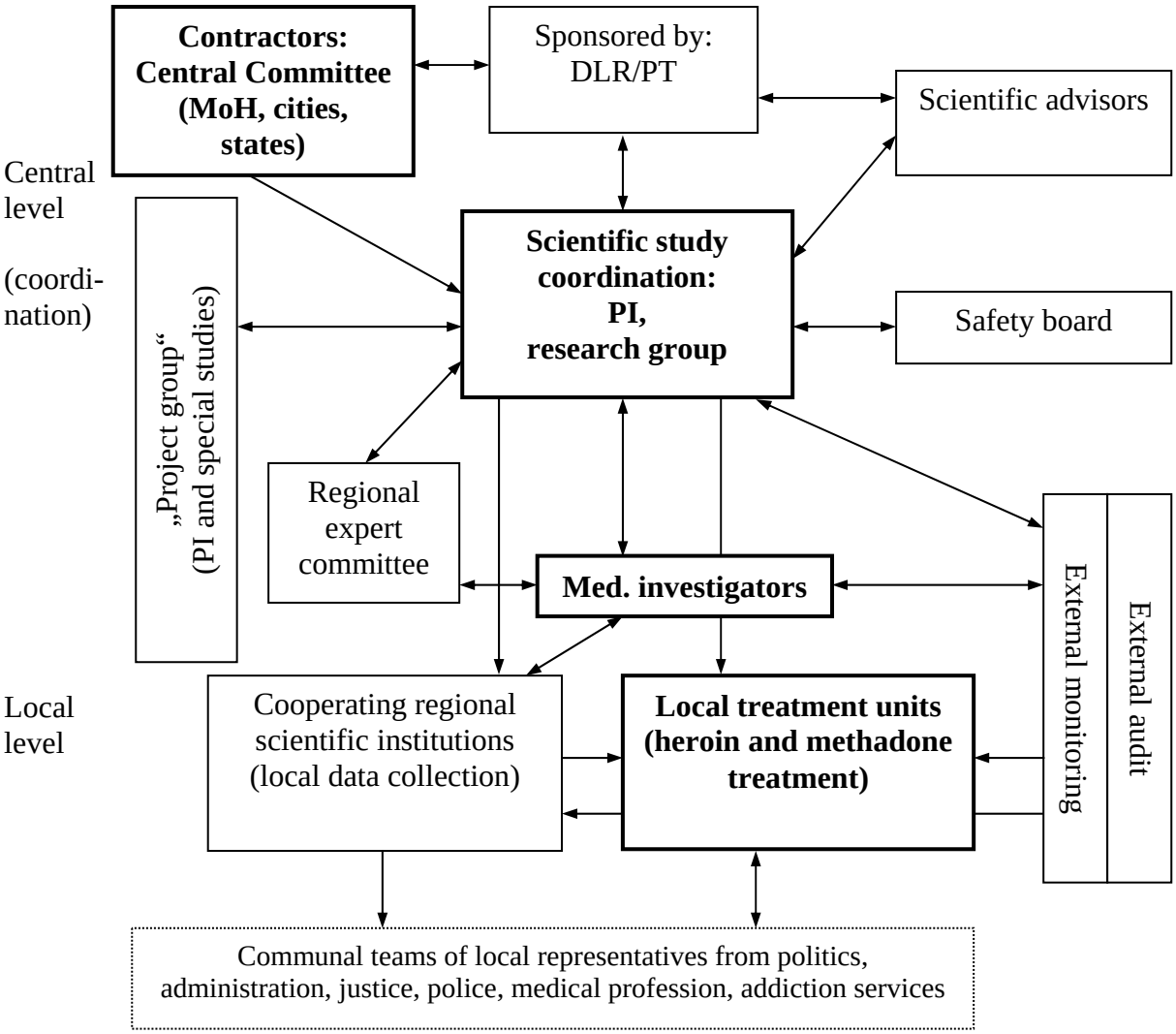
2.8.5 Liabilities and insurance

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.

2.9 Principal investigator and coordination

The model project, conceived as a multi-centre clinical trial with integrated special studies, required a high degree of coordination and cooperation (see figure 2.8). It involved quality assurance to select appropriate training concepts as well as 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 units. The activities were supervised by the principal investigator and coordinated in regular meetings of the project group. Moreover, close cooperation with the external monitoring was necessary. Due to the high scientific significance of the study, a scientific advisory committee including national and international experts was established and consulted throughout the project duration. The conduction of the study was organised and monitored in line with the binding cooperation agreement with the sponsor, the DLR, the Ministry of Health and the participating cities and federal states in the central committee.

Figure 2.8
Cooperation among the parties involved in the clinical trial of heroin-assisted treatment



3. Study groups

The report of the first study phase describes at length the selection of patients and the inclusion and exclusion criteria. The recruitment process was stratified according to the target groups "methadone treatment failures" (MTF) and "not reached" (NR). For organisational reasons, the recruitment process was closed on December 31, 2003. A total number of 1,032 heroin addicts were included in the study, clearly exceeding the required minimum sample size of n=964 (see Naber & Haasen 2006).

3.1 Distribution of the study patients

Of the initial 1,015 subjects, 434 initiated the second study phase (42.8%). 344 of them continued heroin treatment, and 90 patients switched directly from methadone to heroin treatment. 84.3% of the 515 heroin treatment places were filled (again). The distribution among the study centres largely corresponds to the number of initially offered treatment places. With a total of 138 patients, Hamburg is still the largest study centre; however, only 69% of all the heroin treatment places were filled at the beginning of the second study phase (see table 3.1). In Hanover and Frankfurt as well, a number of heroin places remained vacated; Frankfurt is still the second largest study centre with 90 patients. In the small centres of Cologne, Bonn, Karlsruhe and Munich, 100% of the treatment places were (re)occupied.

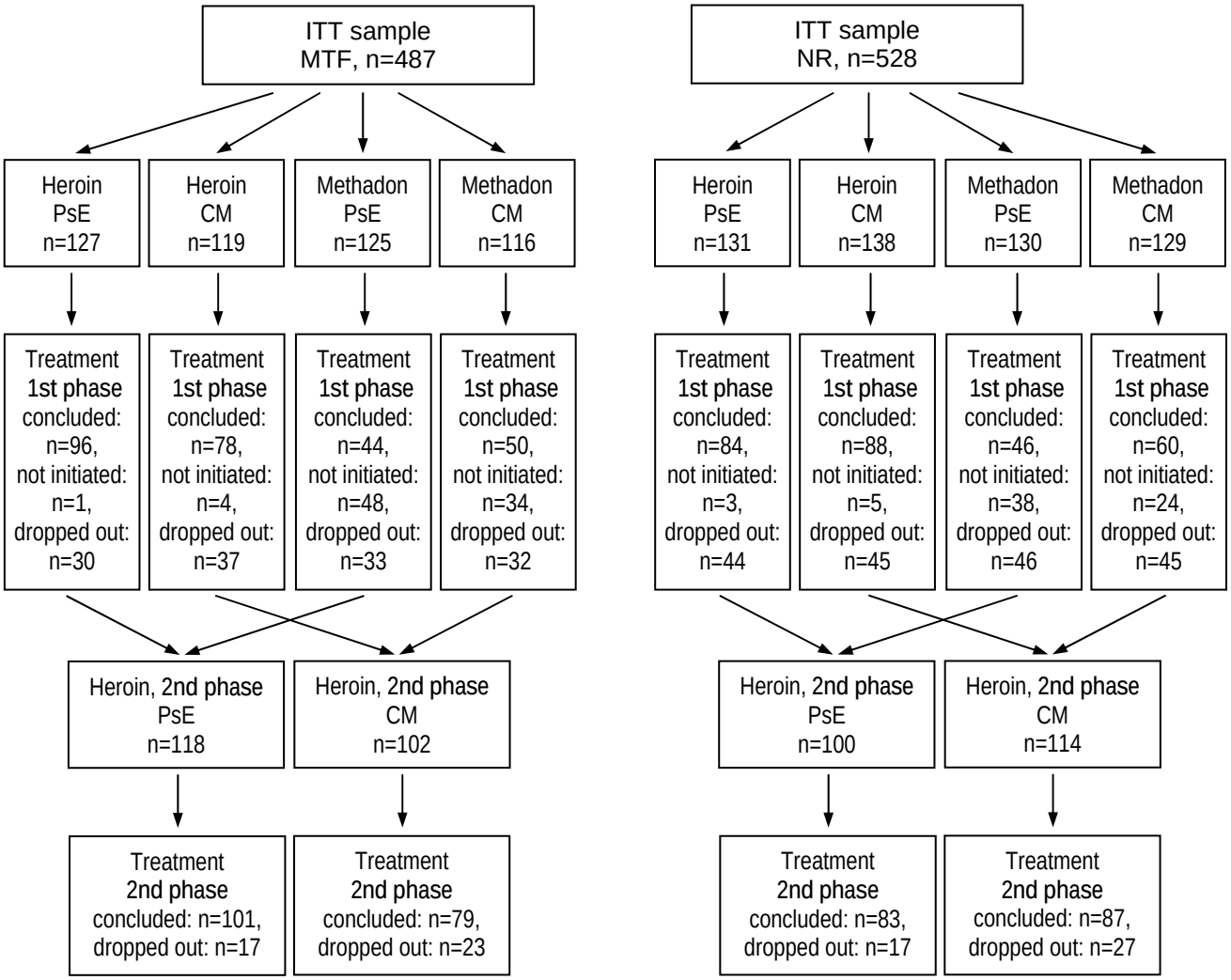
Table 3.1
Number of patients and study groups in the second phase (heroin treatment) in the seven study centres

	2-year heroin	Switchers	Total	% of heroin places
Hamburg	117	21	138	69.0
Hanover	40	9	49	75.4
Frankfurt	70	20	90	93.4
Cologne[a)]	36	15	51	100.0
Bonn	42	8	50	100.0
Karlsruhe	16	10	26	100.0
Munich	23	7	30	100.0
Total	**344**	**90**	**434**	**84.3**

a) In Cologne, a 51st patient was recruited for the second study phase due to temporary incorrect attribution; but no more than 50 heroin treatment places were occupied at any time.

In the second study phase, four subgroups of about equal size were constituted, based upon the strata of the initial sample of the first phase and according to the type of psychosocial treatment (see figure 3.1). The target group strata have now about equal size: Of the second-phase patients, n=220 (50.7%) belong to the MTF stratum and 214 (49.3%) to the NR stratum.

Figure 3.1
Subjects of the first and second study phase according to stratum



A total of 350 patients regularly concluded the treatment of the second phase (80.6%): 80.8% of the patients, who had received heroin in the first year, and 80.0% of the former methadone patients (switchers).[3]

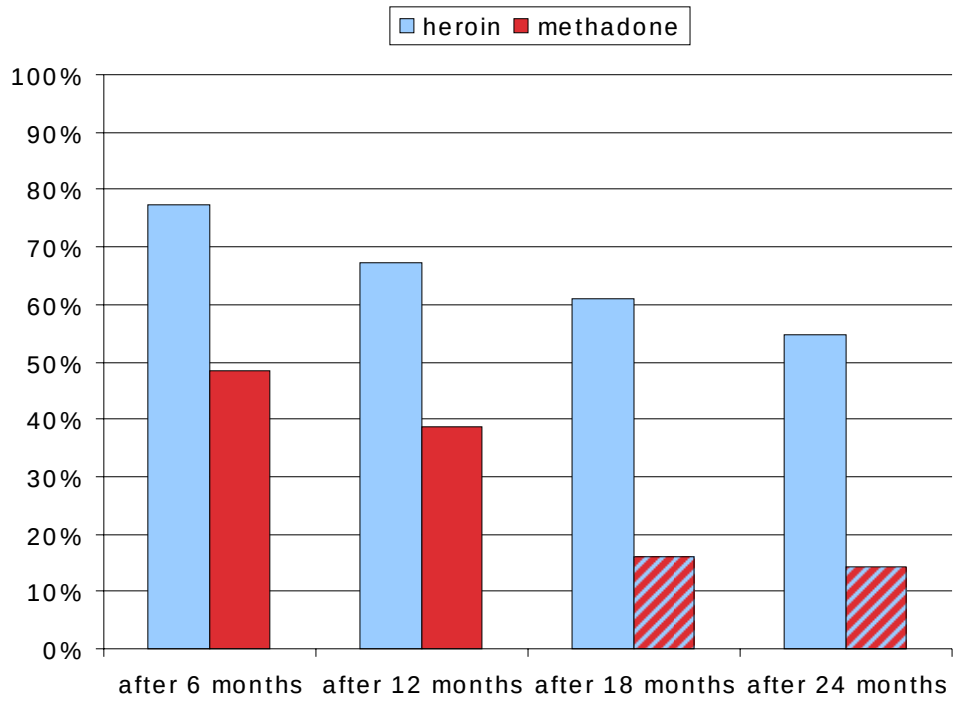
3.2 Retention rate

The retention rate of the 2-year period can only be based on those patients, who were already treated with heroin in the first study phase. After 12 months, 67.2% of the 515 participants of the former experimental group still participated in the study (see Naber & Haasen 2006). After 18 months, 61.0% were still in treatment; 54.8% regularly participated in the heroin treatment during the 2-year study period. Since the methadone control group was not continued in

[3] Regular treatment conclusion relates to the conclusion of the second study phase; it has to be taken into account that the total treatment period was longer than 24 months in some patients. Some patients might still have been in treatment in the 25th or 26th month though there was no regular conclusion (cf. paragraph 3.2).

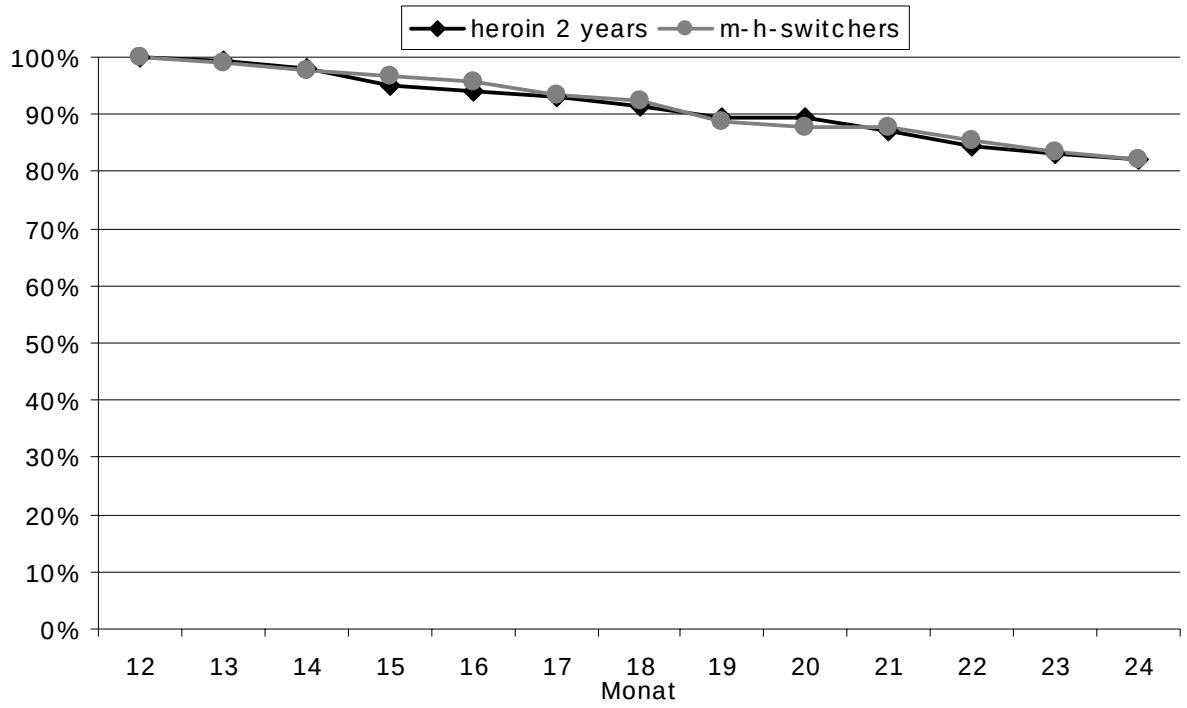
the second year, the retention rate of the second phase can only be determined among the switchers. After 18 months, 16.1% of the former methadone patients were in heroin-assisted treatment, which they had initiated in the second year; after 24 months, 14.3% were still in treatment (see figure 3.2). The remaining methadone patients concluded treatment at the end of the first study phase.

Figure 3.2
Retention rate of heroin and methadone treatment over 24 months (n=1,032)



The following detailed analysis of the retention rate of the second study phase is based only upon the 434 patients, who initiated the treatment of the second phase. The representation of the retention rate refers to the months 13 to 24: month 12 at the end of the first study phase is the baseline of the second phase. As mentioned above, 350 patients regularly concluded the second phase, but 356 patients participated in the study over 24 months. Figure 3.3 shows that both groups – 2-year heroin patients and methadone-heroin switchers – had a parallel, almost linear course so that after 24 months, 82% of each group, who had started the second study phase, were still in treatment (2-year heroin group: 82.0%, switchers: 82.2%, Kaplan-Meier: Log Rank=0.0, p=0.950). Compared to the first year of treatment, the dropout rate decreased. Related to the 2-year observation period, the dropout rate decreases, which is related to patients' increasing stabilisation under heroin treatment.

Figure 3.3
Retention rate of heroin treatment in the second study phase over 12 months (n=434)



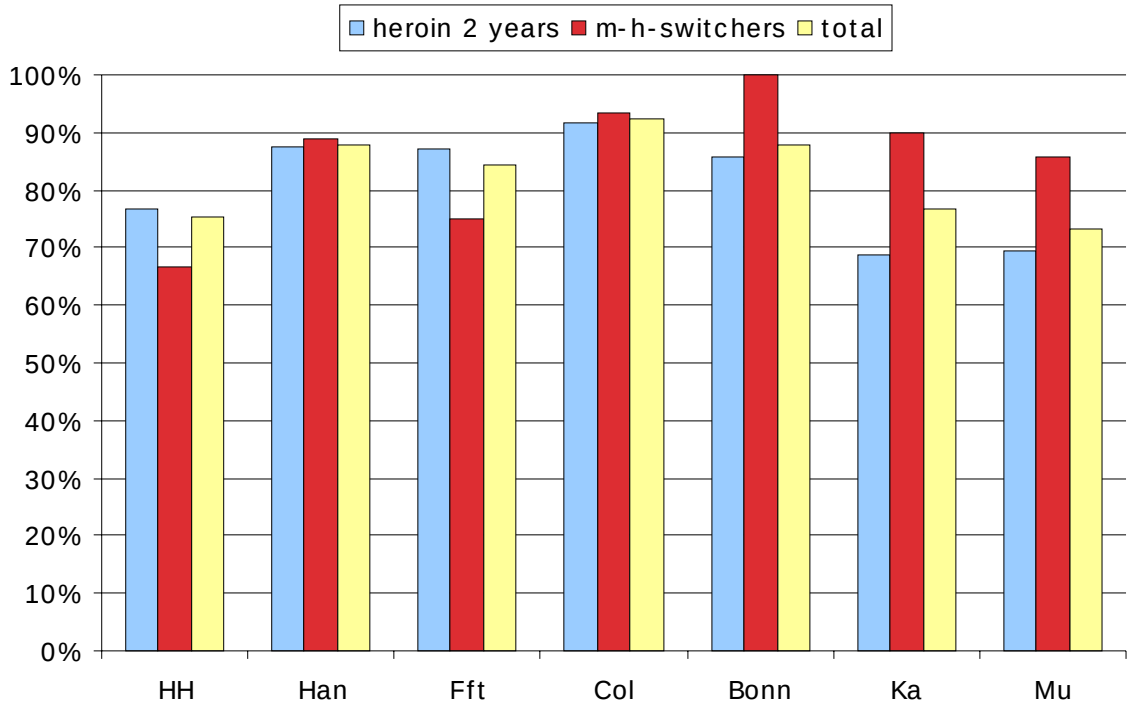
Differences between the sample strata are slight in the second study phase. Similar to the course of the first phase, the percentage of MTF patients still in treatment is somewhat higher in the 2-year heroin group after 24 months (MTF: 85.0%, NR: 79.0%, Kaplan-Meier: Log Rank=2.31, p=0.128). The differences are even slighter in switchers (MTF: 80.9%, NR: 83.7%, Kaplan-Meier: Log Rank=0.14, p=0.704) so that in the second study year, no relationship can be found between target group and retention rate.
A total of 84 patients prematurely dropped out of treatment in the second study phase (19.4%). This occurred after an average of 573 days or ca. 19 months.
The average treatment duration of all patients of the second study phase (n=434) is 701 days, i.e. slightly more than 23 months.[4] There is no longer a difference between the two groups (2-year heroin group: 700 days, switchers: 701 days).

In the second study phase, the 12-month retention rate differed between the study centres. In the first year, the retention rate was lowest in the larger centres of Hamburg and Hanover; in the second year, the retention rate was lowest in Hamburg and in the smaller centres of Karlsruhe and Munich. In these centres and in Bonn, more switchers than 2-year heroin patients persevere in treatment; in Hamburg and Frankfurt, the retention rate is higher in the 2-year heroin group than in the group of switchers (see figure 3.4). Cologne and Bonn still have the highest concluder rates. In Hanover, the retention rate is now also high; in the first year, it

[4] The randomisation date was the baseline for calculating retention rates. (Four days were added to the treatment duration.) 732 days were taken as maximal value for patients, who participated in the study for at least 24 months.

had been particularly low both in the heroin and methadone group. Selective effects are probably responsible, since patients, who coped with the admission and implementation rules of the first year of treatment, are probably better able to comply with treatment conditions also in the second year.

Figure 3.4
Retention rate of heroin treatment in the second study phase over 12 months according to centres (n=434)



The analysis of premature discontinuation (n=84) shows that the most frequent reason is a different addiction treatment – mainly methadone maintenance. If patients, who changed to abstinence treatment, are also counted, 44.0% of the dropouts took up another addiction treatment during the second study phase (see table 3.2). 14.3% of the patients dropped out due to imprisonment, one tenth without giving a reason (9.5%).

Table 3.2
Reasons for premature discontinuation of study treatment during the second study phase

Reason for discontinuation	**2-y heroin**	**Switcher**	**Total**
Exclusion criterion 3: absence from treatment	9.1%	11.1%	9.5%
Exclusion criterion 4: imprisonment	16.7%	5.6%	14.3%
Exclusion criterion 6: patient cannot/does not want to participate	3.0%	16.7%	6.0%
Exclusion criterion 7: violence, threat of violence	3.0%	-	2.4%
Exclusion criterion 9: theft/passing on medication	9.1%	-	7.1%
Other exclusion criterion	4.5%	-	3.6%
Participation refused	1.5%	-	1.2%
Abstinence treatment	15.2%	11.1%	14.3%
Other medical addiction treatment	27.3%	38.9%	29.8%
Side effects/SAEs	1.5%	5.6%	2.4%
Patient died	3.0%	5.6%	3.6%
Other reasons	7.6%	5.6%	7.1%
N	**66**	**18**	**84**

A major part of the patients discontinued treatment because they changed to a different addiction treatment (see above). However, this is not equivalent with the treatment status at the end of the second study phase (after a total of 24 months), since, depending on the time of dropping out, changes could still occur until the last examination time (T_{24}). As not all the patients, who had started the second study phase, could be reached again for the examinations and interviews at T_{24}, the treatment status of almost half of the dropouts is not known (see table 3.3). 28.6% of the dropouts were (again) in maintenance treatment at T_{24}, 7.1% in long-term inpatient treatment and 2.4% in detoxification or a different addiction treatment. Thus, 38.1% of the dropouts were (again) in an approved addiction treatment at the end of the second study phase. They represent 7.4% of the 434 patients of the second study phase.

Table 3.3
Treatment status of dropped out patients at T_{24}

	2-year heroin	**Switchers**	**Total**
Maintenance treatment	24.2%	44.4%	28.6%
Inpatient long-term treatment	6.1%	11.1%	7.1%
Detoxification	1.5%	-	1.2%
Other addiction treatment	1.5%	-	1.2%
Other clinic/hospital	4.5%	-	3.6%
No treatment	9.1%	11.1%	9.5%
In prison	7.6%	-	6.0%
Not known[a)]	45.5%	33.3%	42.9%
N	**66**	**18**	**84**

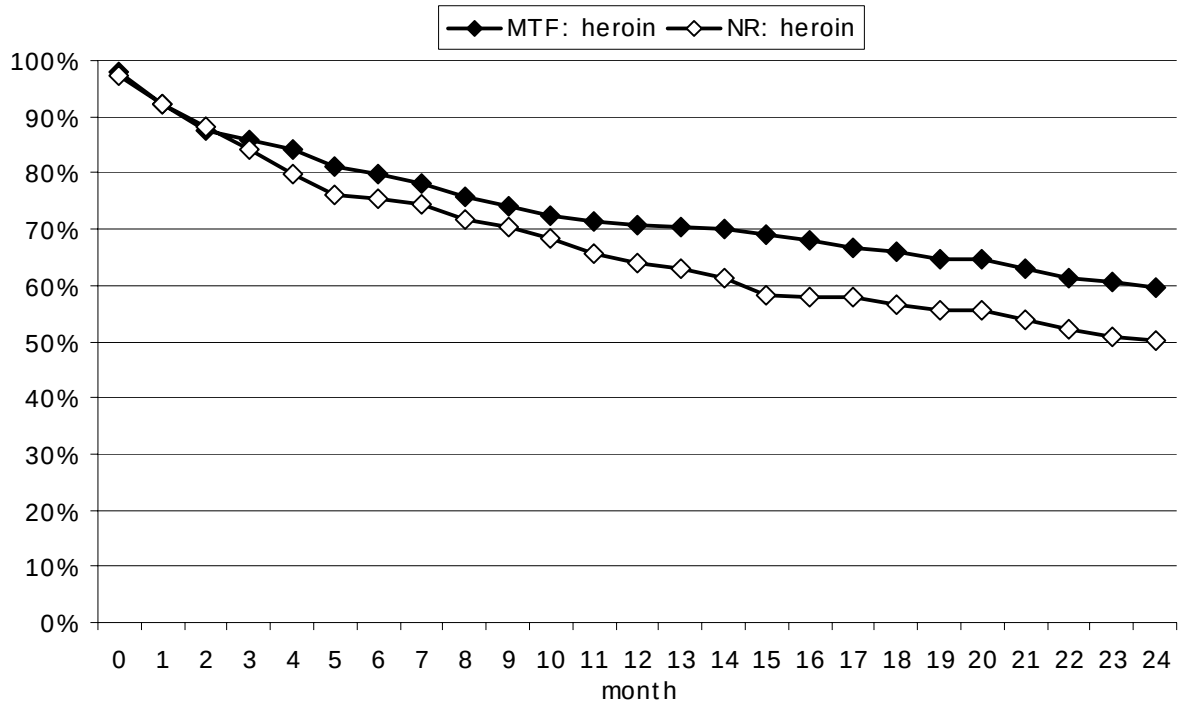
a) The category "not known" includes two cases, who declared their current treatment status to be "study treatment heroin" in the external interview at T_{24}. This discrepancy is due to different survey times: The external interview still occurred during the study treatment prior to the medical investigators' examination. Moreover, "not known" includes four deaths; three of them occurred in the course of the study treatment, one after dropping out.

3.2.1 2-year heroin treatment, end of treatment and follow-up treatments

In this chapter, all 515 heroin patients are reconsidered under following aspects: How many had dropped out prematurely in the course of the 2-year study period; in that case, did they regularly conclude the treatment; did they change to a follow-up treatment; did they just drop out without further treatment? As mentioned above, 54.8% were still in heroin-assisted treatment (n=282) after 24 months, i.e. 56.1% of the initial 503 heroin patients. Figure 3.5 shows that the retention rates of the two target groups MTF and NR are divergent depending on the length of treatment. At T_{12}, the retention rates were not yet different, but the 2-year curves show a statistically significant difference (Kaplan-Meier: Log Rank=4.30, $p<0.05$). The curve of MTF patients is flatter; after 24 months, 59.8% are still in treatment. In the "not reached" group, the proportion of patients still in heroin treatment after 2 years is 50.2% and almost 10% lower. This indicates that patients, who changed directly from methadone maintenance treatment to the study treatment, were apparently better able to follow the conditions of heroin-assisted treatment over a longer period (in the context of the German model project). Though it was possible to show that the two target group strata hardly differ at baseline (cf. Naber & Haasen 2006), the greater treatment experience of the MTF target group is probably an important reason for the better long-term compliance.
Related to the 24-month period of both study phases, patients were in heroin treatment for 514 days (i.e. slightly more than 17 months) on average. This results in a total of 264,513 treatment days.[5]

[5] This figure is based on the exact 24-month period, the number of treatment days being limited here to 732 (see above). As in individual cases heroin treatment went on for a longer time, the exact average for both study phases is 518 days, with a total of 266,211 treatment days.

Figure 3.5
Retention rate of heroin treatment over 24 months according to stratum (n=515)



Information on subsequent treatment of dropped-out patients is derived from two sources. On the one hand, the medical investigator recorded the reason for treatment discontinuation (cf. table 3.2), on the other hand, the current treatment status was explored at the follow-up examinations and the external interviews (cf. table 3.3). This information can be combined to obtain an overview as comprehensive as possible about follow-up treatment after discontinuation of heroin treatment. Starting point is the reason for dropping out, as it provides information on direct treatment switching. If no information is available, it will be checked whether the patient was in some addiction treatment at a later time. These data are completed and combined to form a comprehensive overview over 24 months.

Of the 350 patients, who regularly completed the second study phase, 278 are part of the 2-year heroin group. They represent 54.0% of the 515 originally randomised heroin patients and 55.3% of the patients, who actually started heroin treatment (n=503). Thus, 237 patients dropped out of heroin treatment or did not initiate it in the course of the two study phases (46.0%). Table 3.4 presents the reasons for dropping out. 36.3% of the heroin patients (n=86) immediately changed to a different addiction treatment, most often methadone or buprenorphine maintenance treatment. 8.9% changed to abstinence treatment, if necessary preceded by detoxification.

Table 3.4
Reasons for premature discontinuation of heroin treatment during the first and second study phases

Reason for discontinuation	**Percentage**
Exclusion criterion 3: absence from treatment	11.8%
Exclusion criterion 4: imprisonment	15.2%
Exclusion criterion 6: patient cannot/does not want to participate	2.5%
Exclusion criterion 7: violence, threat of violence	4.2%
Exclusion criterion 9: theft/passing on medication	7.2%
Other exclusion criterion (e.g. longer treatment interruption)	3.8%
Participation refused	3.0%
Abstinence treatment (if necessary previous detoxification)	8.9%
Other medical addiction treatment	27.4%
Side effects/SAEs	0.8%
Patient died (during heroin treatment)	2.1%
Other reasons	13.1%
N	**237**

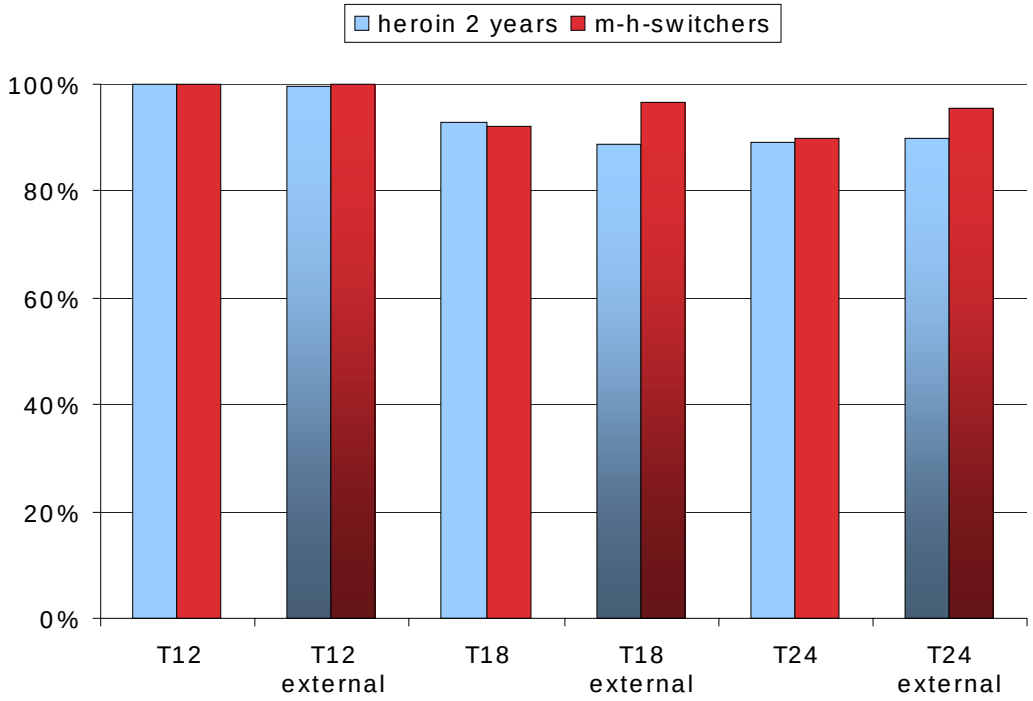
Of the other 151 patients, who prematurely left heroin treatment and did not immediately take up a different treatment, 34 patients were in maintenance treatment and 4 patients in abstinence treatment (detoxification or inpatient long-term treatment) at the follow-up examinations at T_{12} or T_{24}. If these patients are added to the 86 patients, who changed directly to a different addiction treatment, they form a group of 124 former heroin patients in different addiction treatment (immediately or with delay). This corresponds to slightly more than half of all the dropouts (52.3%); related to all randomised heroin patients, they represent one fourth (24.1%), who changed to a follow-up treatment in the course of the 2-year study period.

Changing to follow-up treatment is unevenly distributed among the target groups “methadone treatment failures” (MTF) and “not reached” (NR), a tendency already apparent in the first study phase (cf. Naber & Haasen 2006). Related to the dropouts, 69.6% of the MTF patients and only 39.3% of the NR patients changed to a different addiction treatment (Chi^2=21.5, df=1, p<0.001). Thus, 28.9% of all randomised MTF patients (n=246) succeeded in entering a follow-up treatment after (prematurely) dropping out of the heroin treatment. Only a small number (n=31) were not in addiction treatment within the 2-year period. Apparently, it was more difficult for the “not reached” group (n=269) to start a different treatment after heroin-assisted treatment; only 19.7% did so, 82 of the randomised NR patients did not initiate a follow-up treatment. Against the background of a retention rate that was low anyway among NR patients (see above), the connection of these most severely dependent addicts to an appropriate type of treatment is a particular challenge for the addiction services.

3.3 Participation in examinations and interviews

At T_{24}, 388 patients were examined by the medical investigators. This corresponds to 89.4% of all 434 patients, who started the second study phase. 89.2% were 2-year heroin patients and 90.0% switchers. Thus, a great number of study patients were successfully contacted again for examinations (and analyses) even after two years (see figure 3.6). The methodological bias of statistical analyses that might be caused by the classification of dropouts was thus minimised. A total of 91.0% could be reached again at T_{24} (2-year heroin group: 89.8%, switchers: 95.6%) for the external interviews. The follow-up rates among heroin patients are analogous to the retention rate; about half of the dropouts of the second study phase could be followed up. It was a bit easier to reach patients by the external interviews than by medical examinations.

Figure 3.6
Participation in medical investigators' examinations and external interviews during the second study phase (n=434)



The time intervals between the scientific examinations of the 2-year sample are represented in table 3.5. In this sample, treatment initiation also occurred on average one month after the baseline examination. The average values of the other intervals are exactly within the expected frame. The final T_{24} examination was performed on average 24.3 months after treatment initiation (T_0). The standard deviations point to individually differing intervals. This concerns mainly patients dropped out of the study and reached for examination only after a longer period, and part of the switchers with an overall duration of both study phases exceeding 2 years due to waiting periods related to re-randomisation. Although the intervals between

examinations markedly differed between the study centres in the first study phase, the average T_0-T_{24} intervals are now between 733 (Frankfurt, Bonn) and 751 (Cologne) days in all the centres.

Table 3.5
Time intervals between baseline (T_{-1}) and treatment initiation (T_0) and between T_0 and the subsequent examinations in days. Mean values and standard deviations (in brackets), only performed medical investigators' examinations in the sample of the second study phase

	2-year heroin	**Switchers**	**Total**
T-1 – T0	30.5 (32.6)	29.4 (26.7)	30.3 (31.5)
T0 – T1	31.2 (4.9)	35.6 (10.4)	32.1 (6.6)
T0 – T3	94.7 (11.3)	98.9 (16.2)	95.5 (12.5)
T0 – T6	185.7 (16.8)	190.2 (15.1)	186.6 (16.6)
T0 – T12	366.0 (10.0)	362.8 (14.2)	365.3 (11.1)
T0 – T18	552.6 (16.1)	567.2 (36.9)	555.6 (22.7)
T0 – T24	736.7 (27.6)	752.9 (52.9)	740.1 (34.9)

3.4 Description of patients of the second study phase

The 434 patients of the second study phase consist of 344 patients treated with heroin for 2 years, and 90 switchers maintained with methadone in the first study phase and with heroin in the second phase. As the 2-year patients are expected to be a special group in terms of motivation and need for treatment, they are compared with the other patients (concluders and dropouts) of the first study phase.

The phase 2 patients are about evenly distributed regarding target group strata and kind of psychosocial treatment, similar to the distribution of the original sample of phase one. In the initial sample, 52.0% of the patients were from the stratum "not reached" (NR) and 48.0% from the stratum "methadone treatment failures" (MTF); the P2 sample is more evenly distributed, with 49.3% NR and 50.7% MTF (cf. paragraph 3.1). The difference is not statistically significant (Chi^2=2.23, p=0.135). The situation is similar for the two kinds of PST. The original distribution of 50.5% psychoeducation with drug counselling versus 49.5% case management with motivational interviewing hardly changed in the P2 sample: 50.2% PE/DC versus 49.8% CM/MI (Chi^2=0.29, p=0.864).

Table 3.6 presents a comparison between phase 2 patients and the other patients of phase 1 regarding demographic data and other patient characteristics at baseline (T_{-1}). The table includes all patients of the original ITT sample (n=1,015), differentiating between the 2-year heroin patients and the former methadone patients or switchers.

Table 3.6

Patient characteristics of the phase 2 sample at baseline (T_{-1}) compared to the other patients of the first study phase, according to 2-year heroin patients and methadone-heroin switchers. The standard deviation is shown in brackets. The values marked in grey point out significant differences between the samples.

Characteristic	P2 sample (n=434)			Other P1 patients (n=581)		
	Heroin	Switchers	Total	Heroin	Metha	Total
Gender, male proportion	80.8%	83.3%	**81.3%**	78.4%	79.0%	**78.8%**
Age, years	36.6 (6.6)	37.0 (7.0)	**36.6 (7.6)**	35.4 (6.7)	36.5 (6.8)	**36.2 (6.7)**
Social situation						
Stable housing situation	72.9%	75.6%	**73.4%**	61.2%	68.4%	**66.3%**
Steady partnership	36.9%	37.8%	**37.1%**	27.1%	31.1%	**29.9%**
Children	40.2%	34.4%	**39.0%**	37.1%	36.4%	**36.6%**
Professional training completed	47.5%	50.0%	**48.0%**	41.5%	42.3%	**42.0%**
Main source of income employment	5.2%	5.6%	**5.3%**	4.7%	3.4%	**3.8%**
Main income unemployment funds	20.3%	17.8%	**19.8%**	16.5%	17.6%	**17.3%**
Main source of income welfare	31.1%	35.6%	**32.0%**	34.7%	31.3%	**32.3%**
Main income pension/sickness benefit	3.8%	4.4%	**3.9%**	7.6%	6.6%	**6.9%**
Main source of income illegal	24.1%	21.1%	**23.5%**	18.2%	24.2%	**22.5%**
Main source of income other	15.4%	15.6%	**15.4%**	18.2%	16.9%	**17.3%**
Employment last 30 days	15.5%	15.6%	**15.5%**	9.9%	11.5%	**11.1%**
Debts	84.3%	84.4%	**84.3%**	78.8%	82.6%	**81.5%**
Amount of debts, Euro	13,088 (24,198)	19,550 (42,313)	**14,392 (28,824)**	11,933 (22,632)	22,614 (71,574)	**19,681 (62,256)**
Ever convicted	96.4%	93.3%	**95.8%**	97.6%	96.3%	**96.7%**
Ever in custody or sentenced to prison	72.5%	77.4%	**73.4%**	76.8%	74.6%	**75.3%**
In prison for narcotics offences	40.6%	49.2%	**42.3%**	41.3%	34.9%	**36.9%**
In prison for procuring offences	33.8%	33.9%	**33.8%**	31.0%	35.3%	**33.9%**
Illegal transactions last 30 days	71.7%	70.8%	**71.5%**	76.4%	72.6%	**73.7%**
Number of days	22.4 (10.1)	20.2 (10.4)	**21.9 (10.1)**	19.3 (10.9)	20.7 (10.3)	**20.3 (10.5)**
Physical health						
OTI health scale (0-50)	18.5 (5.2)	18.8 (4.8)	**18.6 (5.1)**	19.2 (5.2)	19.2 (5.5)	**19.2 (5.4)**
Karnofsky index (0-100)	72.5 (12.6)	71.3 (13.0)	**72.3 (12.7)**	69.9 (12.9)	71.2 (13.2)	**70.8 (13.1)**
Nutritional state BMI	22.9 (3.6)	22.6 (3.5)	**22.8 (3.6)**	22.4 (3.3)	22.5 (3.4)	**22.5 (3.4)**
HIV positive	7.6%	6.7%	**7.5%**	10.6%	10.1%	**10.2%**
HCV positive	79.4%	83.1%	**80.2%**	82.8%	81.6%	**82.0%**
Skin abscesses	6.8%	5.7%	**6.6%**	4.8%	7.8%	**6.9%**
Withdrawal symptoms (SOWS, 0-30)	9.5 (6.6)	10.6 (7.1)	**9.7 (6.7)**	9.6 (6.7)	10.1 (7.0)	**10.0 (7.0)**
Echocardiography pathol. finding [a)]	16.9%	14.4%	**16.4%**	15.2%	15.6%	**15.5%**
EKG pathol. finding [a)]	21.5%	21.1%	**21.4%**	12.9%	17.1%	**15.8%**
Abdominal sonograph. pathol. finding [a)]	57.6%	54.4%	**56.9%**	58.5%	52.4%	**54.2%**
Thorax x-ray pathol. finding [a)]	2.9%	2.2%	**2.8%**	1.2%	1.5%	**1.4%**
Mental health						
GSI value, SCL-90-R (T value)	68.8 (10.9)	69.6 (10.5)	**69.0 (10.8)**	69.1 (11.0)	69.7 (9.7)	**69.5 (10.1)**
GSI value, SCL-90-R (raw score, 0-4)	1.13 (0.65)	1.15 (0.55)	**1.13 (0.63)**	1.13 (0.61)	1.21 (0.68)	**1.19 (0.66)**
GAFS (0-100)	54.2 (11.2)	52.0 (11.6)	**53.8 (11.3)**	52.9 (11.6)	53.7 (11.8)	**53.5 (11.7)**
Previous suicide attempts	41.5%	42.5%	**41.7%**	41.2%	42.9%	**42.4%**
Clinical global impression (CGI, 0-7)	4.5 (1.0)	4.6 (1.0)	**4.5 (1.0)**	4.6 (1.0)	4.6 (1.0)	**4.6 (1.0)**
Lifetime diagnosis F2 disorder (at T_1) [b)]	0.6%	1.4%	**0.8%**	-	0.7%	**0.4%**
Lifetime diagnosis F3 disorder (at T_1) [b)]	34.3%	31.0%	**33.7%**	43.6%	34.3%	**38.2%**
Lifetime diagnosis F4 disorder (at T_1) [b)]	40.1%	52.1%	**42.2%**	46.8%	51.5%	**49.6%**
Lifetime diagnosis F5 disorder (at T_1) [b)]	3.1%	4.2%	**3.3%**	6.4%	5.2%	**5.7%**
At least one of these lifet. diagnoses [b)]	57.2%	57.7%	**57.3%**	70.2%	63.4%	**66.2%**

Drug use						
Beginning regular heroin use, age	20.3 (5.4)	20.0 (5.5)	**20.3 (5.4)**	19.4 (5.3)	20.4 (5.2)	**20.1 (5.2)**
Beginning regular cocaine use, age	22.7 (7.6)	23.2 (6.9)	**22.8 (7.4)**	21.8 (7.7)	22.7 (7.0)	**22.4 (7.3)**
Years of regular heroin use [c)]	13.8 (6.3)	13.9 (7.4)	**13.8 (6.5)**	13.6 (6.4)	13.6 (6.2)	**13.6 (6.2)**
Years of regular cocaine use [c)]	6.2 (6.7)	5.8 (6.8)	**6.1 (6.7)**	7.3 (6.9)	6.7 (6.5)	**6.9 (6.6)**
Years of regular benzodiazepine use	4.6 (6.7)	5.9 (7.6)	**4.8 (6.9)**	6.0 (7.5)	5.4 (7.1)	**5.6 (7.2)**
Years of regular multiple use	13.1 (8.4)	14.8 (8.8)	**13.5 (8.5)**	13.0 (8.6)	13.7 (8.1)	**13.5 (8.2)**
Heroin use last 30 days [c)]	96.2%	94.4%	**95.9%**	95.3%	95.8%	**95.7%**
Number of days [c)]	22.7 (9.7)	20.7 (10.5)	**22.3 (9.9)**	21.7 (10.6)	22.5 (9.8)	**22.3 (10.0)**
Cocaine use last 30 days [c)]	72.4%	63.3%	**70.5%**	81.3%	71.6%	**74.4%**
Number of days [c)]	13.7 (11.3)	11.3 (10.1)	**13.3 (11.1)**	16.5 (10.9)	16.0 (11.4)	**16.2 (11.2)**
Benzodiazepine use last 30 days	54.7%	60.0%	**55.8%**	60.6%	56.1%	**57.4%**
Number of days [c)]	15.6 (11.7)	15.8 (11.4)	**15.8 (11.6)**	17.3 (11.3)	16.7 (11.7)	**16.9 (11.6)**
Alcohol use (harmful) last 30 days	16.6%	21.1%	**17.5%**	9.9%	9.8%	**9.8%**
Number of days [c)]	11.7 (11.5)	17.3 (13.1)	**13.1 (12.1)**	12.0 (11.4)	12.2 (12.2)	**12.1 (11.9)**
Multiple use last 30 days	87.4%	92.0%	**88.3%**	86.7%	91.6%	**90.2%**
Number of days [c)]	23.7 (9.1)	23.8 (8.9)	**23.7 (9.1)**	22.9 (9.9)	23.8 (9.3)	**23.5 (9.5)**
Intravenous use last 30 days	97.1%	95.5%	**96.8%**	95.9%	95.3%	**95.5%**
Number of days [c)]	23.5 (9.6)	23.0 (10.0)	**23.4 (9.7)**	23.4 (9.7)	23.6 (9.4)	**23.5 (9.4)**
Drug overdose up to now	69.0%	80.7%	**71.4%**	75.9%	64.6%	**67.9%**
Number of drug overdoses [c)]	6.2 (12.0)	8.2 (14.8)	**6.6 (12.7)**	5.2 (9.9)	5.0 (7.5)	**5.1 (8.3)**
Money spent on drugs last 30 days, Euro	1,022 (1,209)	738 (806)	**963 (1,143)**	1,260 (2,044)	1,123 (1,535)	**1,163 (1,701)**
Money spent on alcohol last 30 d., Euro	29 (56)	31 (55)	**29 (55)**	30 (73)	30 (74)	**30 (74)**
Syringe sharing	9.4%	10.2%	**9.6%**	13.8%	6.7%	**8.8%**
Sharing of injection equipment	17.6%	21.6%	**18.4%**	25.1%	18.1%	**20.2%**
Addiction treatment						
Outpatient detoxification up to now	35.0%	36.9%	**35.4%**	24.1%	34.1%	**31.2%**
Average number [d)]	9.1 (12.6)	10.4 (13.5)	**9.4 (12.8)**	5.6 (9.3)	7.2 (10.7)	**6.8 (10.4)**
Inpatient detoxification up to now	84.6%	93.3%	**86.4%**	85.9%	83.5%	**84.2%**
Average number [d)]	7.6 (7.3)	7.8 (7.4)	**7.6 (7.3)**	7.4 (7.2)	6.5 (6.7)	**6.8 (6.8)**
Maintenance treatment up to now	90.3%	90.1%	**90.5%**	84.8%	90.1%	**88.5%**
Average duration, months [d)]	50.1 (43.6)	56.8 (42.7)	**51.5 (43.4)**	48.4 (46.2)	45.9 (42.4)	**46.6 (43.5)**
Psychosocial treatment up to now	48.5%	69.0%	**52.8%**	51.5%	51.7%	**51.6%**
Average duration, months [d)]	41.4 (42.0)	50.3 (55.2)	**43.9 (46.1)**	37.1 (39.0)	36.1 (35.6)	**36.4 (36.6)**
Outpatient drugfree treatment up to now	12.3%	8.4%	**11.5%**	6.1%	13.1%	**11.0%**
Average number [d)]	1.7 (1.8)	1.4 (0.8)	**1.7 (1.7)**	1.0 (0.0)	1.6 (1.6)	**1.5 (1.4)**
Inpatient drugfree treatment up to now	56.8%	62.5%	**58.0%**	61.4%	55.7%	**57.4%**
Average number [d)]	2.1 (1.4)	2.5 (1.7)	**2.2 (1.5)**	2.2 (1.5)	2.2 (1.5)	**2.2 (1.5)**
Therapeutic flat sharing up to now	24.8%	25.0%	**24.8%**	26.2%	26.8%	**26.6%**
Average number [d)]	1.4 (0.8)	1.3 (1.0)	**1.4 (0.8)**	1.5 (0.7)	1.3 (0.7)	**1.4 (0.7)**
None of these treatments up to now	0.9%	2.2%	**1.2%**	3.5%	1.5%	**2.1%**
N	**344**	**90**	**434**	**171**	**410**	**581**

[a)] Percentages relate to all randomised patients (examination performed: echocardiography: n=890, EKG: 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 includes speedballs (heroin & cocaine). Cocaine use includes crack and speedballs. The average number refers to patients with drug use (last 30 days) or overdoses (number).

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

At first sight, the sample of the second study phase hardly differs from the other patients of the first phase. Therefore, the P2 sample is, at baseline, to a large extent a representative sub-group of all the study patients ever randomised. Statistically significant differences exist in

the domains of housing, partnership and employment and for drug use. Moreover, the 2-year patients were less subject to mental disorders (lifetime diagnoses). The first named differences indicate that patients of the second study phase were initially in a more stable social situation, which is likely to have a favourable prognostic effect on long-term retention in heroin treatment. This was already shown in the analysis of dropouts of the first study phase (Naber & Haasen 2006). Differences are less clear where the consumption patterns are concerned. The P2 patients used cocaine slightly less frequently at T_{-1} – this was also detected among the regular concluders of the first study phase – but had a clearly higher level of harmful alcohol use. On the other hand, they spent less money on drugs.

Thus, the ITT sample characteristics of the entire model project can be applied to the subgroup of the 2-year patients. The majority of the P2 patients are male and in their mid-thirties. One quarter lived in unstable housing conditions prior to treatment initiation (guest-house, homeless, institution), slightly more than one third had a steady partner. Less than half of them had completed professional training, and the current labour situation is rather poor: Only 16% of the 2-year patients had been employed in the last month prior to the study initiation. Sources of income were mainly social funds. Almost all study participants had been sentenced, three quarters had been in prison.

The overall health state of the phase-2 patients is poor at baseline. 19 symptoms on the OTI health scale (Darke et al. 1991; 1992) and an average of 72 points on the Karnofsky index indicate severe health impairments. 80% had a hepatitis C virus infection, and almost 8% were HIV positive. The mental state of the sample was as well very poor at baseline. 69 points (T value) on the Global Severity Index of the SCL-90-R indicate a high degree of mental stress (Franke 1995). In the external assessment by the Global Assessment of Functioning Scale (GAFS), patients reached an average value of only 54 points. Accordingly, the clinical global assessment of the prevalence of mental illness was between “moderate” and “definitely ill”. Two fifths of the P2 patients had attempted suicide (at least) once.

Almost all patients used heroin intravenously prior to the study and 71% cocaine in the last month prior to the baseline examination (T_{-1}). More than half used (prescribed or non-prescribed) benzodiazepines, multiple use was the rule. Almost three quarters had experienced drug overdose at least once, on average almost 7 times.

Almost all the 2-year patients have experience with previous addiction treatments. More than 90% had been in maintenance treatment at some time prior to participating in the model project, on average for a total duration of more than 4 years. 86% had been in inpatient detoxification treatment, on average almost 8 times. 58% of the study patients had experience with inpatient long-term treatment.

4. Switching from methadone to heroin

A special feature of the design of the German model project for heroin-assisted treatment was the chance offered to control group patients to switch to heroin treatment in the second study phase after conclusion of the first phase, (Krausz et al. 2001).[6] As described above, 90 patients could change directly from methadone to heroin maintenance treatment. This occurred on average after 385 days,[7] i.e. after a little more than one year, since there were waiting periods in individual cases due to the switching procedure according to a defined (re-)randomisation plan. In the smaller study centres, 100% of the heroin places were filled (again) (cf. paragraph 3.1). In these centres, a certain number of control group patients, who had regularly concluded the first study phase and wished to switch, were faced with the problem that they were not re-randomised to vacated heroin places and therefore had to leave the study treatment. As a rule, they could continue maintenance treatment within the normal treatment system.

Although switching is not the main focus of the study (which, moreover, is not blinded), a closer consideration of the group of methadone-heroin switchers allows to draw conclusions about immediate and long-term effects of switching the maintenance substance. The course of development in switchers after changing to the new maintenance medication can be particularly informative when compared to the group of patients treated with heroin for 2 years.

The efficacy analysis of the treatment course is based upon all the patients, who started the second study phase (switchers: n=90, 2-year heroin group: n=344), i.e. irrespective of whether the treatment was carried on for 12 months. As described in paragraph 3.3, 89% to 91% of the P2 sample, depending on the examination method (medical investigator vs. external interview), could be followed up at T_{24}. Therefore, the course analysis of the second phase of the model project relies on a solid database, with only a low level of distortion caused by dropouts.

The focus is at first on the issue to what extent the primary outcome measures of the comparative trial of the first phase are reproducible in the second phase, i.e. within the period of 24 months. For this purpose, the target criteria “health improvement” and “decrease of illicit drug use” are calculated according to the existing operationalisation (cf. Verthein et al. 2005) for phases one and two. After concluding the comparative trial, urinalyses for street heroin and hair analyses for cocaine were no longer performed in the second phase; therefore, the calculation of the target criteria is based exclusively on patients’ self-reports. Missing data at T_{24} are again completed according to “last observation carried forward” (LOCF) with data collected at T_{18}. Regarding drug use within the last 30 days, it was possible to substitute data of medical examinations by data from the external interviews. Unlike the primary analysis of the first study phase, the conservative “worst case” analysis strategy (study dropouts of the heroin group are counted as non-responders, dropouts of the methadone group as responders) cannot be applied, but a symmetrical analysis setting is used counting dropouts of both treat-

[6] In the Dutch trial, patients of the control group also had the opportunity to change to heroin treatment (combined with methadone) (van den Brink et al. 1999). The analysis of the results is not yet available.

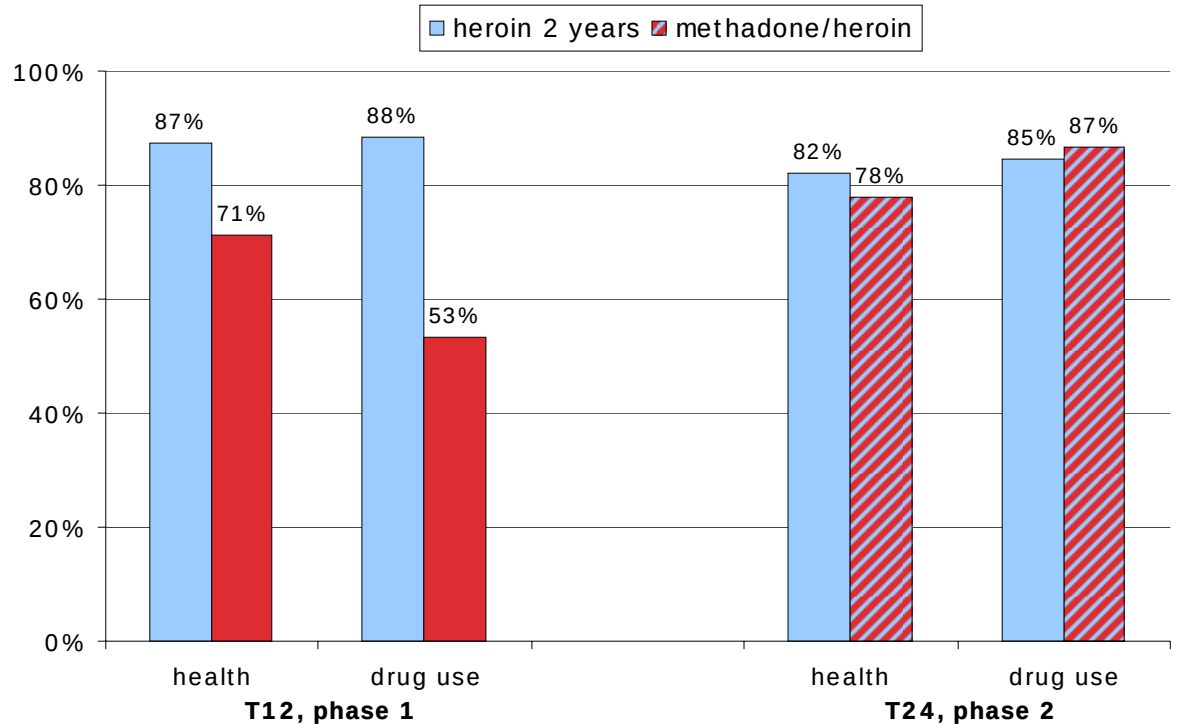
[7] Calculated from the date of randomisation.

ment groups as non-responders.[8] An asymmetric "dropout strategy" would not be appropriate, since patients of both groups of the first study phase are now in heroin-assisted treatment.
Based on this evaluation strategy, significant differences between heroin patients and methadone patients in the response rates of the primary outcome measures are still found in the P2 sample at T_{12} (POM health: OR=2.77, 95%-CI: 1.59-4.82, p<0.001; POM drug use: OR=6.65, 95%-CI: 3.92-11.29, p<0.001). The significant results of the primary analysis of the comparative trial (first study phase) are thus confirmed in the subgroup of the 2-year patients (see figure 4.1). After switching from methadone to heroin, the situation is different at the end of the second study phase: In both primary outcome measures, no significant differences are detected in the response rates between the group of switchers and the 2-year heroin patients after 24 months (POM health: OR=1.30, 95%-CI: 0.74-2.29, p=0.365; POM drug use: OR=0.85, 95%-CI: 0.43-1.66, p=0.624). The response rates of the POM health are between 78% and 82% in both groups, in the POM drug use 85% and 87% respectively.[9] Methadone-heroin switchers succeeded in catching up with the improvements related to health and illicit drug use achieved by the heroin group. In the year following the switching of the maintenance substance, they achieved similar progress to that of heroin patients in the first study phase. These results again confirm the greater efficacy of heroin treatment compared to methadone treatment. Even after one year of successful methadone maintenance, switching to heroin can still achieve better results in the group of severely dependent patients.

[8] Also in the second study phase, all deaths are counted as „non-responders".

[9] The decline of response rates in the heroin group between T_{12} and T_{24} is mainly due to study dropouts (cf. paragraph 3.3), as missing data at T_{24} were processed as „non-response".

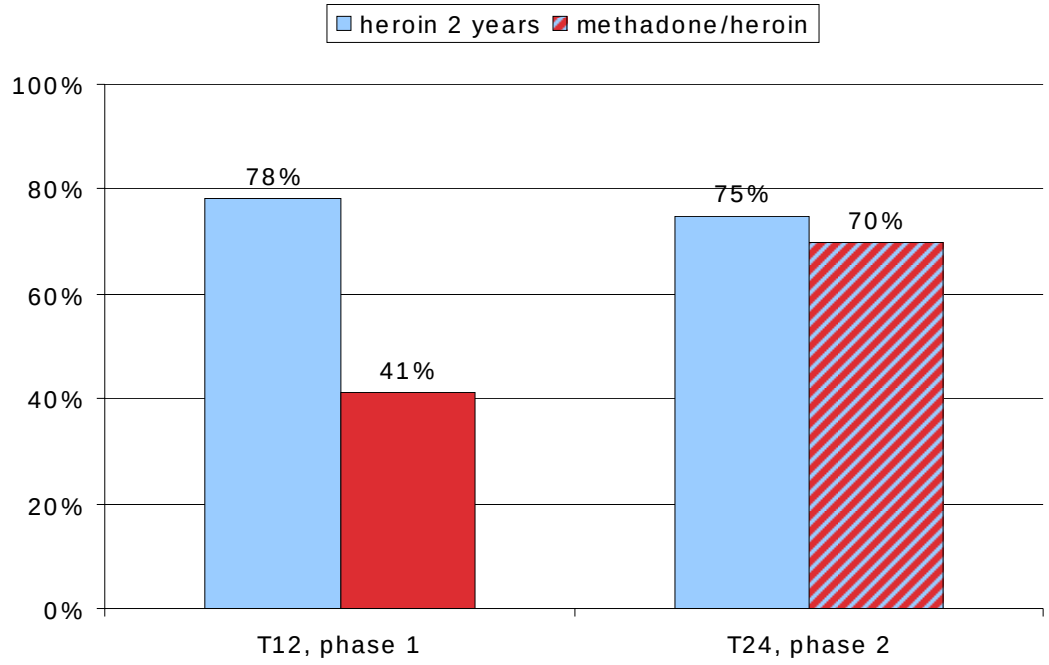
Figure 4.1
Response rates of the primary outcome measures "health improvement" and "reduction of illicit drug use" at T_{12} and T_{24} among 2-year heroin patients (n=344) and methadone-heroin switchers (n=90)



These results are confirmed in the analysis of the "combined" primary outcome measure, which evaluates the treatment response jointly for both primary outcome measures. As expected, the response rates are again lower; the significant group difference at T_{12} (OR=5.14, 95%-CI: 3.14-8.40, p<0.001) disappears at the end of the second study phase (OR=1.27, 95%-CI: 0.76-2.11, p=0.366, see figure 4.2).[10] After two years, the methadone-heroin switchers achieve similar results as patients treated with heroin for 24 months.

[10] Again, the decline of response rates in the heroin group between T_{12} and T_{24} is mainly caused by study drop-outs (cf. paragraph 3.3), since missing data were counted as „non-response" at T_{24}.

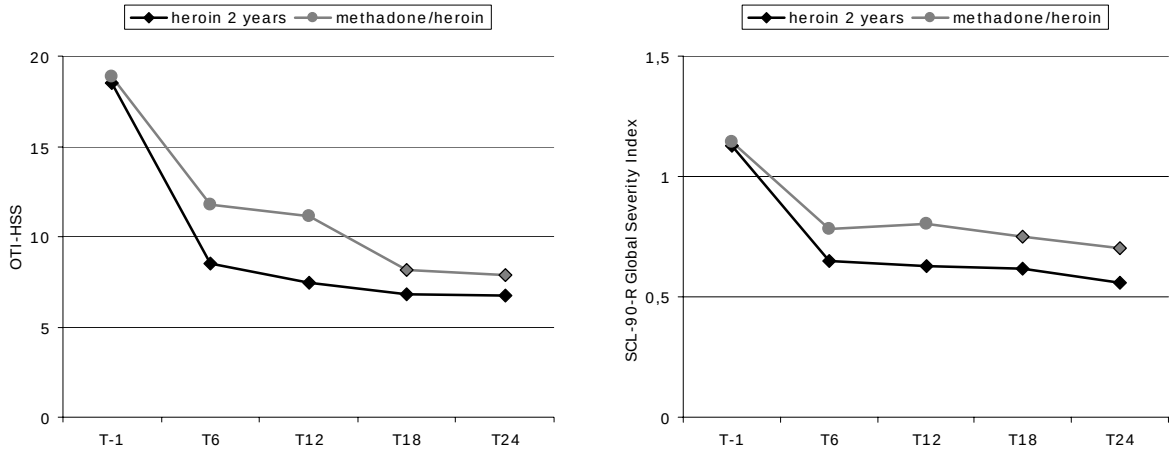
Figure 4.2
Response rates related to both primary outcome measures fulfilled at T_{12} and T_{24} among the 2-year heroin patients (n=344) and the methadone-heroin switchers (n=90)



Improvements in both groups in the first and second study phase are reflected by the course of each target criterion. Physical health improves considerably during the first year of treatment; at T_{12} the heroin group is in better health than the methadone group (cf. Naber & Haasen 2006). In the course of the second phase, physical symptoms improved only slightly in the 2-year heroin group; symptoms markedly decline in switchers after changing from methadone to heroin (see figure 4.3, left side). A comparison of T_{12} and T_{24}, i.e. initiation and end of the second study phase, reveals significant improvements in both groups. The repeated measurement analysis indicates a significant time effect (Pillai's trace=0.107, df=1, $p<0.001$) with significant interaction between the study groups (interaction time with group: Pillai's trace=0.061, df=1, $p<0.001$). An individual analysis of each group with respect to symptoms changes between T_{12} and T_{24} reveals a significant reduction of physical symptoms (t=2.12, df=306, p=0.035) both in switchers (T test for dependent samples: t=5.28, df=80, $p<0.001$) and in the 2-year heroin group.
The results are similar regarding the reduction of mental impairments. Although the group of switchers hardly reaches the degree of symptoms reduction achieved in the 2-year heroin group (see figure 4.3, right side), a significant time effect is obtained when reducing the GSI of the SCL-90-R in the repeated measurement analysis (Pillai's trace=0.017, df=1, p=0.012). The parallel curves between T_{12} and T_{24} however indicate that an interaction between examination period and study group cannot be detected (interaction: Pillai's trace=0.001, df=1, $p<0.512$). In the individual comparison, the methadone-heroin switchers do not show a statis-

tically significant reduction effect (t=1.87, df=80, p=0.065),[11] in the 2-year heroin group, the reduction of mental symptoms, though less marked, reaches statistical significance (t=21.03, df=302, p<0.05).

Figure 4.3
Change in physical health according to the OTI health scale (left) and mental health according to the Global Severity Index (GSI) of the SCL-90-R (right) among the 2-year heroin patients and the methadone-heroin switchers[a)]



a) Missing data at T_6 and T_{12} were completed, if possible, by information collected at the external interviews. OTI-HSS: n_{-1}=434, n_6=428, n_{12}=434, n_{18}=401, n_{24}=388, SCL-90-R: n_{-1}=434, n_6=425, n_{12}=430, n_{18}=400, n_{24}=387.

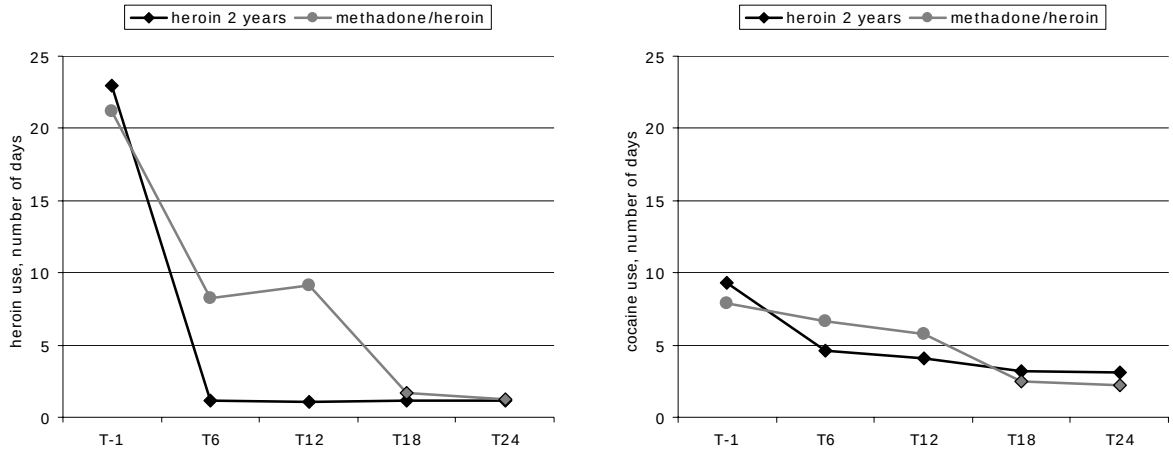
As expected, reduction of street heroin is the most conspicuous positive change after switching from methadone to heroin. The results on street heroin use based on patients' reports show a clear decline.[12] At T_{24}, drug use within the last 30 days (see figure 4.4, left side) no longer differs between the two groups. The repeated measurement analysis finds a significant decline for the interval T_{12} to T_{24} (Pillai's trace=0.186, df=1, p<0.001) and an interaction effect between group affiliation and time (Pillai's trace=0.196, df=1, p<0.001). Accordingly, the individual analysis shows a statistically significant decline of street heroin use in the group of switchers (t=6.65, df=86, p<0.001), but not in the 2-year heroin group (t=-0.48, df=313, p=0.629). This is understandable considering that, in the first study phase, the decline of street heroin among heroin patients (on average) already reached a degree that hardly allows any more substantial reduction.
Cocaine use also declined in both groups, more markedly among switchers than among the 2-year heroin patients in the second study phase (figure 4.4 right side). The repeated measurement model shows a significant reduction of consumption (Pillai's trace=0.066, df=1, p<0.001), and also an interaction between time effect and group effect, clearly seen by the intersecting lines (Pillai's trace=0.033, df=1, p<0.001). The separate statistical analysis shows

11 This is mainly due to the smaller size of the group of switchers. Although symptoms reduction is more marked than in the 2-year heroin group, the inference-statistical test does not yield a significant result.

12 As mentioned above, urinalyses for street heroin were no longer performed in the second study phase.

for both groups a significant reduction of cocaine use during the second study phase (switchers: t=3.90, df=86, p<0.001; 2-year heroin group: t=1.96, df=313, p=0.050).
The slight (though not significant) baseline difference between switchers and 2-year heroin group regarding the number of days of use at T_{-1} hints to a selection effect of the phase-2 sample. As shown above, the intensity of cocaine use is somewhat lower in the 2-year sample at baseline (cf. paragraph 3.4). The lower intensity of use (also of street heroin) is mainly observed in the group of switchers, suggesting that patients of the methadone control group with initially less illicit drug use were better able to regularly conclude the first study phase and change to heroin treatment (cf. Naber & Haasen 2006).

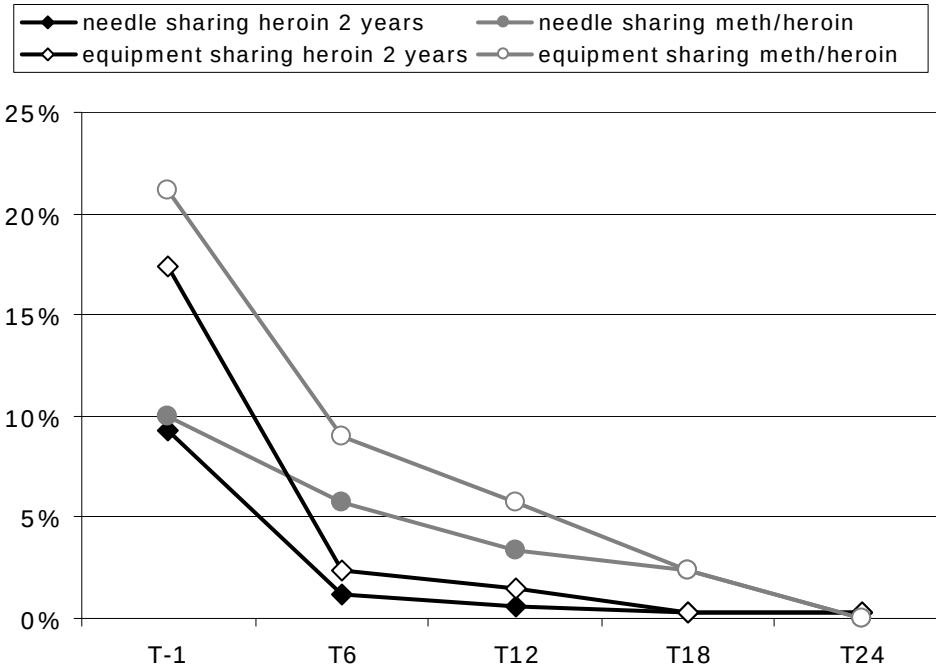
Figure 4.4
Change in street heroin use (left) and cocaine use (right) within the last 30 days based on patients' self-reports at the medical investigators' examinations[a)] among the 2-year heroin patients and the methadone-heroin switchers[b)]



a) Due to the comparability across all examination times, data from the medical investigators' examinations are presented here; missing data are completed from the external interviews.
b) Street heroin: n_{-1}=433, n_6=434, n_{12}=434, n_{18}=413, n_{24}=401, cocaine: n_{-1}=434, n_6=434, n_{12}=434, n_{18}=413, n_{24}=401.

The course of symptoms related to physical and mental health and changes in the use of illicit drugs are further indication of the positive long-term effects of heroin treatment. Both the group of 2-year heroin patients and of methadone-heroin switchers attained further improvements in the main survey domains during the second year of treatment.
A decrease of risk behaviour occurs parallel to the decrease of illicit drug use and concomitant to health improvement. Figure 4.5 shows that, at the end of the second study phase, virtually no patient shares syringes or injection equipment (spoon, filter etc.) with other drug users. The decline of high-risk forms of consumption or application occurs in heroin patients already at an early stage. Switchers need a bit longer: Although a substantial reduction of risk behaviour occurred already during methadone treatment in the first year, high-risk use behaviour is only relinquished after switching to heroin treatment during the second treatment phase. This corresponds with the marked decline of street heroin and cocaine use in the second year of treatment (see above).

Figure 4.5
Change in risk behaviour in terms of shared syringes and injection equipment among the 2-year heroin patients and the methadone-heroin switchers



With the decline of illicit drug use, scene contacts also change. At the end of the first study phase (T_{12}), 47% of the heroin patients still had contacts to the drug scene, compared to two thirds of the methadone group (66%); after two years (T_{24}), the rate is reduced to 41% in the heroin group and 45% in the switchers.
To conclude, the 2-year heroin patients and the group of switchers are compared with respect to other life areas, represented by the *ASI-Composite Scores*. The composite scores (CS) record the extent of problems in the dimensions investigated by the EuropASI on a scale from 0-1; higher values correspond to higher stress level or greater need for treatment (McGahan et al. 1986; Gsellhofer et al. 1999). Apart from the satisfaction with the employment/subsistence situation and alcohol use, the life situation of patients of the second study phase continuously improved in all areas over 24 months (see table 4.1). In the first phase (at T_{12}), the heroin and the methadone group significantly differed in many domains (cf. Naber & Haasen 2006); at the end of the second study phase, the 2-year heroin patients and the switchers achieved comparable or equal progress in almost all dimensions. Only for drug use, there is a significant group difference at $T_{24,}$ mainly caused by the clearly worse condition of the switchers at the beginning of the second study phase (T_{12}).[13] Accordingly, the analysis of the ASI Composite Scores shows a "catch-up effect" in patients, who switched from methadone to heroin.

[13] In order to include changes of the second study phase in the statistical analysis, the variance analysis at T_{24} was performed as covariate with consideration of the values at T_{12}. This explains the missing significance of clearly different values at T_{24} (e.g. in the physical state MED).

Table 4.1

ASI Composite Scores at T_{-1}, T_{12} and T_{24} according to treatment group. Mean values, standard deviations (in brackets) and covariance analysis considering the value at T_{12}

ASI-CS[a)]		**2-year heroin**	**Switchers**	**Total**	**Significance ANCOVA at T24**
MED	T-1	0.41 (0.33)	0.44 (0.33)	0.42 (0.33)	F=0.26, df=1, p=0.613
	T12	0.31 (0.33)	0.40 (0.35)	0.33 (0.33)	
	T24	0.28 (0.33)	0.34 (0.35)	0.29 (0.33)	
ECON	T-1	0.90 (0.25)	0.90 (0.26)	0.90 (0.25)	F=0.10, df=1, p=0.748
	T12	0.84 (0.31)	0.85 (0.30)	0.84 (0.30)	
	T24	0.82 (0.34)	0.81 (0.33)	0.82 (0.34)	
SAT	T-1	0.37 (0.33)	0.29 (0.32)	0.35 (0.33)	F=0.12, df=1, p=0.677
	T12	0.15 (0.27)	0.11 (0.23)	0.14 (0.27)	
	T24	0.18 (0.27)	0.19 (0.26)	0.18 (0.27)	
ALC	T-1	0.12 (0.18)	0.16 (0.22)	0.13 (0.19)	F=2.55, df=1, p=0.111
	T12	0.09 (0.16)	0.21 (0.26)	0.11 (0.19)	
	T24	0.11 (0.18)	0.13 (0.20)	0.11 (0.18)	
DRU2	T-1	0.52 (0.13)	0.53 (0.13)	0.52 (0.13)	F=17.33, df=1, p<0.001
	T12	0.19 (0.15)	0.41 (0.15)	0.24 (0.18)	
	T24	0.19 (0.15)	0.20 (0.15)	0.19 (0.15)	
LEG	T-1	0.41 (0.26)	0.35 (0.26)	0.39 (0.26)	F=0.93, df=1, p<0.336
	T12	0.16 (0.22)	0.27 (0.25)	0.18 (0.23)	
	T24	0.14 (0.20)	0.16 (0.20)	0.14 (0.20)	
FAM	T-1	0.26 (0.20)	0.25 (0.16)	0.26 (0.19)	F=0.00, df=1, p=0.984
	T12	0.08 (0.15)	0.11 (0.17)	0.09 (0.15)	
	T24	0.06 (0.14)	0.07 (0.13)	0.06 (0.14)	
OTH	T-1	0.25 (0.21)	0.29 (0.22)	0.26 (0.21)	F=1.56, df=1, p=0.213
	T12	0.09 (0.15)	0.15 (0.17)	0.10 (0.16)	
	T24	0.06 (0.14)	0.09 (0.15)	0.07 (0.14)	
PSY	T-1	0.23 (0.21)	0.25 (0.20)	0.24 (0.21)	F=0.01, df=1, p=0.914
	T12	0.18 (0.21)	0.24 (0.23)	0.19 (0.21)	
	T24	0.15 (0.19)	0.19 (0.20)	0.16 (0.19)	

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

5. Efficacy of heroin-assisted treatment over two years

The following chapters are devoted to the development of the life situation of patients, who were treated with heroin for two years. In the second year, study treatment was also "heroin-assisted" in an integrated setting based on daily applications of the maintenance medication, regular contacts with physicians, medical examinations and concomitant psychosocial treatment. In comparison with international research, the analysis of the 2-year results of the German study is of particular significance, because there are no comparable studies on long-term effects of heroin-assisted treatment, with the exception of the Swiss 6-year follow-up survey (Güttinger et al. 2002; 2003).
Analyses of the 2-year treatment are based upon all the heroin patients, who initiated the second study phase (n=344). As described in chapter 3.2, not all the 2-year heroin patients regularly concluded the second study phase. 278 patients, i.e. 80.8% of the heroin group, remained in treatment to the end of the second phase. Almost all of them (n=276, i.e. 80.2% of the 2-year group) immediately entered the follow-up phase. Therefore, the description of the course of treatment of the phase-2 sample also includes data of patients meanwhile dropped out. Health development (chapter 5.1), social stabilisation (chapter 5.2) and long-term changes in drug use (chapter 5.3) are analysed in detail. Doses, effects and side effects are described in chapter 5.4.

5.1 Health development in heroin patients

The inclusion criteria of the model project for heroin-assisted treatment ensured the inclusion of the so-called most severely dependent patients, whose situation is mainly characterised by severe physical and mental impairments and social marginalisation. At baseline, four fifths of the 2-year heroin patients had a hepatitis C virus infection (79.4%), 7.6% were HIV positive.[14] The high degree of somatic comorbidity is conspicuous: All HIV-positive patients also have a HCV infection. At the time of baseline examinations (T_{-1}), 6.8% had skin abscesses; related to the last 12 months, the proportion even 19.2% higher.
The initial level of health impairments is even more evident by the degree of internistic disorders, which were explored by medical apparatus. At least one pathological finding was detected in almost three quarters of the patients (72.4%). More than half of the heroin patients suffered from epigastric disorders, most often splenohepatomegaly and parenchymal thickening, detected through sonography (see table 5.1). Hepatomegaly and congestion of portal vein are not statistically related to the HCV infection status. But a significant relationship exists between hepatomegaly and HIV infection: It is found in a particularly high number of

[14] Compared to data from Hamburg of the nineties, the HIV rate of the study patients is slightly higher (cf. Heinemann et al. 1999; Kalke & Raschke 1999). In the recent study on visitors of consumption rooms in Frankfurt of 2004, 10% of the interviewees stated that they were HIV positive (Schmid & Vogt 2005). According to the REITOX report of the DBDD, it must be assumed that less than 5% of the i.v. drug users were HIV positive in 2004. Because of regional differences of HIV prevalence, the severity of the health state among study patients cannot be deducted only from the infection rate. The hepatitis C rate, on the other hand, is in the upper ranges compared to other epidemiological data (Simon et al. 2005).

HIV positive patients (46.2%). Pathological cardiac findings such as valvular defect or dysrhythmia or conduction disturbance were also found in a considerable number of patients. Relationships with the infection status (HCV, HIV) of heroin patients were not likely and not found.

The investigation of consumption behaviour and length of alcohol, heroin or cocaine/crack use hardly confirms the expected relationship between length of drug use and degree of internistic disorders. No influences on cardiological disorders are detected. A relationship is only found between sonographic findings of the epigastrum and the duration of the drug career: Patients with internistic disorders are older (on average 37.3 years compared to 35.6 years), and they have been regularly using street heroin (14.6 vs. 12.6 years) and consuming intravenously (14.7 vs. 12.2 years) for a long time.

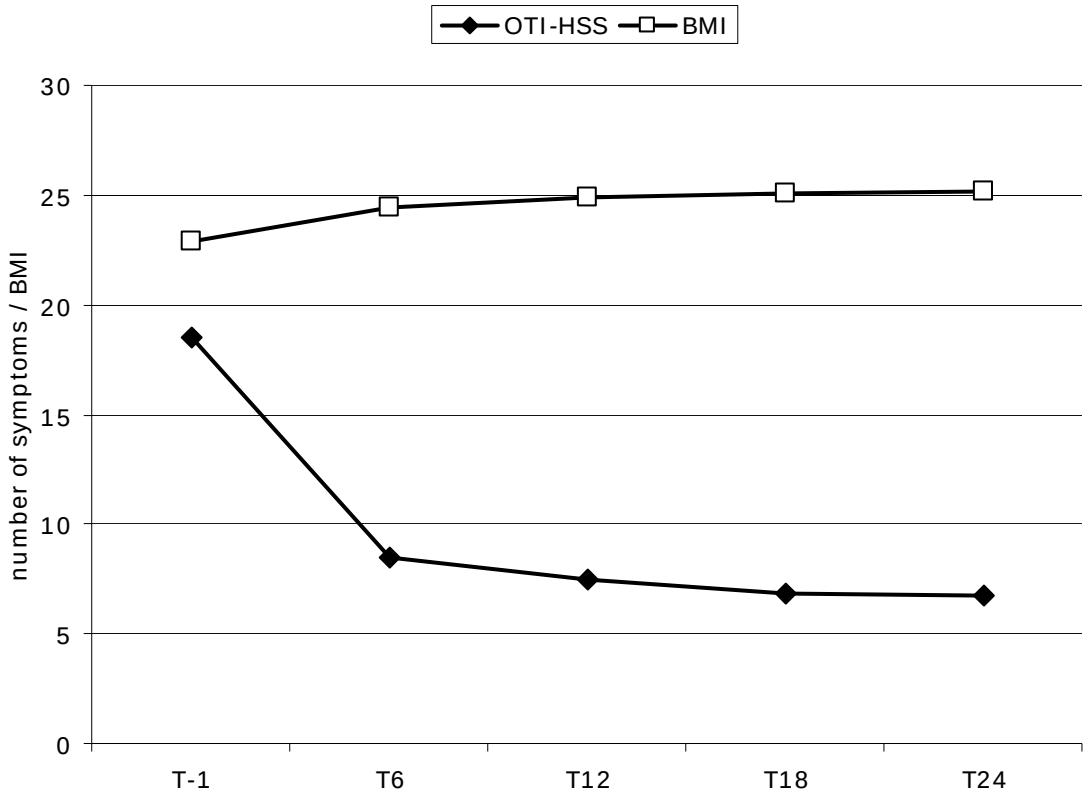
Table 5.1
Medical disorders and pathological findings of the 2-year heroin patients at baseline (T_{-1})[a)]

Medical finding	**%**
Echocardiography, conspicuous finding overall	16.9
Aortic valve	4.1
Mitral valve	10.2
Tricuspid valve	10.2
Pulmonary valve	5.5
Cardiomyopathy	0.3
Pericardial effusion	0.6
EKG, conspicuous finding overall	21.5
Dysrhythmia	4.7
Extra systoles	1.5
Conduction disorders	5.5
Atrial conduction disorders	10.1
Recovery disorders	5.8
Abdominal sonography, conspicuous finding overall	57.6
Hepatomegaly	24.7
Parenchymal thickening	33.1
Parenchymal coarsening	9.9
Congestion of the portal vein	6.7
Focal lesions	0.6
Ascites	0.6
Enlarged spleen	11.0
Enlarged lymph nodes	6.7
Thorax x-ray, conspicuous finding overall	2.9
Inflammatory infiltrations	0.3
Pathological cardiac size	0.3
Congestion	0.3
Pleural fibrosis	1.5
Sources of infection	0.6

[a)] The percentage relates in each case to the total group of n=344 heroin patients, but not all examinations were performed in all the patients (valid data: echocardiography: n=322, EKG: n=330, sonography: n=340, x-ray: n=34).

Physical symptoms were explored by the OTI health scale, and the results were partly reported in chapter 4 (in comparison to the group of switchers). Figure 5.1 presents the course of symptoms across all examination times with 6-month intervals. It is again evident that the greatest progress is achieved in the first months of heroin treatment. In the further course, the degree of improvement declines and the health state stabilises at a satisfying level with an average of 6-7 points. The result of the repeated measurement analysis shows a statistically significant improvement in the course of treatment (Pillai's trace=0.836, df=4, p<0.001). The within-subjects contrasts indicate significant changes between the values of adjacent examination times during the first study phase; differences between examination times of the second phase (T_{12} to T_{18}, T_{18} to T_{24}) are not statistically significant.[15]
At the same time, patients' nutritional state improves. At baseline, the Body-Mass-Index (BMI) is 22.9 points on average; it continuously increases to 25.2 points at the end of the second study phase (see figure 5.1). This positive development is also statistically significant over time (Pillai's trace=0.424, df=4, p<0.001).[16]

Figure 5.1
Changes in physical health according to the OTI health scale and in the nutritional state in terms of Body-Mass-Index (BMI) in heroin patients over 24 months (n=344)



[15] Within-subjects contrasts in the time effect: T_{-1} to T_6: F=929.7, df=1, p<0.001; T_6 to T_{12}: F=29.8, df=1, p<0.001; T_{12} to T_{18}: F=3.6, df=1, p=0.059; T_{18} to T_{24}: F=0.4, df=1, p=0.543. Irrespective of information for individual values in the text, repeated measurement analyses in this chapter are always carried out across five examination times with 6-month intervals.

[16] Within-subjects contrasts in the time effect between examination times: T_{-1} to T_6: F=161.7, df=1, p<0.001; T_6 to T_{12}: F=13.1, df=1, p<0.001; T_{12} to T_{18}: F=3.0, df=1, p=0.087; T_{18} to T_{24}: F=1.4, df=1, p=0.243.

The most frequent physical symptoms at T_{24} were sleep disturbances (52.0%), tiredness (49.3%), expectoration (49.0%) and irregular menses (48.6% of the women). Symptoms such as headaches (30.9%), loss of libido (29.6%), forgetfulness (27.8%), persistent coughing (27.5%), difficult respiration (25.5%), night sweat (23.9%), obstipation (22.5%) and abdominal pain (19.9%), toothache (19.6%) and joint pains (18.6%) occurred sometimes or rarely. With the exception of menses disorders, the decline of all mentioned symptoms was statistically significant compared to baseline (McNemar: $p<0.001$).
The global assessment by medical investigators, measured with the Karnofsky index, confirms the positive health development. The average of 72.5 points prior to heroin treatment (T_{-1}) means that the patients were able to take care of themselves but that their ability to work or to perform "normal" activities was clearly impaired. After one year, the value is 80.2 points, after 2 years 81.0 points on average ("normal activities possible without effort, some symptoms or evidence of illness"). This result is also statistically significant in the repeated measurement analysis (Pillai's trace=0.358, df=4, $p<0.001$).[17]
The ASI composite scores presented in chapter 4 also indicate a positive health development. The average values improve from 0.41 to 0.31 after 12 months and 0.28 points after 24 months. Again, the repeated measurement analysis results in a significant positive time effect (Pillai's trace=0.099, df=2, $p<0.001$; within-subjects contrasts: T_{-1} to T_{12}: F=21.4, df=1, $p<0.001$; T_{12} to T_{24}: F=1.2, df=1, p=0.277). All the results related to the course of physical health point in the same direction: clear improvement during the first study phase and stabilisation of the achieved health state in the second year of treatment.

Changes in mental symptoms are assessed by the scores of global mental impairments (GSI) of the SCL-90-R, of the level of psychosocial functioning (GAFS) and of the global clinical impression (GCI). Figure 5.2 clearly shows continuous improvement in all the criteria over the 2-year treatment period. The Global Severity Index of the SCL-90-R declines from an average of 1.13 points at T_{-1} to 0.63 points at T_{12} and 0.56 points at T_{24} (repeated measurement analysis: Pillai's trace=0.458, df=4, $p<0.001$).[18] The GSI raw values correspond to standardised t-values of 68.8 points at T_{-1} and 55.3 points at T_{24}. Mental impairment of heroin patients was very pronounced at baseline with almost 2 standard deviations above normal value (50 points) and decreased almost to normal in the course of the 2-year treatment. The clinical impression by medical investigators improved from a mean value of 4.5 ("moderately ill" – "clearly ill") to 4.0 points at T_{12} and 3.8 ("slightly ill" – "moderately ill") at the end of the second study phase (repeated measurement analysis: Pillai's trace=0.285, df=4, $p<0.001$).[19] The psychosocial level of functioning also takes a definitely positive course: After 24 months, the relatively low average GAFS score of 54.2 points at T_{-1} increases to 66.8

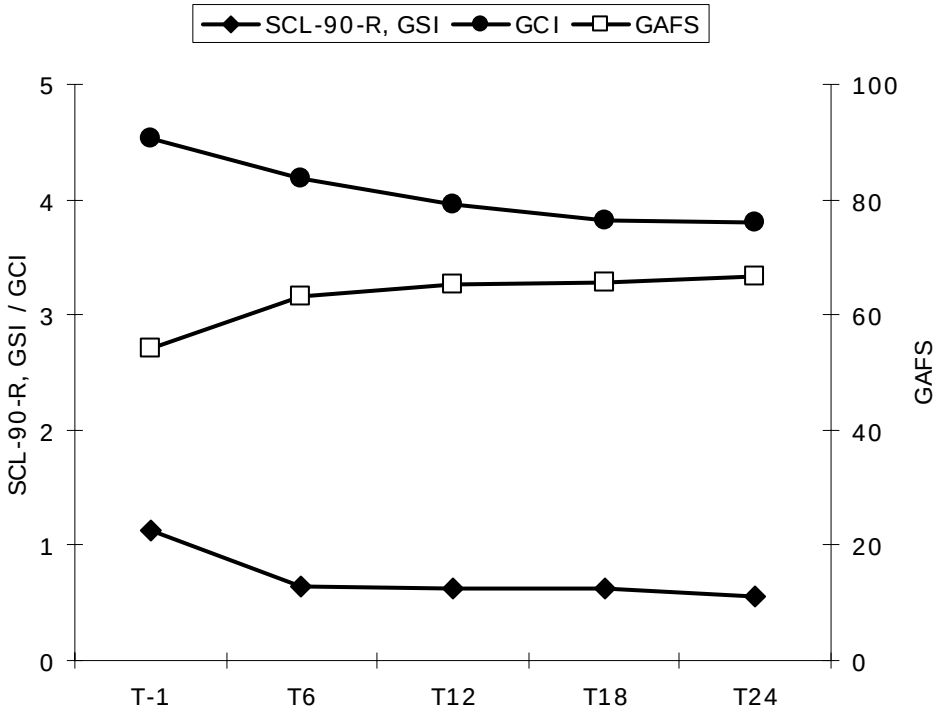
[17] Within-subjects contrasts in the time effect between times of examination: T_{-1} at T_6: F=81.2, df=1, $p<0.001$; T_6 at T_{12}: F=15.4, df=1, $p<0.001$; T_{12} at T_{18}: F=0.2, df=1, p=0.621; T_{18} at T_{24}: F=0.4, df=1, p=0.530.

[18] Within-subjects contrasts in the time effect between times of examination: T_{-1} at T_6: F=183.8, df=1, $p<0.001$; T_6 at T_{12}: F=1.1, df=1, p=0.303; T_{12} at T_{18}: F=0.0, df=1, p=0.846; T_{18} at T_{24}: F=8.0, df=1, $p<0.01$.

[19] Within-subjects contrasts in the time effect between times of examination: T_{-1} at T_6: F=22.9, df=1, $p<0.001$; T_6 at T_{12}: F=38.6, df=1, $p<0.001$; T_{12} at T_{18}: F=11.7, df=1, $p<0.01$; T_{18} at T_{24}: F=0.6, df=1, p=0.459.

points indicating "light" mental symptoms or "light difficulties regarding social or professional efficiency" (repeated measurement analysis: Pillai's trace=0.509, df=4, p<0.001).[20]

Figure 5.2
Change in mental health according to the Global Severity Index (GSI) of the SCL-90-R, the GAFS and the global clinical impression (GCI) in 24-month heroin patients (n=344)

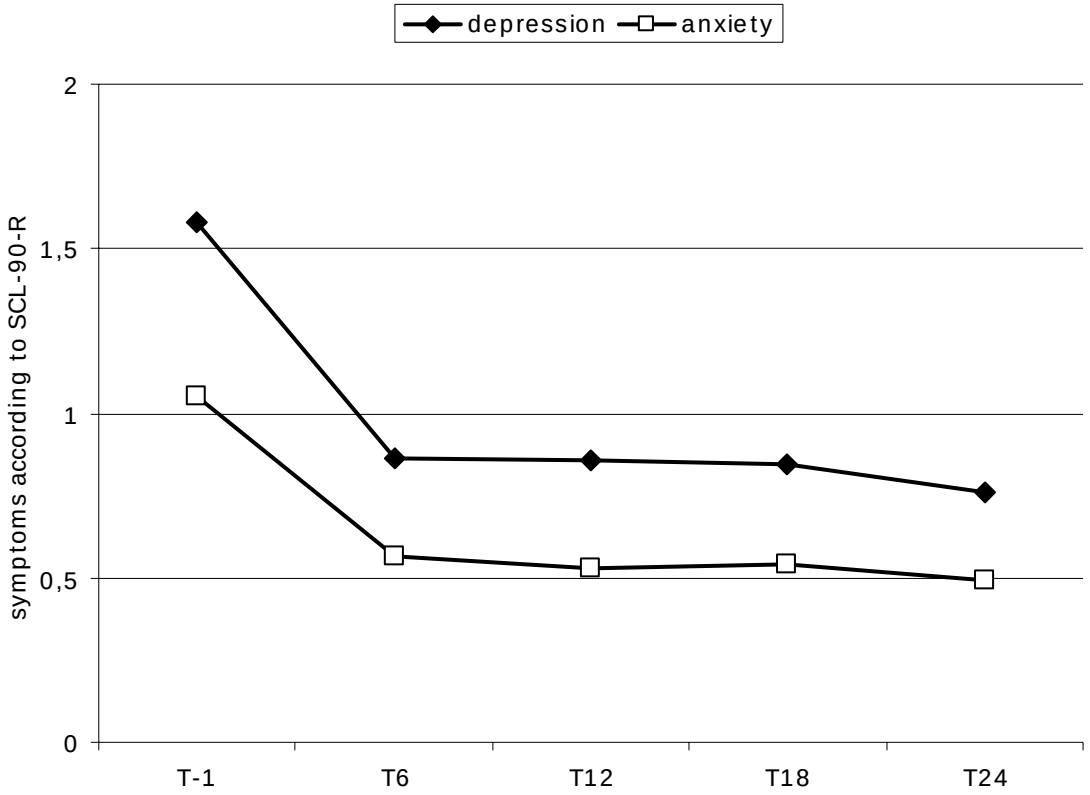


Mental symptoms such as depressivity and anxiety (explored by SCL-90-R) not only clearly declined at treatment initiation but an additional, though less marked improvement is seen at the end of the second year of treatment (see figure 5.3). Improvement in both symptoms is statistically significant in the course of 24 months (repeated measurement analyses: depression: Pillai's trace=0.496, df=4, p<0.001; anxiety: Pillai's trace=0.355, df=4, p<0.001).[21]
The values of the ASI Composite Score for the mental state continuously improve: from an average of 0.23 at T_{-1} to 0.18 at T_{12} and to 0.15 at T_{24} (repeated measurement analysis: Pillai's trace=0.109, df=2, p<0.001; within-subjects contrasts: T_{-1} to T_{12}: F=18.3, df=1, p<0.001; T_{12} to T_{24}: F=2.6, df=1, p=0.108). Thus, all study results including mental symptoms point to the same positive direction. A marked improvement during the first study phase is followed by a phase of stabilisation or further slight improvements in the second study phase.

[20] Within-subjects contrasts in the time effect between times of examination: T_{-1} at T_6: F=147.7, df=1, p<0.001; T_6 at T_{12}: F=23.4, df=1, p<0.001; T_{12} at T_{18}: F=1.8, df=1, p=0.181; T_{18} at T_{24}: F=3.4, df=1, p=0.066.

[21] Within-subjects contrasts in the time effect between examination times: depressivity: T_{-1} to T_6: F=227.0, df=1, p<0.001; T_6 to T_{12}: F=0.0, df=1, p=0.982; T_{12} to T_{18}: F=0.0, df=1, p=0.905; T_{18} to T_{24}: F=10.0, df=1, p<0.01; anxiety: T_{-1} to T_6: F=114.2, df=1, p<0.001; T_6 to T_{12}: F=2.3, df=1, p=0.134; T_{12} to T_{18}: F=0.4, df=1, p=0.510; T_{18} to T_{24}: F=5.7, df=1, p<0.05.

Figure 5.3
Changes in depression and anxiety according to the SCL-90-R in 24-month heroin patients (n=344)



Two fifths of the heroin patients had attempted suicide at least once prior to the study treatment (41.5%). 14 of them (4.2%) had attempted suicide in the 12 months preceding the initial examination (T_{-1}). Another five suicide attempts, by five different patients, became known during heroin treatment, one in the first study phase and four in the second phase. Three of the patients, who attempted suicide in the second year of treatment, had already attempted suicide earlier in their life. Three other patients still participated in the study treatment after two years, one patient changed to detoxification treatment. The treatment status of the fifth patient at T_{24} is not known. With one exception, depression was particularly marked in these patients prior to treatment initiation. In these four patients, the overall mental impairment according to GSI (SCL-90-R, T value) ranged very high, with 73-80 points, so that a basic depressive disorder can be assumed.[22]

Mental disorders according to ICD-10 among the study participants have been described in paragraph 3.4. 57.2% of the 2-year heroin patients have at least one lifetime diagnosis of the F2, F3, F4, or F5 spectrum. This considerable burden of comorbidity corresponds to the well-known results of pertinent studies (e.g. Krausz et al. 1998). If comorbidity is subjectively experienced as mental impairment, its significance for the course of treatment or the further course of the "addiction career" has been emphasised (Cacciola et al. 2001; Verthein et al.

[22] At T_1, an affective disorder was found in three patients (12-month prevalence), an affective and an anxiety disorder in one patient.

2005). As for comorbidity within the last 11-12 months prior to treatment,[23] 45.0% of the heroin patients had a F2, F3, F4, or F5 disorder. Affective disorders (F3) were most prevalent with 27.5% followed by neurotic, stress and somatoform disorders (F4, most often anxiety disorders) with 26.9%. A schizophrenic or delusional disorder (F2) occurred only in one patient (0.3%), behavioural disorders with physical conspicuousness (F5, mainly eating disorders) were diagnosed in 5 patients (1.5%).
Table 5.2 shows that, during the entire 2-year course, patients with current F3, F4 or F5 disorders at baseline suffer more from mental impairments than patients without this additional psychiatric diagnosis. The (few) patients with eating disorders (F5) are particularly afflicted by depressive or anxiety symptoms, which is also reflected by the values of the ASI Composite Scores. With the exception of the latter, the mental burden decreases in all patient groups in the course of treatment. Although the degree of mental stress remains higher in the psychiatric comorbid patients during treatment, their participation in heroin-assisted treatment has an overall positive effect on the course of symptoms.

Table 5.2
12-months prevalence of F3, F4 or F5 disorders at treatment initiation (after one month at T_1) and mental symptoms according to SCL-90-R (mean values across 3 measurement points) and ASI-CS values in the 2-year heroin patients[a)]

SCL-90-R		**F3**	**F4**	**F5**	**None**
GSI	T-1	1.34	1.21	1.75	1.00
	T12	0.74	0.72	1.55	0.53
	T24	0.66	0.63	1.72	0.49
Depression	T-1	1.88	1.64	2.40	1.44
	T12	1.04	0.93	1.77	0.75
	T24	0.94	0.88	2.13	0.64
Anxiety	T-1	1.23	1.20	1.92	0.91
	T12	0.63	0.71	1.52	0.40
	T24	0.58	0.63	1.88	0.40
ASI Composite Score (PSY)	T-1	0.31	0.28	0.51	0.19
	T12	0.26	0.22	0.55	0.13
	T24	0.23	0.20	0.59	0.11

a) As only one patient suffered from an F2 disorder, the values are not considered in this table.

5.2 Development of the social situation and legal behaviour

The majority of the most severely dependent patients lead a marginalised social life. Their situation is characterised by unstable housing conditions, unemployment, irregular income, debts, limited social contacts, criminalised life condition devoid of solidarity, and by the so-

[23] Standardised diagnostics of mental disorders according to ICD-10 by CIDI occurred at T_1, i.e. after one month of treatment.

called procuring stress and stress of police prosecution. Many heroin addicts are hardly (or only with great difficulties) able to cope with their basic needs such as self-determined living, sleeping and regular nourishment. As a rule, they receive support only by scene acquaintances or the staff of low-threshold drug services or maintenance units if contacts have been established.

The first study phase showed that improvements of patients' social situation are rather slow (Naber & Haasen 2006). But positive long-term changes towards the stabilisation of the social situation were remarkable in the group of heroin patients, who entered the second study phase. The housing situation had markedly improved at T_{24}: At baseline (T_{-1}), 72.9% lived in stable housing conditions,[24] this rate increased to 80.2% at T_{12} and to 87.4% after another year (at T_{24}).[25] In the statistical comparison, both the changes between baseline and T_{12} and those in the second year of treatment are significant (McNemar: T_{-1} to T_{12}: Chi^2=9.8, n=342, p<0.01; T_{12} to T_{24}: Chi^2=8.6, n=308, p<0.01). After 24 months, only a minority still live in precarious housing conditions (12.6%); these are mainly patients, who did *not* regularly conclude the second study phase (42.4%). Only 9.1% of the treatment concluders still have an unstable housing situation (Chi^2=29.8, df=1, p<0.001). Patients' subjective satisfaction increases accordingly. At baseline, only 35.7% of the heroin patients are satisfied with their housing situation, after 12 months, the proportion increased to 51.5%, it is stable with 51.0% after 2 years.

Many long-term heroin addicts have only few reliable social contacts outside the drug scene. A steady partnership is not the rule either, for young as well as for older heroin addicts; most often, the partner is also drug dependent or his centre of interests is around the drug scene. At baseline (T_{-1}), only 36.9% had a steady partner. This proportion was stable during the two years of treatment. After 12 months, 34.7% lived in a steady partnership, and after 24 months, 35.0% (McNemar: T_{-1} to T_{12}: Chi^2=0.7, n=343, p<0.396; T_{12} to T_{24}: Chi^2=0.0, n=308, p<0.885). But the satisfaction with relationships increased. At baseline, 38.2% were satisfied with their relationships, this proportion increased to 51.2% after one year and stabilised at this level (51.5%) after another year. As a rule, these are patients, who live in a stable partnership.

40.2% of the heroin patients have own children at baseline. This proportion did not change in the course of treatment; it is 40.1% at T_{24}.[26] For the entire period, the percentage of men and women with own children is similar.[27] At baseline, only 11.5% of the mothers and 13.8% of

[24] Analogous to the report of the first study phase, the categories „own apartment", „apartment of partner", „living with parents/relatives" und „flat sharing/room" are combined to „stable" housing situation (Naber & Haasen 2006). It should be kept in mind that, in the case of drug addicts, the two latter categories do not always indicate a stable and safe housing situation; therefore, the positive proportion might be an overestimation.

[25] The percentages of all patients with valid data are reproduced (T_{-1}: n=343; T_{12}: n=343; T_{24}: n=309). This applies also to all further results, though it must be considered that in the t-tests for statistical significance, missing data are excluded (in pairs). For the housing situation for instance, values among patients with valid data do not differ much from those described above at all times of examination (n=309): stable housing situation at T_{-1}: 73.7%, at T_{12}: 80.8%, at T_{24}: 87.4%.

[26] Calculated on the basis of n=309 valid data.

[27] Proportion with children at T_{-1}: men: 40.4%, women: 39.4%; at T_{12}: men: 40.2%, women: 40.9%; at T_{24}: men: 40.2%, women: 40.0%. The differences between men and women in all the 1,015 patients described in the report of the first study phase does not apply to the group of the 2-year heroin patients.

the fathers lived with their children (total: 13.3%). This changed only insignificantly in the course of heroin treatment. After 12 months, only 11.7% (mothers: 15.5%, fathers: 10.8%) of the parents (mothers: 12.5%, fathers: 15.3%) lived with their children in one household and after 24 months, 14.8%. The children of most patients still live with the other parent (see table 5.3). The children of one tenth of the parents live with adoptive or foster parents after two years, the children of 8.2% with grandparents or other relatives. Although the proportion of men and women with children is similar, the accommodation of children is mainly a problem of the mothers. Children of fathers mainly live with the other parent, but the residence of children of mothers treated with heroin differs. Both at baseline and after 2 years of heroin treatment, these children mainly live with adoptive or foster parents, with grandparents or even in a children's home (see table 5.3). This indicates that, in case of parental problems of female heroin addicts, children's accommodation tends to be managed by public administration while in the case of heroin dependent fathers, their children most often stay in the care of their mothers.

Overall, familial relationships clearly improve in the course of heroin treatment. The corresponding ASI Composite Score declines from an average of 0.26 at baseline to 0.08 after one year. At the end of the second year of treatment, it slightly declines further to 0.06 points (repeated measurement analysis: Pillai's trace=0.469, df=2, $p<0.001$; within-subjects contrasts: T_{-1} to T_{12}: F=195.6, df=1, $p<0.001$; T_{12} to T_{24}: F=1.9, df=1, p=0.169).

Table 5.3
Residence of heroin patients' children at baseline (T_{-1}), after 12 (T_{12}) and after 24 months (T_{24})[a)]

Residence of children		**Fathers**	**Mothers**	**Total**
With patient	T-1	0.9%	3.8%	1.5%
	T12	-	15.4%	2.9%
	T24	7.1%	8.3%	7.4%
With patient and partner	T-1	12.8%	7.7%	11.9%
	T12	10.8%	-	8.8%
	T24	8.2%	4.2%	7.4%
With other parent	T-1	63.3%	7.7%	52.6%
	T12	64.0%	3.8%	52.6%
	T24	62.2%	4.2%	50.8%
With grandparents/relatives	T-1	7.3%	23.1%	10.4%
	T12	7.2%	19.2%	9.5%
	T24	5.1%	20.8%	8.2%
With adoptive/foster parents	T-1	8.3%	30.8%	12.6%
	T12	6.3%	26.9%	10.2%
	T24	6.1%	29.2%	10.7%
In children's home	T-1	1.8%	7.7%	3.0%
	T12	0.9%	11.5%	2.9%
	T24	1.0%	4.2%	1.6%
Somewhere else	T-1	5.5%	19.2%	8.1%
	T12	10.8%	23.1%	13.1%
	T24	10.2%	29.2%	13.9%

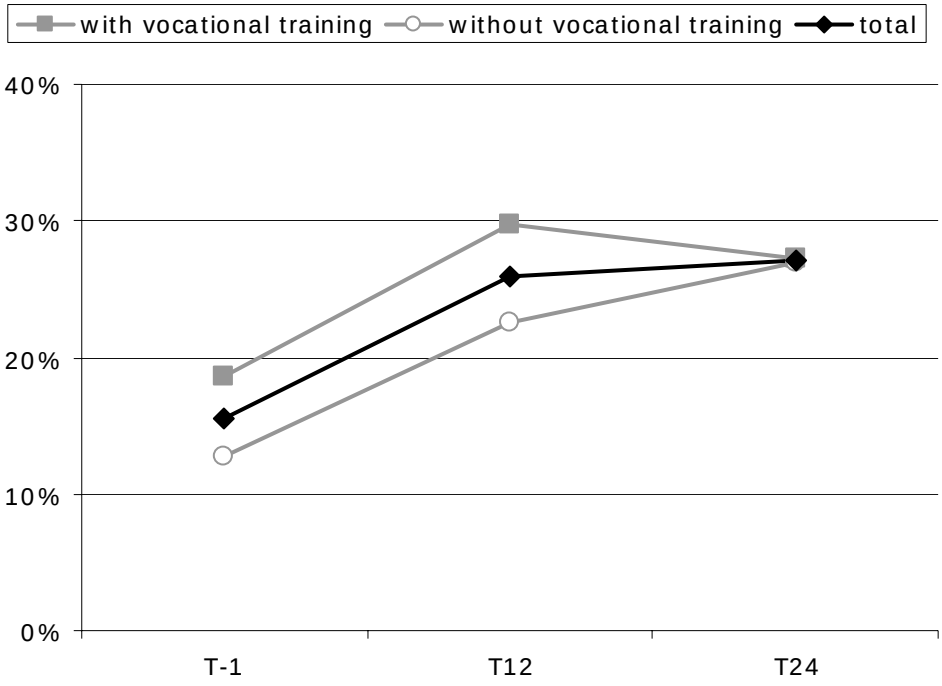
[a)] T_{-1}: n=135; T_{12}: n=137; T_{24}: n=122.

The labour market situation is still difficult for heroin patients. Although a number of patients succeeded in (again) securing a job within the 2-year treatment phase, industrial rehabilitation is still the main problem of long-term drug addicts. This is probably the point, where most types of treatment reach their limits, since the general situation on the labour market leaves only low chances of reintegration. At least half of the heroin patients fulfil at least formally the conditions required for regular employment: At baseline, 43.3% had completed secondary modern school (Hauptschulabschluss), one fourth (25.9%) have O-level (Mittlere Reife) and 15.1% have either a high-school diploma (Abitur) (10.8%) or advanced technical college entrance qualification (Fachhochschulreife) (4.4%). 15.7% have no school leaving certificate; their rate is definitely higher than in the general population.[28] On average, heroin patients had 9.9 years of general education. 47.5%, i.e. almost half of the study patients, completed profes-

[28] As the average age at baseline is 37 years, graduation figures must be compared with those of the mid-eighties. At that time (1985) the rate of persons, who had no school-leaving certificate, was just above 8%. 37% graduated from secondary school, basic level, and 44% O-level. The remaining 29% reached matriculation standard (federal statistical office: Basic and structural data according to Ebner 2005). Thus, the overall educational level of heroin patients is below the average of the general population.

sional training: three quarters apprenticeships (75.3%, proportion of all patients: 34.6%) and 18.4% school education (overall: 8.4%). 3.2 of the patients are university or polytechnic graduates (overall: 1.5%).
At baseline (T_{-1}), 15.5% were currently (within the last 30 days) in regular employment. This proportion clearly increased in the course of treatment (T_{24}: 26.9%, see figure 5.4). It was possible to mediate more than 10% of the study participants into employment within two years (McNemar: T_{-1} to T_{24}: Chi^2=12.7, n=309, p<0.001). At the beginning, a relationship was found with the type of graduation, but in the course of treatment, it seems to be less important whether training was completed (see figure 5.4). However, a number of political changes occurred on the labour market in the last years, mainly affecting the so-called second labour market, which is of particular importance for drug addicts with their limited professional chances. The introduction of "1-euro jobs" or the extended possibilities of „marginal jobs" will probably facilitate the transition to regular employment for patients without completed training.

Figure 5.4
Current employment of heroin patients prior to treatment, after 12 and after 24 months in relation to their training



The differences between the participating cities are conspicuous. The large and medium-sized study centres have difficulties in integrating patients into the labour market, while the smaller centres of Karlsruhe and Munich are definitely successful. But a closer look reveals that in Karlsruhe, a rather high rate of heroin patients were employed already at baseline. Table 5.4 shows that – with the exception of Hanover – all the other study centres also succeeded in markedly increasing the proportion of study patients in employment.

Table 5.4
Current employment of heroin patients prior to treatment and after 24 months in the seven study centres

	HH	Han	Fft	Col	Bonn	Ka	Mu	Total
T-1	13.8	15.0	17.1	8.3	16.7	43.8	8.7	15.5
T24	22.9	16.2	27.3	23.5	20.0	73.3	47.6	26.9

Not only the difficult labour market situation, but also heroin patients' poor health and their long "abstinence" from the labour context due to addiction limit their chances of finding (again) regular employment through adequate job offers. At the initiation of heroin treatment, the physicians "attest" complete working ability to not even one forth of the patients (23.6%). The majority were fit for work only in a restricted way (46.1%), and the remaining 30.0% were not fit at all.[29] The situation clearly changed under heroin treatment. After 12 months, a major part (48.1%) was still only fit for work in a restricted way, but the proportion of unrestricted fitness to work increased to 40.2%. This level stabilised after 24 months (fit to work: 40.4%, fit to work in a restricted way: 44.6%, not fit to work: 13.7%).[30] Under this aspect, heroin patients' chances to work must be assessed in a differentiated way. Of the patients with unrestricted fitness to work, 39.7% are employed after 12 months and even 43.4% after 24 months (see table 5.5). A slight increase is also found in patients with restricted fitness to work. In patients assessed unfit to work due to poor health, the employment situation hardly changes.

Table 5.5
Current employment situation depending on heroin patients' working ability at baseline (T_{-1}), after 12 (T_{12}) and after 24 months (T_{24})[a)]

		Not fit to work	Fit to work in restricted way	Fit to work	Total[b)]
Employment last 30 days	T-1	10.7%	13.9%	25.0%	15.5% *
	T12	5.6%	19.5%	39.7%	26.2% ***
	T24	9.8%	18.5%	43.4%	27.5% ***

a) T_{-1}: n=341; T_{12}: n=336; T_{24}: n=298.
b) Chi^2-Test: * p<0.05, ** p<0.01, *** p< 0.001.

In accordance with the positive developments of the employment situation, the income structure of heroin patients also changes. Gainful employment becomes more important as main source of income, but governmental funds still rank first with a total of 76% (at T_{24}) (see table 5.6).[31] The marked decrease of illicit sources of income is conspicuous. Compared to baseline, the proportion of patients who make a living mainly from illicit sources, declines from

29 In one patient, it was explicitly stated that his fitness to work could not be explored or assessed.
30 See previous footnote.
31 The shift from social welfare benefits to unemployment support between T_{12} and T_{24} is probably mainly due to the reorganisation of social legislation ("Hartz IV").

24% to 2% after 2 years. Thus, the development of the income structure also reflects heroin patients' improved integration during the 2-year treatment. The corresponding ASI Composite Score for the economic situation also develops in a significantly positive way, although the average values of 0.90 at T_{-1}, 0.84 at T_{12} and 0.82 at T_{24} still indicate a high degree of problems in this field (repeated measurement analysis: Pillai's trace=0.049, df=2, p<0.01; within-subjects contrasts: T_{-1} to T_{12}: F=9.7, df=1, p<0.01; T_{12} to T_{24}: F=0.9, df=1, p=0.342).

Table 5.6
Heroin patients' main source of income at baseline (T_{-1}), after 12 (T_{12}) and after 24 months (T_{24})

Source of income	**T-1**	**T12**	**T24**
Employment	5.2%	9.6%	12.4%
Unemployment benefit	20.3%	24.0%	44.8%
Welfare	31.1%	55.3%	31.4%
Pension, sickness benefit	3.8%	5.0%	5.9%
Partner, relatives, friends	3.8%	1.8%	1.0%
Dealing with drugs	16.9%	1.5%	1.3%
Other illicit income	7.3%	0.3%	0.7%
Prostitution, pimping	4.1%	0.6%	1.3%
Loan, savings	1.2%	-	0.7%
Begging	3.8%	0.6%	0.7%
Other	2.6%	1.5%	-
N	**344**	**342**	**306**

As stated above, only slightly more than one third of the heroin patients have a steady partner after two years. Only 22.3% live with their partner (at T_{24}), the majority of the patients live alone (55.5%). This hardly changed in the course of the 2-year treatment. The stabilisation of the housing situation described above does not correspond to an increase of social contacts. However, the proportion of patients living with alcohol or drug abusing persons declines. At baseline, their proportion was 35.1%, after 12 months 29.8% and after 24 months 20.9% (McNemar: T_{-1} to T_{24}: Chi^2=14.3, n=284, p<0.001). Therefore, at baseline, more than half of the heroin patients, who stated not living alone (or in an institution), lived with drug or alcohol users (54.7%). Their proportion had not changed after 12 months (54.4%); a decrease to 45.5% was only found after 2 years of treatment. This reveals that a major part of heroin patients' ordinary social contacts are still persons with drug or alcohol problems.[32] As these contacts result from the partnership and housing situation, changing the situation will be difficult for the heroin patients and requires intensive support.

The vast majority state that they have good friends or persons, on whom they can rely in emergencies. This proportion slightly increases from 82.1% at baseline to 87.4% and 88.3% respectively after 12 and 24 months. But in two thirds of the patients, these contacts are at most 1 to 3 persons. It is particularly positive that almost none of these persons is connected

[32] The decreased proportion of patients living with persons with an alcohol or drug problem, as described above, also relates to patients living in an institution or having no fixed abode.

to the drug scene (T_{-1}: 60.3%, T_{12}: 62.2%, T_{24}: 66.7%). The social situation of study participants without reliable friends (11.7% at T_{24}) is likely to be characterised by great loneliness and isolation. 41.9% of the heroin patients report having met new friends or acquaintances within the last 2 years.[33] The circle of friends of heroin patients expands, the number of "good friends" increases from an average of 1.8 at baseline to 2.0 after 12 months and 2.1 after 24 months.

The ASI Composite Score, which refers to the burden of problems in social relationships (outside the family), markedly improves. The value was an average of 0.26 points at baseline, 0.09 after 12 months and 0.06 points after 24 months. The repeated measurement analysis reveals a significantly positive time effect across the 2-year treatment period (Pillai's trace=0.443, df=2, $p<0.001$; within-subjects contrasts: T_{-1} to T_{12}: F=138.0, df=1, $p<0.001$; T_{12} to T_{24}: F=4.6, df=1, $p<0.05$).

The number of patients, who spend most of their spare time with relatives or friends/acquaintances with *no* alcohol or drug problem, also increased. The proportion was only 15.3% at baseline, increased under treatment to 22.2% after one year and to 31.5% after two years (McNemar: T_{-1} to T_{24}: Chi^2=24.7, n=298, $p<0.001$). But at the end of the 2-year treatment, a major part of patients are still mostly alone in their spare time (43.7%). Overall, leisure activities developed positively in the course of treatment. 61.6% of the heroin patients report leisure activities at baseline, 69.6% after 12 months and 72.7% at the end of the second study phase (McNemar: T_{-1} to T_{24}: Chi^2=13.4, n=305, $p<0.001$). The average number of hobbies and leisure activities increased from 1.4 at T_{-1} to 1.6 at T_{12} and finally to 1.7 at T_{24}. The reported activities are mainly hobbies such as reading, going to the movies, playing music and hearing music, computer games, painting and drawing, and sports such as bicycling, swimming and jogging. In relation to the increased leisure activities, the proportion of patients frequently bored decreases from 54.2% at baseline to 41.1% after one year and 34.3% after 2 years (McNemar: T_{-1} to T_{24}: Chi^2=37.1, n=308, $p<0.001$). Regarding patients' satisfaction with their leisure activities, there is a similar positive trend. 15.7% are satisfied with their leisure activities at T_{-1}, and 35.7% at T_1. At T_{24}, the value had increased only slightly to 37.5%.

Overall, the development of (drugfree) social contacts and social activities under the 2-year heroin treatment was positive. It cannot be ignored that a complete separation from the drug context takes time and involves problems of increased loneliness in many patients.

Two collateral studies of the German model project, concluded in autumn and at the end of 2006, are concerned with the delinquency behaviour of heroin patients. A short overview presents legal conflicts and patient-reported illegal activities in the course of the 2-year treatment. The initial judicial situation of heroin patients was shortly described in paragraph 3.4. Almost all of them had been legally convicted prior to the study treatment, three quarters were on remand or sentenced to prison. Convictions were not investigated explicitly for the last 12 months prior to the study;[34] in this one-year period, 22.2% of the heroin patients were in cus-

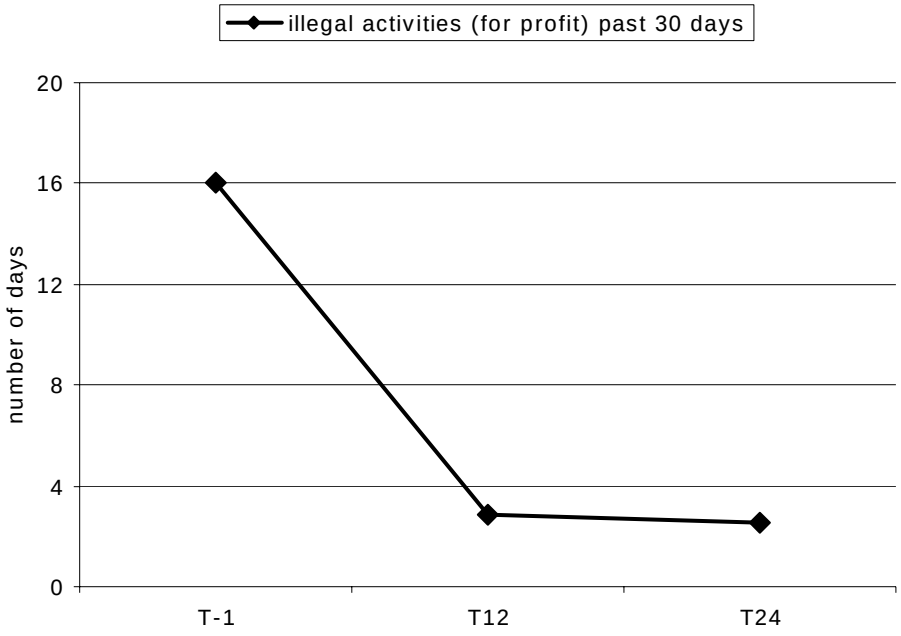
[33] Due to the relatively high number of missing data (missing data = 112), this statement relates to all 344 patients. If related only to valid data, the proportion would be 62.1%.

[34] In the first year, the proportion of convicted patients was 38.7%, in the second year 31.4%.

tody or served a prison sentence. This proportion declined to 6.0% in the first year of study treatment and to 4.2% in the second year.

As a rule, convictions and imprisonments refer to offences, which happened some time ago. Therefore, these administrative events are hardly suited to adequately describe patients' "criminal" development.[35] Moreover, the formulation of the inclusion criteria was an attempt to exclude patients with predictable imprisonments from the study (cf. Naber and Haasen 2006). The ASI Composite Score is again used as measurement of global change. The value decreased on average from 0.41 at baseline to 0.16 at the end of the first and 0.14 at the end of the second study phase. This is a statistically significant decrease over the entire 2-year period, mainly due to the marked improvement during the first year of treatment (repeated measurement analysis: Pillai's trace=0.480, df=2, p<0.001; within-subjects contrasts: T_{-1} to T_{12}: F=214.8, df=1, p<0.001; T_{12} to T_{24}: F=1.2, df=1, p=0.280). Criminal behaviour is explored by the standard EuropASI question exploring the involvement in illegal dealings within the last 30 days. These were affirmed by 71.7% at the baseline examination. At T_{12}, still 24.5% reported to be involved in illegal activities, the percentage did not further decline and was 24.4% at T_{24}. With respect to the average number of days with illicit activities, the drastic decline within the first study phase is again conspicuous (see figure 5.5). During the second study phase, the value stabilised at the low level of 2.6 days (repeated measurement analysis: Pillai's trace=0.488, df=2, p<0.001; within-subjects contrasts: T_{-1} to T_{12}: F=244.8, df=1, p<0.001; T_{12} to T_{24}: F=0.1, df=1, p=0.813).

Figure 5.5
Heroin patients' involvement in illicit activities (within the last 30 days) prior to the treatment, after 12 and after 24 months



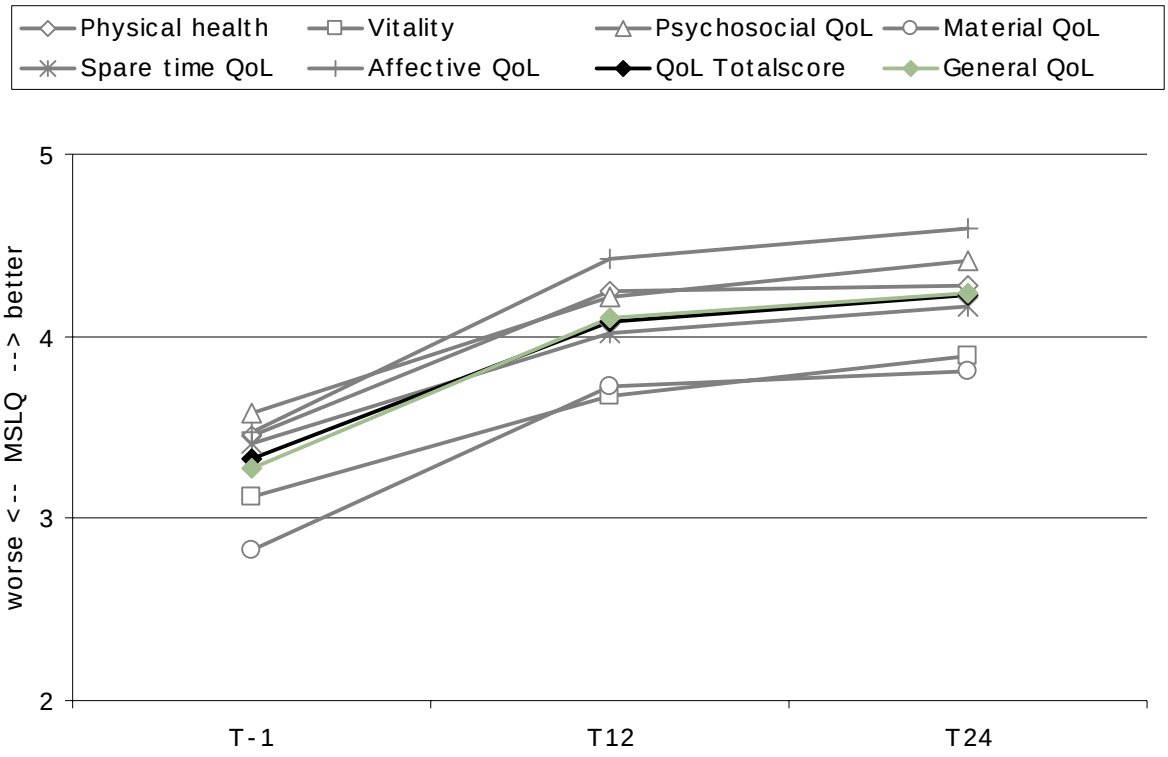
[35] In the context of the collateral criminological study, the light field analysis gives more information on offences at the base of convictions and imprisonments.

In the last years, concepts of quality of life increasingly enter evaluation studies of addiction treatments, either as a formal target criterion to measure the effect of an intervention, or as a descriptive characteristic to describe the course of parallel developments related to changing symptoms (Perneger et al. 1998; Deering et al. 2004; Giacomuzzi et al. 2003). In the heroin study, the overall quality of life was explored with the multidimensional instrument MSLQ (Pukrop et al. 1999) (cf. Naber & Haasen 2006). The core module of this quality of life inventory consists of six dimensions: "physical health", "vitality", "psychosocial QL", "material provision", "leisure time QL" and "affective/emotional QL". In addition to the QL sum score that combines the values of all the dimensions of the core module, an assessment of the overall quality of life is collected. In addition, specific modules on the quality of life in the fields of family, partnership, children and profession exist, but they are not now considered for the analysis.

Figure 5.6 shows that quality of life improved in all the documented areas in the course of the 2-year treatment. The QL sum score is exactly parallel to the overall assessment of quality of life. The repeated measurement analysis shows a significant time effect in both fields (QL sum score: Pillai's trace=0.452, df=2, $p<0.001$; overall quality of life: Pillai's trace=0.347, df=2, $p<0.001$).[36] In addition to the marked improvement during the first year of treatment, further positive developments occurred in some areas (vitality, affective QL, psychosocial QL) also in the second year. The greatest progress was apparently achieved in the affective or emotional quality of life. Quality of life also greatly improved where patients' material needs are concerned, though the situation is still problematic.

[36] Within-subjects contrasts: QL sum score: T_{-1} to T_{12}: F=217.3, df=1, $p<0.001$; T_{12} to T_{24}: F=7.0, df=1, p<001; QL sum score: T_{-1} to T_{12}: F=122.1, df=1, $p<0.001$; T_{12} to T_{24}: F=2.0, df=1, p=0.156.

Figure 5.6
Development of quality of life in heroin patients (according to MSLQ)[a)] prior to treatment, after 12 months and after 24 months



a) The quality of life is represented according to following scale: “very bad” (1), “bad” (2), “rather bad” (3), “neither nor” (4), “rather good” (5), “good” (6), “very good” (7).

5.3 Alcohol and drug use

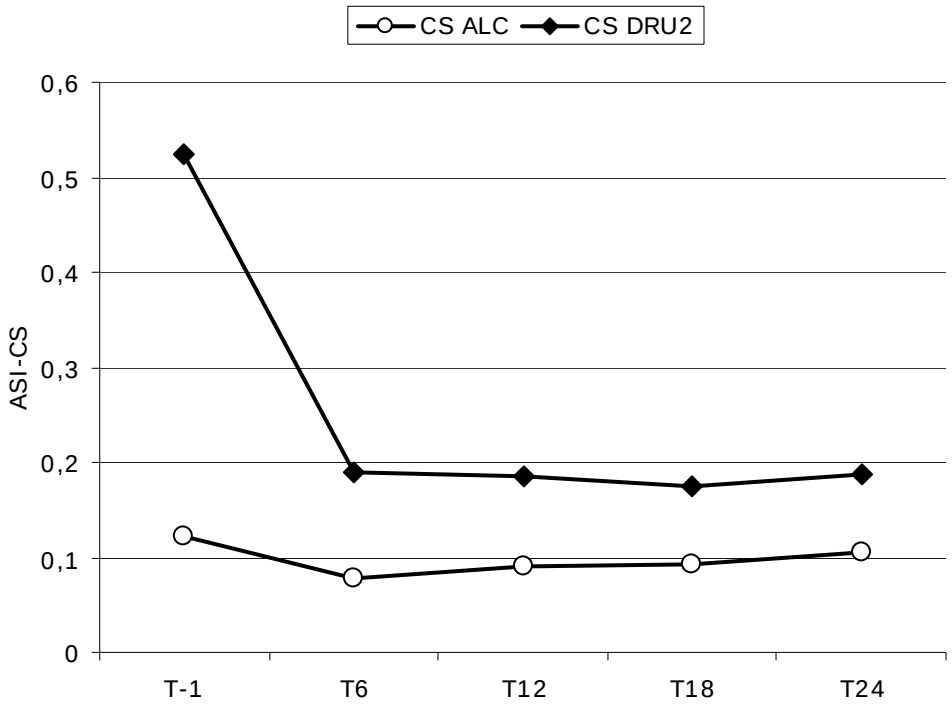
Each addiction treatment focuses on the reduction or abstinence of drug or alcohol use. In heroin-assisted treatment, where illicit substances are substituted by pharmacologically pure heroin – i.e. illicit street heroin is substituted by an equally effective medication -, attention is attached to the co-use of other, mainly illicit drugs. Although a so-called main drug can be identified in most addictive patients (normally at the base of the addiction diagnosis), long-term drug addicts rarely use only one particular substance. Polyvalent use most often prevails: Certain substances are used consecutively or simultaneously in order to produce specific effects or states of intoxification. Modes of application also differ, most often depending on the available quality of the substance.
The report of the first study phase already indicates a decline of co-use. Street heroin, cocaine, benzodiazepines and cannabis use decreased in both groups. The decrease of street heroin and cocaine use (number of days of use) was significantly greater in the heroin than in the methadone group. Alcohol use also more markedly declined among heroin patients than among methadone patients (Naber & Haasen 2006).

Across the two study phases, co-use declined in the 2-year heroin group at treatment initiation and stabilised at a comparatively low level in the further course. Compared to the global criteria of the ASI Composite Scores for alcohol and drug use, the course pattern is identical with a statistically significant decline in the course of time (repeated measurement analysis: alcohol: Pillai's trace=0.098, df=4, p<0.001; drugs: Pillai's trace=0.844, df=4, p<0.001).[37] A slight increase of alcohol use is found in the second year of treatment; but it is not alarming in face of the overall low consumption level (see figure 5.7). However, this result hints at a small group of patients with potentially problematic alcohol use. At baseline, 16.6% used alcohol above the level of harmful drinking within the last 30 days (according to the EuropASI definition); this proportion declined only slightly to 10.3% after one year and was at 12.5% after two years of heroin treatment. They drink alcohol on 23 days on average, on 18 days to a harmful extent (at least in the long run). This is also reflected by the amounts of drinking. The patients concerned drink on average 12.3 consumption units of alcohol daily, which corresponds to about 2.5 litres of beer.[38] In comparison, the other patients (without endangering alcohol use) drink only 2.3 consumption units of alcohol daily (corresponding to about 0.5 litres of beer).

[37] Within-subjects contrasts: alcohol: T_{-1} to T_6: F=23.0, p<0.001; T_6 to T_{12}: F=2.3, p=0.133; T_{12} to T_{18}: F=0.0, p=0.987; T_{18} to T_{24}: F=2.9, p=0.089; drugs: T_{-1} to T_6: F=881.4, p<0.001; T_6 to T_{12}: F=0.6, p=0.446; T_{12} to T_{18}: F=1.1, p=0.289; T_{18} to T_{24}: F=2.0, p=0.155.

[38] Consumption units: beer: 0.5 l beer = 2.5 CU, 1 l beer = 5 CU; wine: 0.2 l glass = 2.5 CU, 0.7 l bottle of wine = 9 CU; spirits: 0.02 l liquor or similar = 1 CU, double liquor (0.04 l) = 2 CU, bottle (0.7 l) = 35 CU. The values mentioned in the text are the added amounts of beer, wine and spirits. As it cannot be excluded that patients partly stated alternative (and not additional) use of e.g. wine or beer on one day, the calculated amount for one day is rather the upper limit.

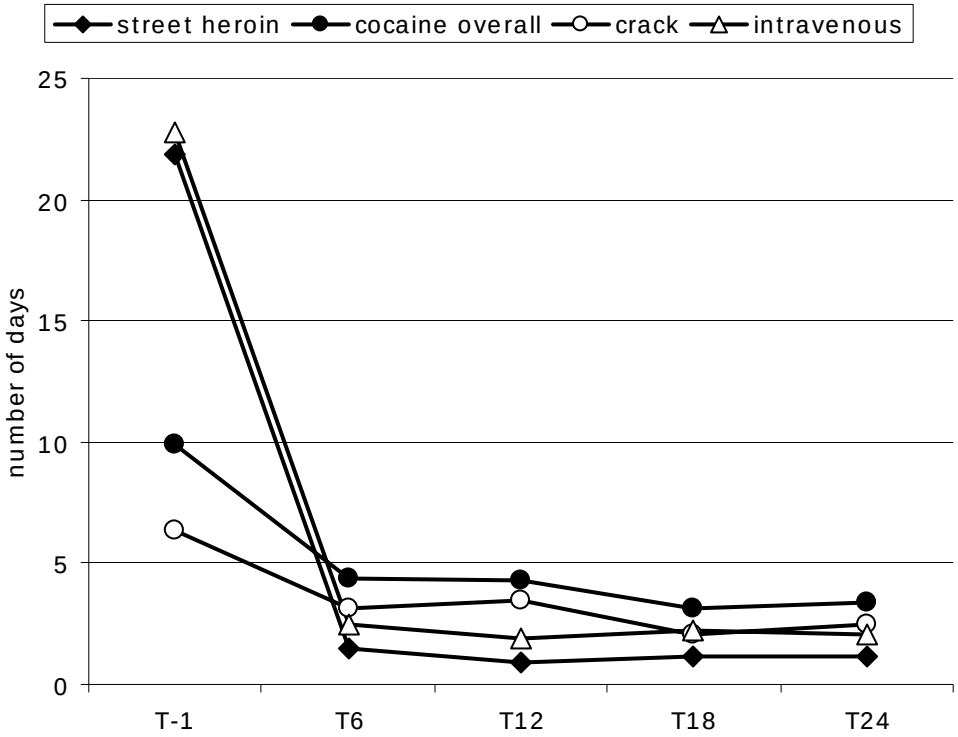
Figure 5.7
Development of alcohol ("ALC") and drug use ("DRU2") of heroin patients according to the ASI Composite Scores (CS) during the first and second study phase



The pattern of the course presented in the Composite Scores is also found in the development of street heroin, cocaine and crack use and intravenous use. Figure 5.8 shows that again, the decline of "hard" drug use is most marked in the initial phase and stabilises in the further 2-year course (repeated measurement analysis: street heroin: Pillai's trace=0.790, df=4, p<0.001; cocaine: Pillai's trace=0.283, df=4, p<0.001; crack: Pillai's trace=0.157, df=4, p<0.001; iv use: Pillai's trace=0.800, df=4, p<0.001).[39] Cocaine and crack use further decline in the second year of treatment so that on average, cocaine is used on 3.4 days and crack on 2.5 days in the 24th month of treatment.

[39] Within-subjects contrasts: street heroin: T_{-1} to T_6: F=982.9, p<0.001; T_6 to T_{12}: F=4.3, p<0.05; T_{12} to T_{18}: F=0.4, p=0.542; T_{18} to T_{24}: F=0.2, p=0.649; cocaine: T_{-1} to T_6: F=75.7, p<0.001; T_6 to T_{12}: F=0.5, p=0.492; T_{12} to T_{18}: F=5.6, p<0.05; T_{18} to T_{24}: F=0.2, p=0.693; crack: T_{-1} to T_6: F=30.0, p<0.001; T_6 to T_{12}: F=0.1, p=0.799; T_{12} to T_{18}: F=7.5, p<0.01; T_{18} to T_{24}: F=0.6, p=0.452; iv use: T_{-1} to T_6: F=885.5, p<0.001; T_6 to T_{12}: F=0.8, p=0.372; T_{12} to T_{18}: F=0.4, p=0.554; T_{18} to T_{24}: F=0.3, p=0.605.

Figure 5.8
Development of the co-use of hard drugs (days of use within the last month) according to patients' reports at the external interview during the first and second study phase



The average number of days of use conveys an overall impression of the intensity of co-use; the 30-day prevalence shows how many patients still use the substance. The same clear decline is found here, too. The decline is, however, continuous during the entire course of treatment, also in the second year of treatment (see table 5.7). This is particularly true for cocaine and crack use, where the proportion of users further declines by 14.5% and 8.0% respectively in the second year. I.v. drug use declines accordingly between T_{12} and T_{24}. After 24 months, the proportion of patients using street heroin or crack (at least once within the last 30 days) is 45.2%. On average, they use street heroin on 2.6 days within the last month, and cocaine (or crack) on 7.5 days.

Table 5.7
Co-use of street heroin, cocaine, crack and i.v. use according to patients' report at the external interview during the first and second phase. 30-day prevalence for each examination time

	T-1	**T6**	**T12**	**T18**	**T24**	**Significance Cochrane test**
Street heroin	96.2%	29.5%	20.8%	19.1%	18.4%	Q=577.0 ***
Cocaine total	72.4%	56.7%	51.9%	43.2%	37.4%	Q=120.9 ***
Crack	37.8%	32.2%	33.2%	24.8%	25.2%	Q=28.6 ***
I.v. use	97.1%	45.5%	34.7%	33.3%	28.9%	Q=344.1 ***

Weekly urinalyses were performed also in the second year of treatment.[40] For cocaine, benzodiazepines and cannabis, a continuous decline of positive urine samples is found in the course of the 2-year treatment (see figures 5.9 and 5.10). The proportion of positive samples for cocaine declines from more than 50% to 25%-30% in the last 6 months. Positive samples for benzodiazepines are rather frequent, but there is also a decline from 60% at baseline to 50%-55% in the first year and 40%-45% in the second year. Similar to the first study phase, it must be considered that urinalyses cannot differentiate between prescribed and self-procured benzodiazepines. The decline of cannabis is less marked, although it continuously declines in the second year. 45% of samples were positive for cannabis in the first year and decline to about 35% in the last weeks of the second year of treatment. Amphetamines are negligible: The proportion of patients with positive urine samples is between 0% and 2%.

Figure 5.9
Use of cocaine (left) and benzodiazepines (right) during the first and second study phase based on the results of weekly urinalyses

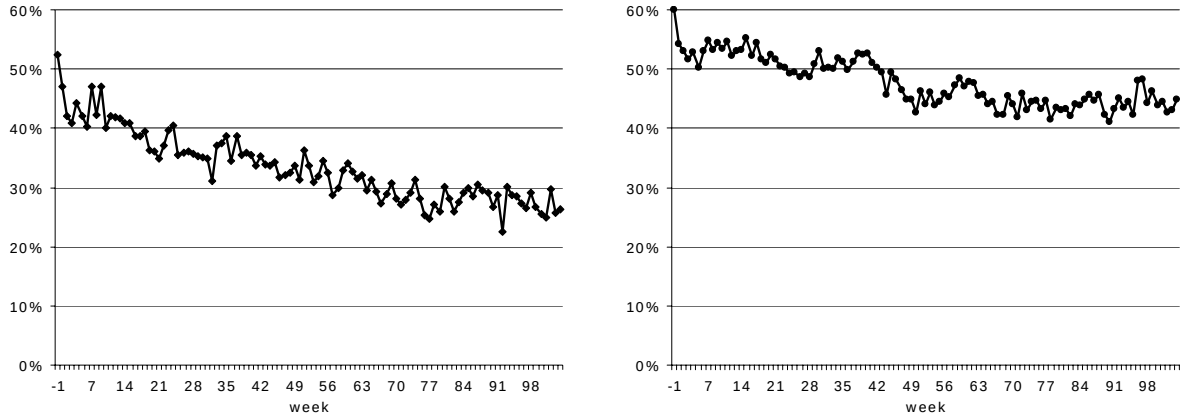
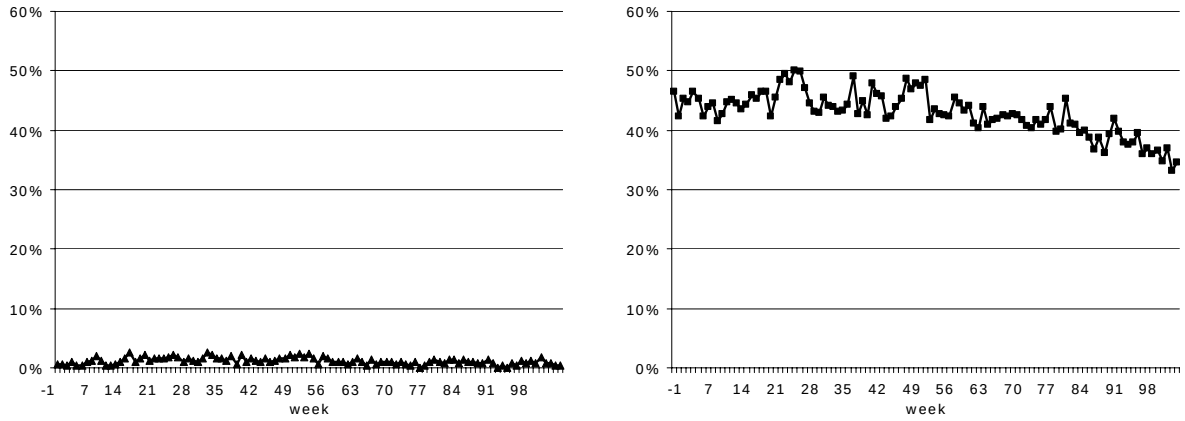


Figure 5.10
Use of amphetamines (left) and cannabis (right) during the first and second study phase based on the results of weekly urinalyses



[40] Laboratory tests for street heroin were no longer performed in the second study phase.

The decrease of i.v. drug use is connected with the decline of risk behaviour: the shared (unhygienic) use of syringes or injection equipment such as tins, spoons or filters. Positive changes in risk behaviour (in both groups of the second phase) were described in chapter 4. Among the 2-year heroin patients, a drastic decline occurs regarding the sharing of syringes, needles or injection equipment; in the second year it is virtually non-existent. At baseline, 9.3% occasionally "exchanged needles" and 17.4% shared the injection equipment; this proportion declined to 0.3% each after 24 months.[41] This significant health preventive effect of heroin treatment deserves particular attention, mainly in the context of potential medical treatment of HIV or HCV infections, as it minimises future re-infection risks and ensures better success of antiretroviral therapies.
In accordance with the reduction of (illicit) drug use, heroin patients' contacts to the drug scene decline. 89.2% visited the drug scene more or less regularly in the last 30 days prior to treatment initiation, on average on 18.5 days. After 12 months, this proportion markedly decreased to 46.8% and after 24 months to 41.4% (Cochrane test: $Q=238.9$, $df=4$, $p<0.001$). The number of days at the scene significantly decreased to an average of 5.3 days at T_{12} and 5.2 days at T_{24} (repeated measurement analysis: Pillai's trace=0.551, $df=4$, $p<0.001$).

As mentioned above, 45.2% of the heroin patients still use street heroin and/or cocaine (at least once within the last month) after 2 years. 20.7% use one of these substances at least weekly (more than 4 days in the last month) and are thus more or less regular users of hard (illicit) drugs. The question arises whether these patients are different from those, who were better able to reduce their drug use under heroin treatment. These patients are not among those, who drink too much alcohol (dangerous use on an average of 0.8 days vs. 2.6 days), their cannabis use is also lower that that of other patients (6.4 vs. 7.4 days). But they use more benzodiazepines (10.4 vs. 7.6 days), and it can be assumed that it is not only "illicit" co-use, but benzodiazepines are frequently prescribed for the therapeutic regulation of addiction problems and mental disturbances. This is also indicated by the mental burden of patients, who use hard drugs: With an average of 0.75 points on the Global Severity Index of the SCL-90-R and 63.2 points on the GAF scale, they have lower values than other patients (GSI: 0.52, GAFS: 67.4). Their physical health is also poorer: The OTI value is, with an average of 8.4 symptoms, higher than in patients without regular drug use (6.4 points). In this group (about one fifth of all the heroin patients), poor health is thus associated with a higher degree of co-use. Moreover, their proportion among the dropouts is significantly elevated with 37.5%. Among the regular concluders, only 18.7% regularly use hard drugs. Even after 2 years of heroin-assisted treatment, a particular need for treatment is apparent requiring further therapeutic efforts.

5.4 Dosage, effects and side effects

According to the study protocol, heroin doses may be individually adapted to patients' needs. The average daily dose related to all the heroin patients of the first study phase was 442 mg.

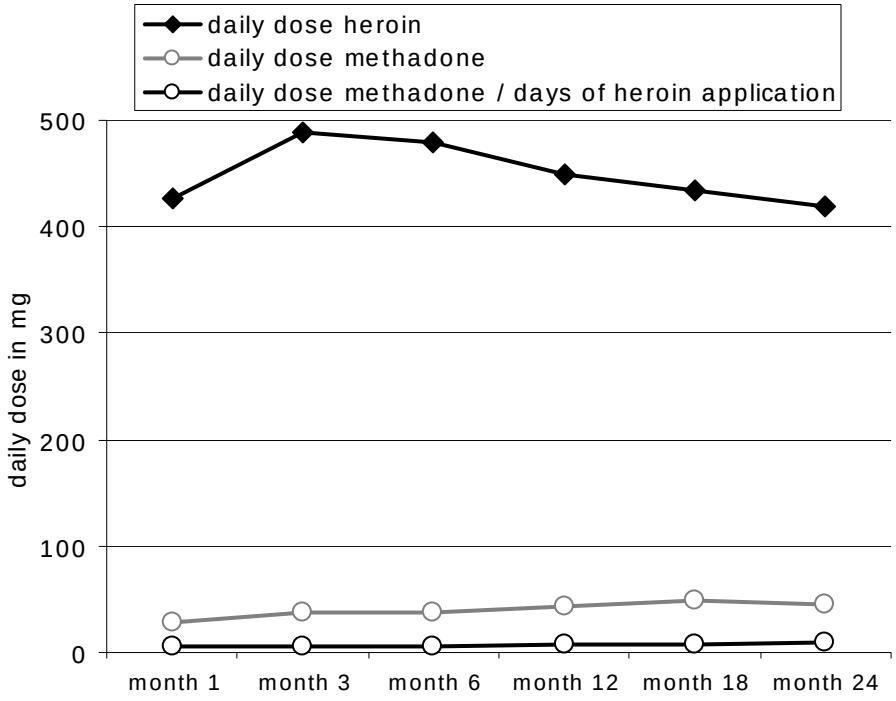
[41] Cochrane test across all examination points: syringe sharing: $Q=57.2$, $df=4$, $p<0.001$; sharing of injection equipment: $Q=107.5$, $df=4$, $p<0.001$.

Additional methadone that patients might receive for the night amounted to slightly less than 8 mg d,l methadone daily, related to all the days with heroin application (cf. Naber & Haasen 2006). The mean daily dose, including heroin and additional methadone, was thus lower than in the Dutch heroin project (van den Brink et al. 2003). Moreover, the first study phase showed that the mean heroin dose decreases in the course of treatment and that the originally expected (adverse) effect of patients requiring ever higher doses did not happen. There were differences between the centres: The dosage in Karlsruhe was lowest (344 mg), in Cologne highest (528 mg).

The course of dosage of released diacetylmorphine (and additionally prescribed methadone) over 2 years of treatment will be described hereafter. Related to all the heroin patients, the average daily dose is 452 mg over 24 months. It was 470 mg in the first study phase and lower in the second phase with 425 mg diacetylmorphine per day.[42] This is also reflected by the course of treatment. The mean daily dose was 427 mg in the first month of treatment with a maximum average dose of 489 mg in the third month (see figure 5.11). After that, the daily dose continuously decreased, settling at an average daily dose of 420 mg diacetylmorphine in the 24th month of treatment. These results definitely refute the initially expressed apprehension that patients would demand ever higher heroin doses. On the other hand, the dose of additionally prescribed methadone slightly increased: from 28 mg in the first month to 46 mg after two years. The 2-year average is 40 mg of methadone (first year: 38 mg, second year: 47 mg). Related to all the days of heroin application, the average daily dose of "really" issued additional methadone is 7.0 mg over 24 months. A slight increase is found here, too, from 6.4 mg at baseline to 9.3 mg at the end of the second study phase (first study year: 6.2 mg, second study year: 7.8 mg).

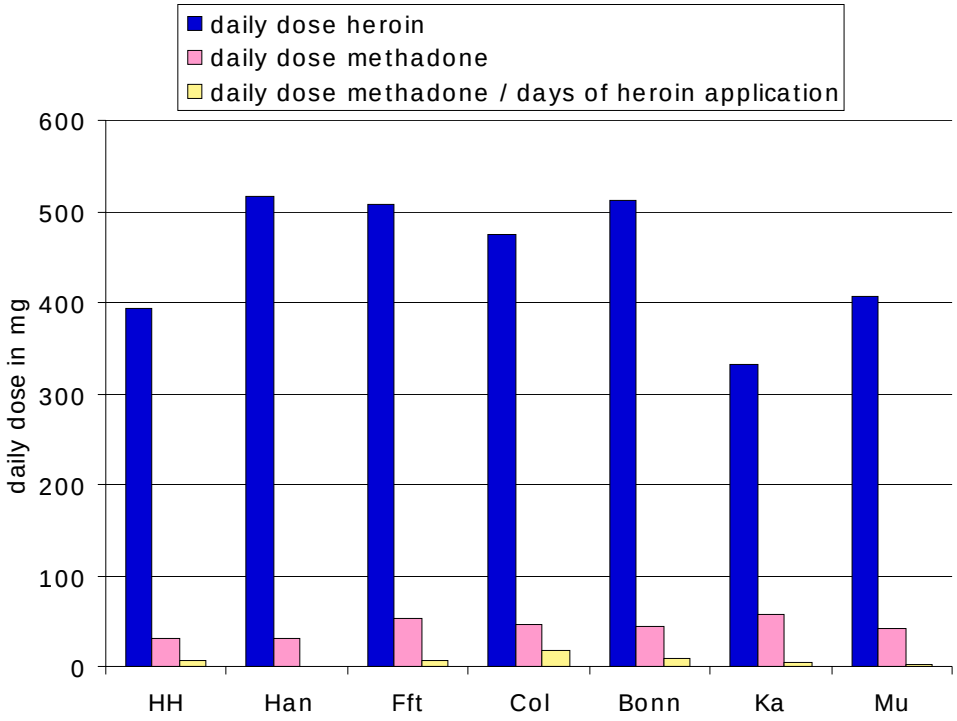
[42] This chapter is devoted only to the effects in 2-year heroin patients. However, it should be mentioned that the average dose of methadone-heroin switchers is, with 505 mg diacetylmorphine (in the second study phase), higher than the dose of the 2-year heroin patients.

Figure 5.11
Average daily dose of the study medication (in mg) in the 1st, 3rd, 6th, 12th, 18th and 24th month of treatment in 2-year heroin patients



Similar to the first study phase, dosage is handled differently in the different study centres. If the overall mean value of all the daily doses over 24 months are considered, the daily dose is still lowest in Karlsruhe with 331 mg of heroin and highest in Hanover with 517 mg (see figure 5.12). In contrast, only a low amount of additional methadone is issued in Hanover, on average 31 mg, related to all the days of heroin application even slightly less than 1 mg. In Hamburg, too, the amount of additionally prescribed oral methadone is low, with a mean daily dose of 30 mg (6 mg related to all days of heroin application). In Karlsruhe, the low heroin dose seems to be compensated by an average of 56 mg of methadone (related to all the days of heroin issuing: 4 mg).

Figure 5.12
Average daily dose of the study medication (in mg) over the entire period of the 2-year study treatment according to study centre

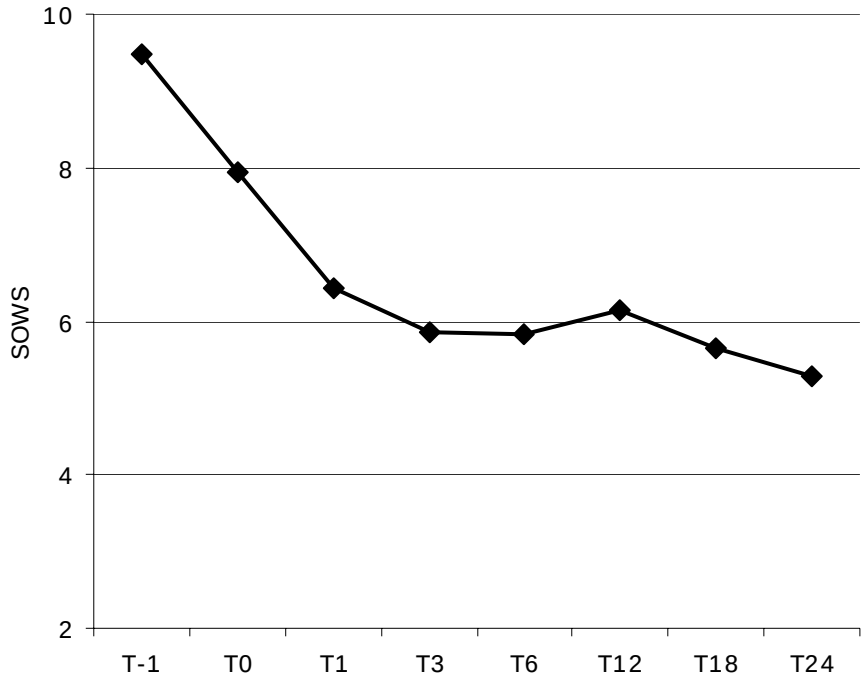


The individual maximum dose was defined according to the patient's condition and well-being within the following limits: 1,000 mg per day, 400 mg per individual dose; due to subjective effects, fluctuations occurred in the course of treatment. The assumption that fluctuations are related to withdrawal symptoms cannot be confirmed. No significant correlation is found between the degree of withdrawal symptoms and the dosage at any examination time, which indicates that patients' individual dose is correct, at least for the suppression of withdrawal symptoms. This concerns both the heroin dose and the additional methadone. The course of withdrawal symptoms, explored by the Short Opiate Withdrawal Scale (SOWS) (Gossop 1990), is represented in figure 5.13. A clear, statistically significant decline is found in the first months,[43] after the third month, the withdrawal symptoms stabilise at a low level (corresponding to 6 of a maximum of 30 points) (repeated measurement analysis: Pillai's trace=0.305, df=7, $p<0.001$). An additional slight decrease to an average of 5.3 points is found in the second study phase.[44]

[43] Similar to the course of physical health according to OTI-HSS, a marked decline of withdrawal symptoms occurred even prior to the initiation of the study treatment (T_0) (cf. Naber & Haasen 2006). As the SOWS also reflects the overall physical condition, such improvements can be explained by the health examinations performed prior to the heroin treatment and treatment measures during the baseline examination (T_{-1}) and the intensive care during the recruitment process.

[44] Within-subjects contrasts: T_{-1} to T_0: $F=1229$, $p<0.01$; T_0 to T_1: $F=15.3$, $p<0.001$; T_1 to T_3: $F=4.9$, $p<0.05$; T_3 to T_6: $F=0.0$, $p=0.990$; T_6 to T_{12}: $F=0.7$, $p=0.408$; T_{12} to T_{18}: $F=2.7$, $p=0.100$; T_{18} to T_{24}: $F=1.3$, $p=0.253$.

Figure 5.13
Course of withdrawal symptoms (SOWS) in heroin patients during the first and second study phase



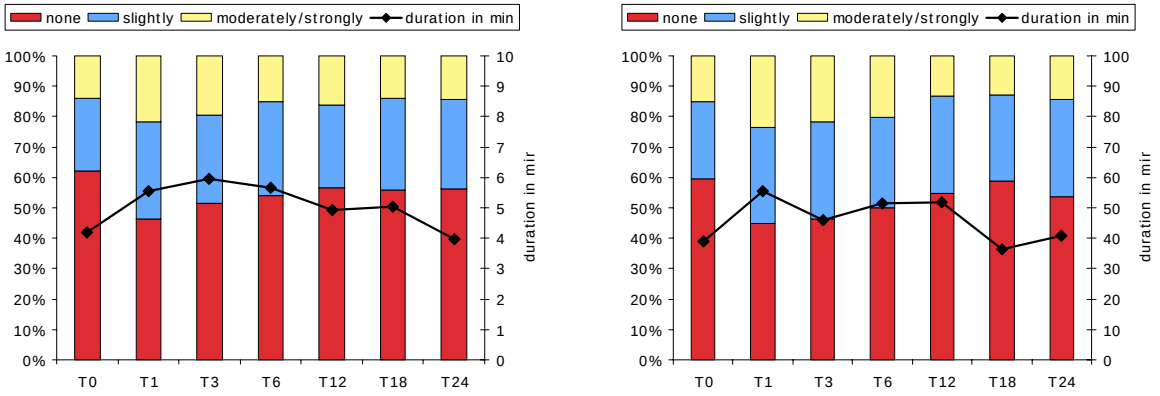
Co-use of street heroin, cocaine and other substances also declines in the course of treatment (see paragraph 5.3); a relationship with the degree of withdrawal symptoms can be assumed. It could be expected that patients might react to withdrawal symptoms with increased drug use (mainly street heroin and/or benzodiazepines). The analysis at almost all examination points based on the ASI Composite Score for drug use shows significant low to medium correlations.[45] But they cannot be related to a single substance. Benzodiazepines are most likely to be frequently taken against strong withdrawal symptoms;[46] for street heroin, cocaine and cannabis, no significant correlations are found at any time of examination. Therefore, the use of benzodiazepines, again mainly medically prescribed, could be a reaction to physical (withdrawal) symptoms.
Looking at the immediate (desired) intoxication effects of heroin application, this shows that the intensity and duration of the "kick" and of the feeling of euphoria decline in the course (see figure 5.14). The proportion of patients feeling a medium to strong "kick" increases from 14.0% to 21.6% after one month, which can be explained by slowly vanishing distrust of the effect of the study medication. The percentage drops to 16.0% after 12 months, and stabilises at about 14% in the second year of treatment. The "kick" lasts 4-6 minutes on average and also declines from the third month of treatment. The feeling of euphoria has a similar course:

[45] Pearson correlations: SOWS with composite score DRU2: r_{-1}=.10, p=0.058; r_6=.20, p<0.001; r_{12}=.23, p<0.001; r_{18}=.28, p<0.001; r_{18}=.18, p<0.05.

[46] Pearson correlations: SOWS with benzodiazepine use last 30 days: r_{-1}=.07, p=0.226; r_6=.04, p=0.444; r_{12}=.09, p=0.114; r_{18}=.13, p<0.05; r_{18}=.16, p<0.01.

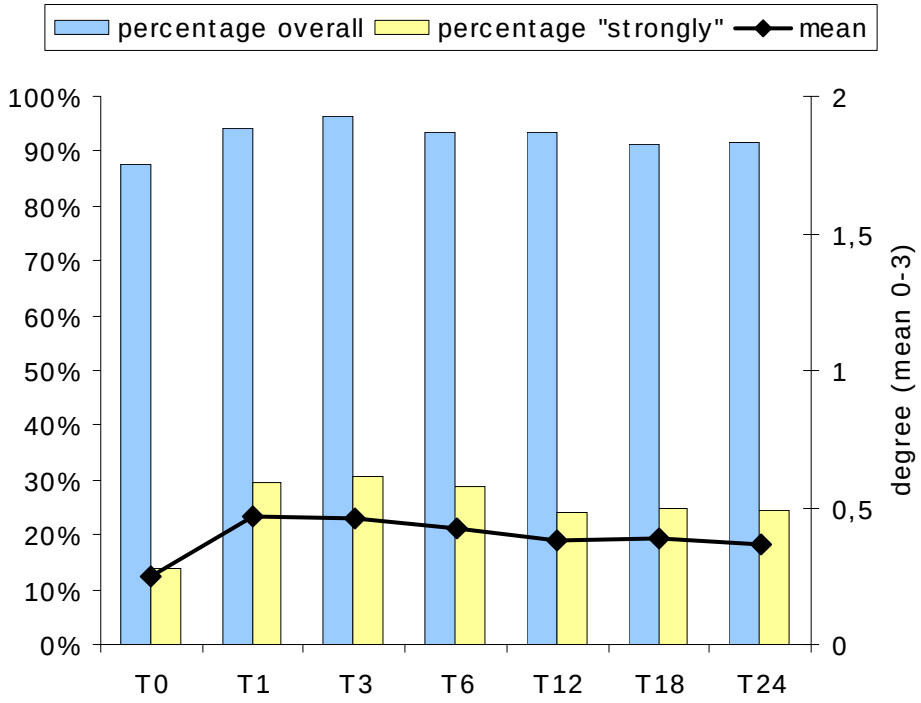
The duration fluctuates between 36 and 56 minutes with a tendency to decline. It implies that, in the course of treatment, habituation of the immediate effect of heroin after application occurs. It underlines the status of heroin as medically prescribed medication. It is remarkable that about half of the heroin patients do not experience any “kick” or euphoria after the application of the study medication.

Figure 5.14
Euphoric effects: “kick/flash” (left) and feelings of euphoria (right) immediately after application of the study medication in the course of the 2-year heroin treatment



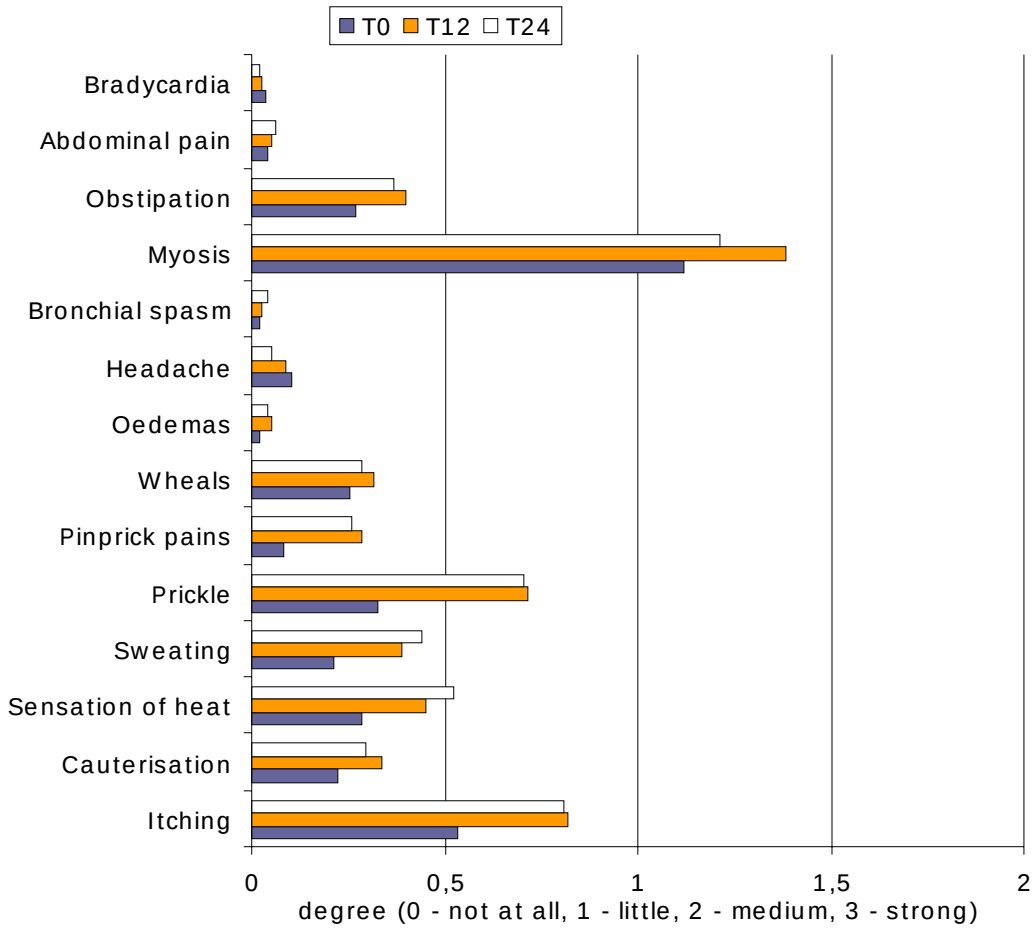
In addition to the event-related documentation of adverse events (cf. chapter 7), undesired effects of the study medication were also directly explored. For each time of examination, the extent of opioid-related symptoms or side effects was assessed. Data were collected on 14 individual symptoms such as itching, sweating or obstipation on a 4-degree scale (0=“not at all“, 1=“a little“, 2=“medium“, 3=“strong“); another eight severe symptoms such as apnea, convulsion were documented for the interval since the last examination. As these symptoms are related to the study medication, the value at treatment initiation (T_0) is considered as baseline, taking into account that these data are based only on the effects of the very first (few) heroin applications. Figure 5.15 shows that for almost 90% of the heroin patients, such side effects occur in the entire course of treatment. The subjectively felt degree of symptoms is rather low. This can be seen on the one hand by the degree of symptoms, which is on average below 0.5 corresponding to a value between “not at all” and “somewhat”. Moreover, it shows that the proportion of patients with strong symptoms (at T_1 to T_6) is at most 30%. A slight decrease is found for the entire course of 2-year treatment, which indicates an increasing habituation of the heroin effect (and the whole range of treatments).

Figure 5.15
Proportion of patients and average degree of adverse effects of heroin during the first and second study phase. Overview related to 14 potential individual symptoms



Upon closer examination of the side effects, only miosis occurs to an appreciable average degree (see figure 5.16). The range of skin symptoms caused by increased histamine release, such as itching, prickling, etc. is also noticeable. The development of all these symptoms is, however, extremely low and impairments by the adverse effects hardly to be expected. The symptoms hardly changed in the second study phase.

Figure 5.16
Average degree of adverse attendant symptoms of heroin at T_0, T_{12} and T_{24}.



In case of side effects, relationships with the dose of the maintenance substance are investigated first of all. However, a linear relationship with the heroin dose cannot be established at any point of examination. Focusing on patients with “strongly” developed attendant symptoms (cf. figure 5.15) shows that they receive a slightly lower dose of heroin in the later course of treatment (from T_6). But differences of the average doses are not statistically significant at any time so that e.g. potential underdosage cannot be concluded. For the second obviously influencing factor, the co-use of street heroin, a relationship between the intensity of consumption (number of days) and the extent of side effect is not found either at any examination time.

Eight additional symptoms, assessed as severe or even life threatening, were explored at each examination time. Table 5.8 shows that these symptoms are extremely rare and occur in only a low proportion of patients. Fits of convulsion should be mentioned, which can occur at times in individual patients. In order to adequately treat these severe potential symptoms, patients are required to stay on the premises of the outpatient unit for 30 minutes after heroin application. Later damages in consequence of these complications could thus be avoided (cf. also chapter 7, adverse events).

Table 5.8
Severe adverse attendant symptoms in heroin patients during the first and second study phase[a)]

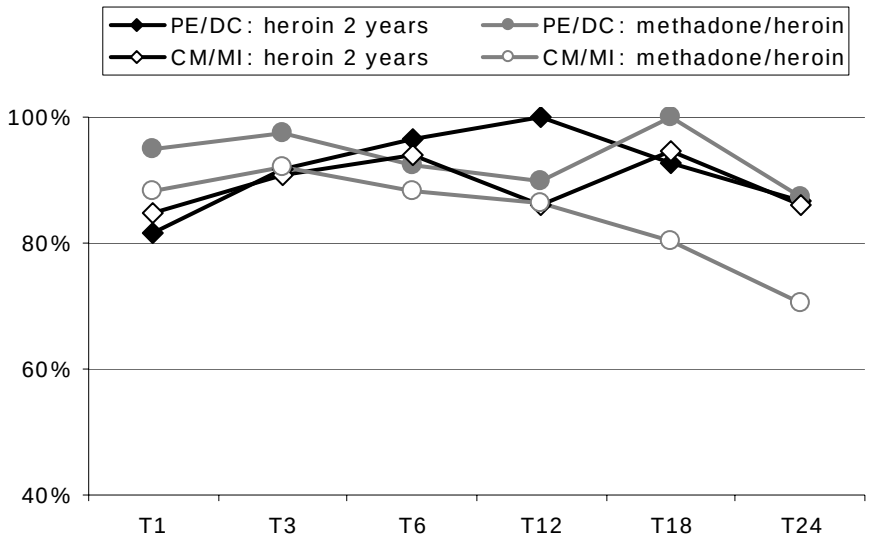
Symptom	**T6**	**T12**	**T18**	**T24**
Bradypnea	0.3%	1.5%	0.7%	0.7%
Apnea	0.3%	1.2%	0.7%	0.4%
Cyanosis	0.6%	1.2%	1.0%	-
Muscle spasms	0.9%	0.3%	-	-
Convulsion	1.5%	2.4%	2.3%	2.1%
Pulmonary edema	-	0.3%	0.3%	0.4%
Loss of consciousness	1.2%	1.2%	1.0%	0.4%
Hypotension	-	-	0.3%	0.7%

a) Non of these symptoms was present at T_0.

6. Utilisation and acceptance of psychosocial treatment

Concomitant psychosocial treatment was continued in the second study phase, either in the form of psychoeducative groups with drug counselling (PE/DC) or case management with motivational interviewing (CM/MI). The differential effects of the two forms of psychosocial treatment and their utilisation and acceptance were extensively analysed in the framework of the collateral study concerning Psychosocial Treatment in the first study year (cf. Kuhn et al. 2006). The present analysis deals with the course of psychosocial treatment over two years of treatment. As the internal documentation of performances and activities was no longer evaluated in the second study phase, the results presented here are based upon CRF data (medical and external) and the separate PST survey, the so called booklets, which were filled in by the treatment staff every six months (cf. Krausz et al. 2001).
First of all, participation in PST is extremely high among the 2-year patients. During the first study phase, participation ranges between 80% and 100% (see figure 6.1). In the course of the second year of treatment, utilisation slightly decreases in the 2-year heroin group with PE/DC, though the overall level is still high. In the group of methadone-heroin switchers treated with case management, PST participation continuously declines from the 3rd month, but is still 71% in the 24th month.

Figure 6.1
Utilisation of psychosocial treatment in 2-year heroin patients and switchers according to the type of PST across both study phases; data of medical investigators (n=434)



In the second study phase, treatment intensity, i.e. the number of individual or group sessions in the course of the two years of treatment, declines among the 2-year heroin patients. Among the methadone-heroin switchers, the frequency of treatment only slightly decreases in the PE/DC branch; among case management patients, there is even a slight increase in the second year of treatment, after a comparably low frequency in the first year (see table 6.1). The resulting picture is not uniform over the 2 years of the study. If individual and group sessions

are combined, the group of switchers in the *psychoeducation branch* has the greatest treatment intensity with an average of 63 sessions, the 2-year heroin patients have 50 sessions. Thus, the success of switchers under heroin treatment, described in chapter 4, is associated with rather intensive (though slightly declining compared to the first study phase) psychosocial treatment. As for *case management*, the 2-year heroin patients continue to be treated with a high frequency of contacts; in switchers, the intensity of (individual) sessions increases and is then no longer different from the other CM/MI heroin patients, again analogous to the positive effects in the second year of treatment.

Table 6.1
Average number of individual and group sessions in 2-year heroin patients and switchers according to PST across the 2 study phases

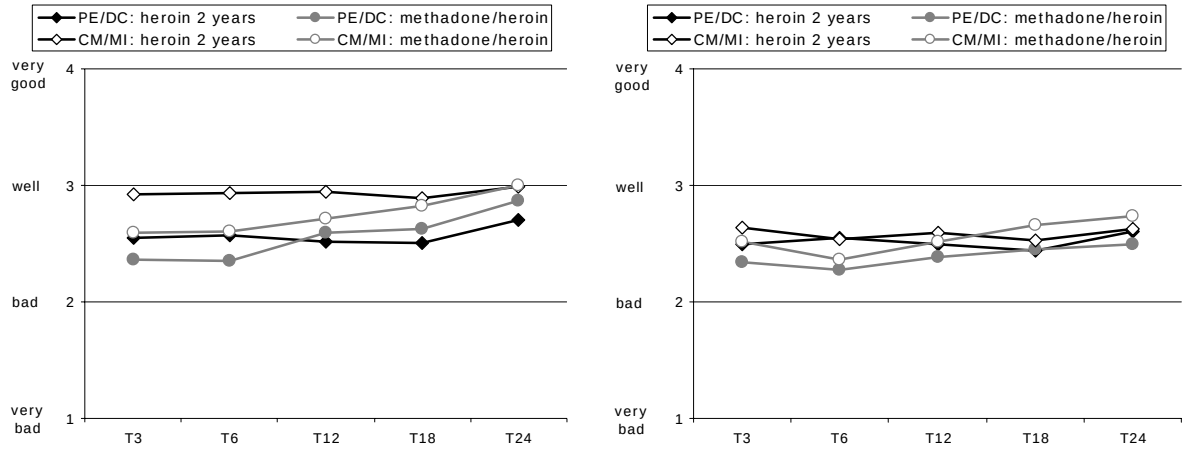
		Phase 1	**Phase 2**	**Total**
PE/DC	Heroin 2 y: individual sessions	21.2	14.9	36.1
	Heroin 2 y: group sessions	10.5	3.9	14.4
	M-H switchers: individual sessions	25.4	22.6	48.0
	M-H switchers: group sessions	9.6	5.8	15.4
CM/MI	Heroin 2 y: individual sessions	33.0	28.7	61.8
	M-H switchers: individual sessions	25.5	28.9	54.3

According to the psychosocial drug counsellors of the PE/DC branch of PST, (treatment) relations to patients are moderate on average (ranging between “rather bad” and “rather good”) with differences between 2-year heroin patients and switchers during the first study phase. The therapist-patient relationship improves in both groups in the second year of treatment (see figure 6.2, left side). Case managers describe their relationship to heroin patients as “rather good” for the entire 2-year period. However, in the first year of treatment, the therapist-patient relationship was less good in the group of methadone-heroin switchers; in the second study phase, i.e. under heroin treatment, its quality improved and reached the level of the 2-year heroin group. Overall, the quality of the relationship with the patient is somewhat better in case management.[47] However, the kind of medication also influences the relational quality in both types of psychosocial treatment; it is better in the case of patients treated with heroin (during the first study phase). Therapists’ assessment of patients’ active involvement in the psychosocial treatment process does not reveal any relevant differences between PE/DC and CM/MI.[48] Among the 2-year heroin patients, the average commitment across 24 months is assessed as satisfactory, ranging between “rather good” and “rather bad” (see figure 6.2, right side). Switchers are slightly less committed in the first year, but after switching to heroin, their commitment reaches the level of the other patient group in the second year of treatment.

[47] At all examination times, there are significant differences in favour of CM/MI (T-test combined for 2-year heroin group and switchers: T_3: t=-4.1, p<0.001; T_6: t=-4.3, p<0.001; T_{12}: t=-4.9, p<0.001; T_{18}: t=-4.7, p<0.001; T_{24}: t=-3.3, p<0.01).

[48] T-test combined for 2-year heroin group and switchers: T_3: t=-1.8, p=0.068; T_6: t=0.3, p=0.975; T_{12}: t=-1.4, p=0.176; T_{18}: t=-1.5, p=0.135; T_{24}: t=-0.7, p=0.494.

Figure 6.2
Patient-therapist relationship (left), patients' commitment (right) according to psychosocial therapists' assessment in the course of the 2-year study treatment

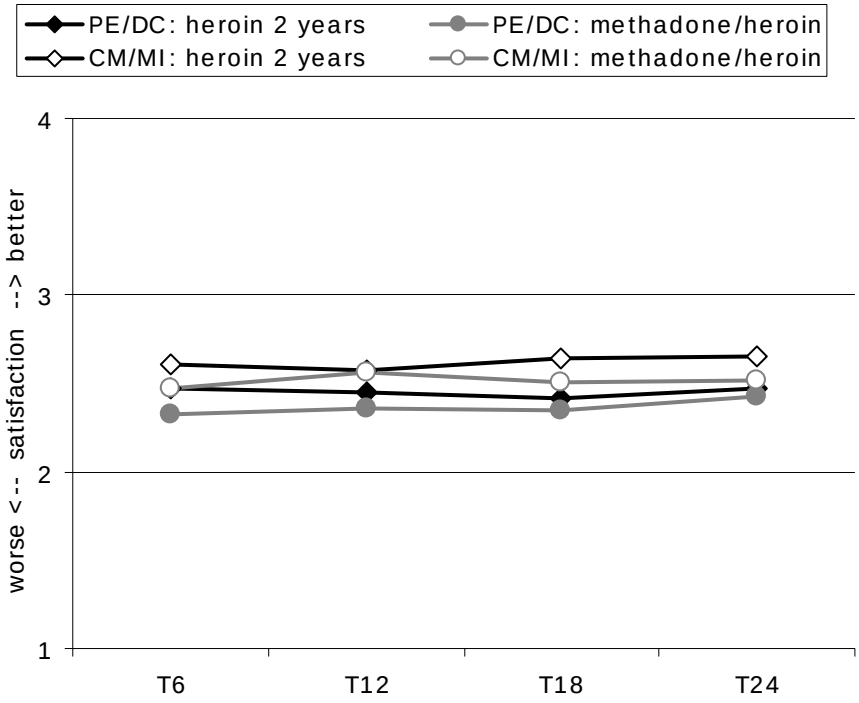


Patients' satisfaction with psychosocial treatment was investigated with the Treatment Perceptions Questionnaire, TPQ (Marsden et al. 2000), at the external interview every six months. The overall satisfaction with psychosocial treatment is greater for patients treated with case management and motivational interviewing (see figure 6.3).[49] It is also conspicuous that, already in the first year of treatment, satisfaction with PST of methadone-heroin switchers treated with CM/MI is comparable to that of 2-year heroin patients treated with psychoeducation and drug counselling. It is evident that satisfaction is related to the quality of the patient-therapist relationship, which is also assessed higher by case managers (see above).[50] Switching of the study medication has almost no influence on the satisfaction with psychosocial treatment.

[49] There are significant differences in favour of CM/MI at all examination times (T-test for 2-year heroin group and switchers combined: T_6: t=-2.3, p<0.05; T_{12}: t=-2.4, p<0.05; T_{18}: t=-3.6, p<0.001; T_{24}: t=-2.8, p<0.01).

[50] Pearson correlation between patient-therapist relationship and treatment satisfaction (all patients): T_6: r=.24, p<0.001; T_{12}: r=.17, p<0.01; T_{18}: r=.12, p<0.05; T_{24}: r=.17, p<0.01.

Figure 6.3
Satisfaction with psychosocial treatment (measured with TPQ) in 2-year heroin patients and switchers according to type of PST in the course of the 2-year study treatment

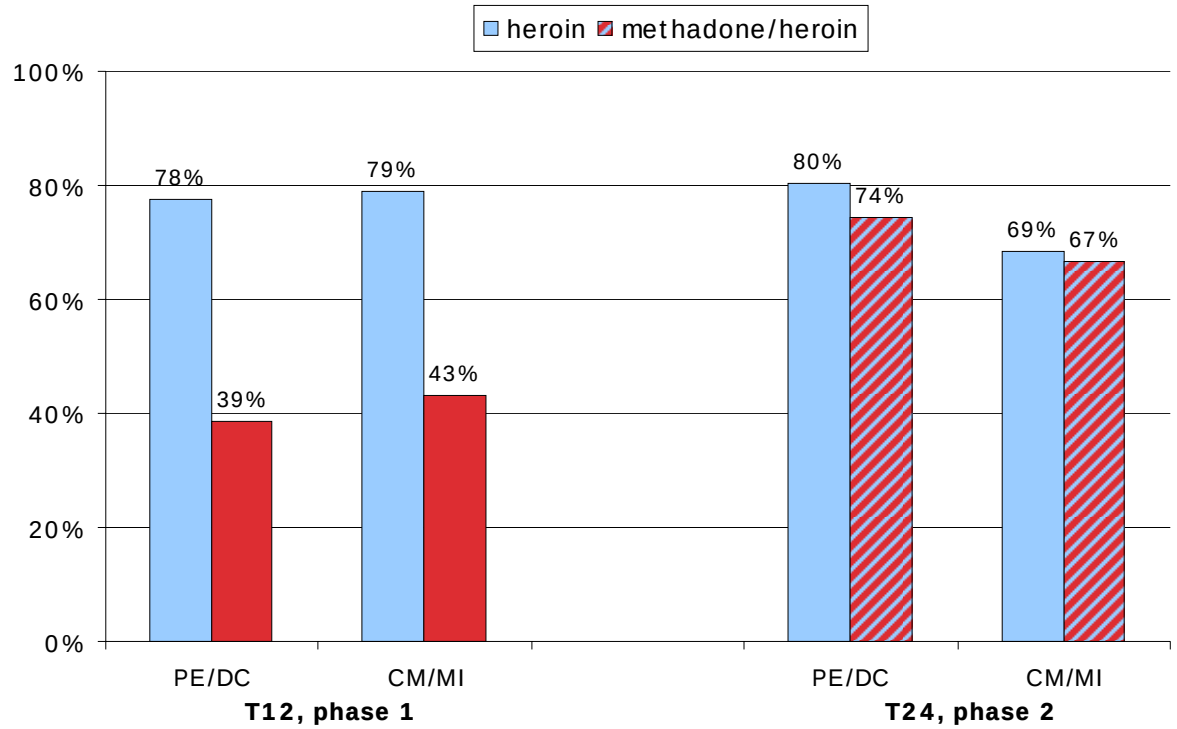


The long-term effects of study treatment reveal that acceptance and satisfaction with the respective treatment are not necessarily directly related to the treatment effects. If the combined primary outcome measure is considered, i.e. the proportion of responders in the two criteria "state of health" and "illicit drug use", no significant difference between the two types of psychosocial treatment is found at the end of the first study phase (T_{12}) (cf. Naber & Haasen 2006; Kuhn et al. 2006). After 24 months, however, the response rates of patients treated with case management and motivational interviewing are clearly below the rates of PE/DC patients, both for the 2-year heroin patients and the switchers (see figure 6.4). The odds ratio of the logistic regression model is 1.96 (95%-CI: 1.14-3.39, p=0.015) and refers to a statistically significant superiority of the combination of psychoeducation and drug counselling. No significant influence is found for the factors treatment group (2-year heroin vs. switchers, p=0.285), target group stratum (MTF vs. NR, p=0.679) and study centre (p=0.106).[51] It is moreover conspicuous that patients treated with heroin and case management for two years have worse primary outcome measures in the second year of treatment, while patients treated with heroin and psychoeducation and drug counselling increase their response rates. This might be partly due to the higher rate (84.4%) of regular treatment concluders among PE/DC patients.[52] Only 76.9% of the CM/MI patients completed the study treatment of the second phase.

[51] Goodness of Fit nach Hosmer & Lemeshow: χ^2=12.83, df=8, p=0.118.

[52] In the primary outcome measure, study dropouts are counted as non-responders (cf. chapter 4).

Figure 6.4
Response rates of patients, who fulfil both primary outcome measures, at T_{12} and T_{24} according to type of PST (n=434)



The differences between centres, discussed in the context of the collateral study on Psychosocial Treatment, are not traceable in the multivariate analysis model at the end of the second study phase. This is also true if the analysis of effects only considers the centres, where both types of PST were offered (Hamburg, Hanover, Frankfurt) (OR=1.90, 95%-CI: 1.10-3.28, p=0.022). Here, too, the response rates of the PE/DC group are significantly higher than among CM/MI patients (at T_{24} (n=277): PE/DC: 2-year heroin 81.0%, switchers 61.9%; CM/MI: 2-year heroin 65.1%, switchers 55.2%.). The effects are independent of the factors target group stratum (p=0.570) and study centre (p=0.573), but there is an influence of the treatment group: The 2-year heroin patients still have higher response rates than the methadone-heroin switchers (OR=1.93, 95%-CI: 1.01-3.71, p=0.048).[53] Therefore, the catching-up effect described in chapter 4 among patients switching from methadone to heroin after one year, is not quite so pronounced in the centres of Hamburg, Hanover and Frankfurt. But even in the centres offering both PE/DC and CM/MI, differences are found between the two types of PST regarding the effects of heroin treatment.
A combination of traditional drug counselling and psychoeducative groups has probably better long-term effects than "motivational case management" in the group of severely dependent patients treated with heroin; this finding deserves further analyses beyond the present report. It is possible to state (without going into details) that responders are overall more satisfied with psychosocial treatment at T_{24}, but the greater treatment satisfaction of patients treated with case management is not reflected by higher retention rates and greater effects. Against

[53] Goodness of Fit nach Hosmer & Lemeshow: χ^2=8.13, df=8, p=0.421.

the background of similar treatment intensity in both PST groups, this is unusual and should also be further analysed.

7. Safety analyses across two years

Adverse events that occurred during the first and second study phase are described separately for the 2-year heroin patients and patients, who switched from methadone to heroin after the first study phase. To conclude, deaths are described that occurred in the second study phase.

7.1 Adverse events (AEs)

7.1.1 Recording of AE reports

The participating study centres recorded for each patient the adverse events (AEs) that occurred during the study period. For the entire study period, eight CRF pages were provided for each participant to document AEs. Nine AEs could be described on one page, which allowed a complete and comprehensive documentation of all adverse events.
According to the GCP guidelines, the recording of following data was standardised, in addition to the description of the AEs:

- Date of beginning and end, and whether AE is ongoing
- Time of beginning and end
- Degree of severity
- Measures taken concerning the 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 comprehensive, therefore, the data set at the base of the analysis can be considered to possess a high degree of completeness. Only the category recording the times of beginning and end of the AE has, with the exception of convulsions, major gaps so that an analysis related to these data was dropped. Likewise, it was not possible to calculate the relationship between the AEs and the dose of study medication. Data of the beginning of the event were often vague (often only month or year) and therefore prevented a clear attribution to dosage data.
Qualified personnel (doctors) of the principal investigator's team in Hamburg took care of the coding in ICD-10 diagnoses using the programme "ICD-10-Navigator Medizin, ORIS Version 4.0" (Oris, 2001). Therefore, it is possible to categorise and evaluate the AEs in terms of diagnoses and symptoms.

7.1.2 Description of adverse events

Overall, 7,257 AEs were documented among the 434 patients of the 2-year study group in the course of the two study phases. There were only three heroin patients with no reported AEs.
The safety analysis is limited to AEs that occurred between randomisation and the end of the second study phase or the discontinuation of treatment (in the second year). The number of AEs to be analysed is thus reduced to 6,813 (see table 7.1). This is due to the fact that, on the one hand, medical investigators had already started documentation prior to treatment initiation

(from T_{-1} onwards) and, on the other hand, events, pertaining to the follow-up phase, were already described on the AE sheets of the first and second study phase.

Table 7.1
Number of documented adverse events (AEs)

	N	Prior to study initiation	After 24 months	Between randomisation and T24	Total
Heroin patients	341	205	127	**5,130**	5,462
Methadone-heroin switchers	90	92	20	**1,683**	1,795
Total	431	297	147	**6,813**	7,257

The number of recorded AEs considerably differs between the first and second study year. More than two thirds of the AEs in the period of observation occurred in the first year of treatment, irrespective of the patient group (2-year heroin patients or methadone-heroin switchers) (see table 7.2).

Table 7.2
Number of documented adverse events (AEs) in the first and second study year

	N	1st study year	2nd study year	Total
Heroin patients	341	3,753 (73.2%)	1,377 (26.8%)	5,130 (100%)
Methadone-heroin switchers	90	1,198 (71.2%)	485 (28.8%)	1,683 (100%)
Total	431	4,951 (72.7%)	1,862 (27.3%)	6,813 (100%)

Patients, who received heroin for two year, had on average 11.0 AEs in the first study year and 4.0 AEs in the second year. Patients of the group of switchers reported an average of 13.3 AEs under methadone in the first study year and 5.4 AEs under heroin in the second year. The average frequency of AEs for each patient considerably declined in both groups in the second study year. In the second year of treatment, where switchers also received heroin, they had on average one AE more than patients, who received heroin from the start. This proves that switching from methadone to heroin does not result in a great increase of new AEs that are possibly typical for heroin (for a differentiated consideration see chapter 7.1.4). Moreover, table 7.3 shows that the frequency of AEs, related to treatment in the second study year, clearly declined.

Table 7.3
Treatment duration in days and AEs in the first and second study year

	1st study year		2nd study year	
	Treatment duration	**Duration until occurrence of an AE**	**Treatment duration**	**Duration until occurrence of an AE**
Heroin patients	366	33.4	334	83.5
Methadone-heroin switchers	371	27.9	363	67.2

Tables 7.4 to 7.7 show the results concerning the assessments of the degree of severity, the causal relationship with the study medication, steps taken with respect to the study medication and the outcome of the adverse event.
Overall, only 5.0% of all recorded AEs in the group of the 2-year heroin patients and 4.7% of the AEs in the group of switchers were assessed as “severe” (see table 7.4). Related to the treatment days, a “severe” AE was recorded on average every 933.3 treatment days in the heroin group and every 796.6 treatment days in the switcher 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 7.2.

Table 7.4
Severity of AEs according to the first and second study year and study groups (number, %)

Degree of severity of AEs	**2-year heroin**			**Methadone-heroin switchers**		
	Phase 1	**Phase 2**	**Total**	**Phase 1**	**Phase 2**	**Total**
Minor	2,257 (60.3%)	753 (54.9%)	3,010 (58.9%)	617 (51.8%)	277 57.1%)	894 (53.3%)
Medium	1,263 (33.8%)	547 (39.9%)	1,810 (35.4%)	512 (43.0%)	186 (38.4%)	698 (41.6%)
Severe	193 (5.2%)	63 (4.6%)	256 (5.0%)	58 (4.9%)	21 (4.3%)	79 (4.7%)
Not applicable	29 (0.8%)	8 (0.6%)	37 (0.7%)	5 (0.4%)	1 (0.2%)	6 (0.4%)
Total	**3,742** (100%)	**1,371** (100%)	**5,113** (100%)	**1,192** (100%)	**485** (100%)	**1,677** (100%)

In about 60% of all AEs, there was no causal relationship with the study medication, neither in the 2-year heroin group nor in the group of switchers (see table 7.5). A potential to certain relationship was found in 19.3% of all AEs (2-y heroin: 19.8%; M-H switchers: 17.7%). In the heroin group, an AE with causal relationship with the study medication occurred every 235.7 days, in the group of switchers only every 212.4 days. The differences between the two study groups will be analysed more closely in the paragraphs 7.1.3 and 7.1.4.

Table 7.5
Causal relationship between AEs and study medication according the first and second study year and the two study groups (number, %)

Causal relationship with study medication	**2-year heroin**			**Methadone-heroin switchers**		
	Phase 1	**Phase 2**	**Total**	**Phase 1**	**Phase 2**	**Total**
None	2,177 (58.2%)	924 (67.4%)	3,101 (60.7%)	684 (57.1%)	304 (62.7)	988 (58.7%)
Unlikely	738 (19.7%)	258 (18.8%)	996 (19.5%)	291 (24.3%)	105 (21.6%)	396 (23.5%)
Possible	572 (15.3%)	130 (9.5%)	702 (13.7%)	188 (15.7%)	42 (8.7%)	230 (13.7%)
Likely	188 (5.0%)	42 (3.1%)	230 (4.5%)	31 (2.6%)	27 (5.6%)	58 (3.5%)
Definite	66 (1.8%)	17 (1.2%)	83 (1.6%)	3 (0.3%)	7 (1.4%)	10 (0.6%)
Total	**3,741** (100%)	**1,371** (100%)	**5,112** (100%)	**1,197** (100%)	**485** (100%)	**1,682** (100%)

A very high proportion of the documented AEs (92.5%) did not require any change of medication, neither for the study medication heroin nor for methadone or heroin in the group of methadone-heroin switchers (see table 7.6).

Table 7.6
Initiated actions related to the study medication according to the first and second study year and the two study groups (number, %)

Actions	**2-year heroin**			**Methadone-heroin switchers**		
	Phase 1	**Phase 2**	**Total**	**Phase 1**	**Phase 2**	**Total**
No change	3,450 (92.1%)	1,253 (91.3%)	4,703 (91.9%)	1,151 (96.2%)	440 (90.7%)	1,591 (94.6%)
Reduced	128 (3.4%)	43 (3.1%)	171 (3.3%)	17 (1.4%)	20 (4.1%)	37 (2.2%)
Increased	24 (0.6%)	7 (0.5%)	31 (0.6%)	9 (0.8%)	4 (0.8%)	13 (0.8%)
Temporarily discontinued	77 (2.1%)	44 (3.2%)	121 (2.4%)	7 (0.6%)	11 (2.3%)	18 (1.1%)
Discontinued	5 (0.1%)	1 (0.1%)	6 (0.1%)	- -	2 (0.4%)	2 (0.1%)
Not applicable	62 (1.7%)	25 (1.8%)	87 (1.7%)	13 (1.1%)	8 (1.6%)	21 (1.3%)
Total	**3,746** (100%)	**1,373** (100%)	**5,119** (100%)	**1,197** (100%)	**485** (100%)	**1,682** (100%)

A very low percentage of all adverse events (3% altogether) resulted in consequences for the patient's health (see table 7.7). 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 7.2 on severe adverse events (SAEs).

Table 7.7
Outcome of the adverse event according to the first and second study year and the two study groups (number, %)

Outcome of AE	**2-year heroin**			**Methadone-heroin switchers**		
	Phase 1	**Phase 2**	**Total**	**Phase 1**	**Phase 2**	**Total**
Restored	3,080 (82.4%)	1,058 (77.2%)	4,138 (81.0%)	891 (74.6%)	370 (76.3%)	1,261 (75.1%)
Restored with consequences	68 (1.8%)	51 (3.7%)	119 (2.3%)	65 (5.4%)	17 (3.5%)	82 (4.9%)
Ongoing	563 (15.1%)	252 (18.4%)	815 (16.0%)	223 (18.7%)	93 (19.2%)	316 (18.8%)
Patient died	- -	3 (0.2%)	3 (0.1%)	1 (0.1%)	1 (0.2%)	2 (0.1%)
Not known	26 (0.7%)	6 (0.4%)	32 (0.6%)	15 (1.3%)	4 (0.8%)	19 (1.1%)
Total	**3,737** (100%)	**1,370** (100%)	**5,107** (100%)	**1,195** (100%)	**485** (100%)	**1,680** (100%)

7.1.3 Adverse events classified according to ICD-10

Each documented adverse event was coded with up to three ICD-10 diagnoses. Only one AE could not be described with an ICD-10 diagnosis (random nr.: 70036, AE: burning). 6,812 first diagnoses were attributed; a second diagnosis was attributed in 525 AEs and a third diagnosis in 60 AEs. The following analysis only considers the first diagnoses, as they classify the main symptom. The ICD-10 diagnoses were combined to higher-ranking categories according to their content and analysed with respect to the frequency of their occurrence. Table 7.8 presents the detailed list of the higher-ranking categories.

Table 7.8
List of the higher-ranking ICD-10 categories

Category	**Designation of category**	**ICD-10**
1	Infectious gastrointestinal diseases	A09
2	Infectious 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	B35 – B49
7	Pediculosis and other infectious diseases	B85 – B89, B99
8	Neoplasms (benign or malign)	D7.9, D2 – D4
9	Diseases of the blood and of hematogenic organs	D5 - D7
10	Endocrinal, nutritional and metabolic diseases	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	Poisonings	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 7.9 informs about the frequency of adverse events for each higher-ranking ICD-10 category, according to 2-year heroin patients and methadone-heroin switchers. For the sake of clarity (also in tables 7.10. and 7.11), there is no differentiation according to first and second study phase, particularly as each category contains only few cases.

Table 7.9
Frequency of the AEs in the higher-ranking ICD-10 categories according to study groups

Category	2-y heroin		M-H switchers		Total	
	Number	%	Number	%	Number	%
1	72	1.4	21	1.2	93	1.4
2	30	0.6	7	0.4	37	0.5
3	43	0.8	24	1.4	67	1.0
4	15	0.3	2	0.1	17	0.2
5	4	0.1	3	0.2	7	0.1
6	38	0.7	12	0.7	50	0.7
7	13	0.3	2	0.1	15	0.2
8	6	0.1	3	0.2	9	0.1
9	41	0.8	21	1.2	62	0.9
10	17	0.3	6	0.4	23	0.3
11	6	0.1	0	0.0	6	0.1
12	168	3.3	50	3.0	218	3.2
13	17	0.3	3	0.2	20	0.3
14	61	1.2	32	1.9	93	1.4
15	23	0.4	12	0.7	35	0.5
16	60	1.2	27	1.6	87	1.3
17	16	0.3	9	0.5	25	0.4
18	203	4.0	43	2.6	246	3.6
19	20	0.4	5	0.3	25	0.4
20	54	1.1	10	0.6	64	0.9
21	51	1.0	19	1.1	70	1.0
22	54	1.1	24	1.4	78	1.1
23	156	3.0	46	2.7	202	3.0
24	399	7.8	107	6.4	506	7.4
25	31	0.6	16	1.0	47	0.7
26	64	1.2	32	1.9	96	1.4
27	96	1.9	36	2.1	132	1.9
28	237	4.6	55	3.3	292	4.3
29	40	0.8	6	0.4	46	0.7
30	159	3.1	41	2.4	200	2.9
31	118	2.3	31	1.8	149	2.2
32	364	7.1	112	6.7	476	7.0
33	81	1.6	29	1.7	110	1.6
34	67	1.3	28	1.7	95	1.4
35	72	1.4	24	1.4	96	1.4
36	87	1.7	23	1.4	110	1.6
37	2	0.0	1	0.1	3	0.0
38	245	4.8	104	6.2	349	5.1
39	353	6.9	116	6.9	469	6.9
40	122	2.4	31	1.8	153	2.2
41	64	1.2	27	1.6	91	1.3
42	29	0.6	11	0.7	40	0.6

43	124	2.4	44	2.6	168	2.5
44	686	13.4	230	13.7	916	13.4
45	58	1.1	27	1.6	85	1.2
46	314	6.1	121	7.2	435	6.4
47	47	0.9	23	1.4	70	1.0
48	70	1.4	15	0.9	85	1.2
49	32	0.6	12	0.7	44	0.6
Total	**5,129**	**100.0**	**1,683**	**100.0**	**6,812**	**100.0**

The only higher-ranking ICD-10 category with a frequency of occurrence above 10% (2-y heroin: 13.4%; M-H switchers: 13.7%) includes only one ICD-10 diagnosis (R5). This diagnosis subsumes, however, 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 7.4%, the second most frequently documented AEs (2-y heroin: 7.8%; M-H switchers: 6.4%), followed by diseases of the skin and the subcutis (category 32) with 7.0% (2-y heroin: 7.1%, M-H switchers: 6.7%) and by symptoms of the digestive system and the abdomen (category 39) with 6.9% (2-y heroin: 6.9%; M-H switchers: 6.9%). Also above 5% were injuries by external causes with 6.4% (2-y heroin: 6.1%; M-H switchers: 7.2%) and symptoms of the circulatory and the respiratory system with 5.1% (2-y heroin: 4.8%; M-H switchers: 6.2%) (see table 7.10).

Table 7.10
ICD-10 categories combined according to their frequency of occurrence

	ICD-10 categories	**%**
Individual cases / very rare (less than 0.1%)	37	2.0
Rare (less than 1%)	2, 4, 5, 6, 7, 8, 9, 10, 11, 13, 15, 17, 19, 20, 25, 29, 42, 49	36.8
Occasionally (1-10%)	1, 3, 12, 14, 16, 18, 21, 22, 23, 24, 26, 27, 28, 30, 31, 32, 33, 34, 35, 36, 38, 39, 40, 41, 43, 45, 46, 47, 48	59.2
Often (more than 10%)	44	2.0

Table 7.11 presents an overview of the higher-ranking 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, likely or certain relationship with the heroin or methadone medication. AEs with no or unlikely relationship with the study medication are presented under the heading "no relationship".

Table 7.11

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

ICD-10 category	2-y heroin						M-H switchers					
	Relationship			No relationship			Relationship			No Relationship		
	low	med.	severe	low	med.	severe	low	med.	severe	low	med.	severe
1	11	14	-	27	17	2	4	1	-	9	7	-
2	-	1	-	11	16	2	-	-	-	1	5	-
3	-	-	-	35	8	-	-	-	-	18	6	-
4	-	-	-	7	6	2	-	-	-	-	2	-
5	-	1	-	-	1	2	-	-	-	-	1	2
6	-	-	-	31	6	1	-	-	-	6	6	-
7	-	-	-	6	5	1	-	-	-	2	-	-
8	-	-	-	3	2	1	1	-	-	1	-	-
9	2	1	-	26	11	1	-	3	-	10	8	-
10	1	-	-	13	2	-	-	-	-	3	3	-
11	2	-	-	1	3	-	-	-	-	-	-	-
12	43	32	**11**	28	22	8	9	10-	-	12	13	5
13	-	-	-	-	11	6	-	-	-	1	-	-
14	1	1	-	15	36	8	1	2	**1**	11	14	3
15	-	1	**2**	3	12	5	-	1	**1**	2	6	2
16	26	16	**1**	6	6	3	10	7	-	4	6	-
17	6	4	-	5	1	-	4	-	**1**	3	1	-
18	24	43	**32**	58	35	8	5	11	**1**	13	12	1
19	-	-	**1**	9	9	1	-	-	-	2	3	-
20	3	1	-	31	16	3	-	1	-	4	4	-
21	23	2	-	22	4	-	6	2	-	7	4	-
22	3	-	-	38	12	1	4	1	-	11	5	1
23	14	11	**3**	66	52	7	4	-	-	19	20	3
24	1	1	**1**	212	173	9	1	-	-	62	40	4
25	-	-	-	6	15	10	-	-	-	1	8	7
26	-	-	-	31	30	3	-	2	-	5	22	3
27	5	7	**2**	29	47	6	1	2	-	12	18	3
28	3	2	-	123	98	7	-	-	-	3	25	-
29	2	2	-	17	19	-	-	-	-	2	3	1
30	9	9	**1**	104	34	2	4	-	-	19	18	-
31	59	21	**5**	15	12	5	15	1	**2**	6	6	1
32	36	28	**2**	193	94	10	2	1	-	43	59	7
33	2	1	-	53	24	1	1	-	-	18	10	-
34	1	4	-	28	28	6	-	-	-	13	15	-
35	2	1	-	47	21	1	-	2	-	15	7	-
36	6	-	-	39	38	1	6	2	-	9	4	2
37	-	-	-	-	1	1	-	-	-	-	1	-
38	15	11	**6**	158	49	5	8	-	-	63	33	-
39	66	35	**2**	155	91	4	14	16	-	41	44	1
40	17	12	**1**	77	13	2	2	3	-	19	7	-
41	17	7	-	34	6	-	5	3	-	14	5	-
42	6	3	-	13	6	1	2	-	-	8	1	-
43	30	14	**2**	56	20	2	13	4	-	22	4	1

44	95	36	**3**	384	149	14	43	22	**1**	106	51	5
45	1	2	**-**	29	24	2	-	7	**-**	4	14	2
46	5	10	**3**	158	126	8	1	4	**-**	53	52	9
47	11	14	**2**	12	5	3	5	4	**-**	5	6	2
48	11	16	**3**	20	17	2	6	-	**1**	5	2	1
49	1	-	**2**	11	11	4	-	-	**-**	3	5	2

Severe AEs with a relationship to the study medication are rather rare compared to the total number of reported AEs. In the 2-year heroin group, 85 AEs (8.4%) fall in this category, in the group of switchers, only 8 AEs (2.7%) (see table 7.12). A more detailed description of these AEs in terms of symptoms is presented in paragraph 7.1.4.

Table 7.12
Number of the AEs according to their relationship with the study medication and the degree of severity

Degree of severity	**Relationship with study medication**	**2-year heroin**			**Methadone-heroin switchers**		
		Phase 1	**Phase 2**	**Total**	**Phase 1**	**Phase 2**	**Total**
Low	No relationship	1,784	661	2,445	474	243	717
	Relationship	469	92	561	143	34	177
Medium	No relationship	974	471	1445	437	149	586
	Relationship	288	76	364	75	37	112
Severe	No relationship	128	43	171	55	16	71
	Relationship	65	20	85	3	5	8
Not applicable	No relationship	25	5	30	5	1	6
	Relationship	4	1	5	-	-	-

7.1.4 Symptom analysis of AEs

The Swiss trials (among others) discovered that heroin injections in particular might produce convulsions (Seidenberg & Honegger 1998). The 2-year heroin group and the group of switchers differ with respect to the occurrence of convulsions. Heroin patients suffered more often from convulsions under study conditions than methadone-heroin switchers (see table 7.13). In the 2-year heroin group, a total of 73 convulsions were reported as AEs related to the study medication; 31 of them were assessed as “severe”. In the group of methadone-heroin switchers, only five convulsions of medium severity occurred in connection with the study medication. In the group of patients, who received heroin during the entire 2-year study period, the reported convulsions related to the study medication declined from 43 in the first year of treatment to 30 in the second year; in the group of patients, who received methadone in the first year and heroin in the second year, the frequency of convulsions increased. The five reported convulsions with relationship to the study medication occurred in the second year, i.e. under heroin medication.

Table 7.13
Frequency of convulsions in the heroin and methadone group according to the degree of severity and the time of treatment

		Low	Medium	Severe	Not applicable	Total
2-y heroin phase 1	No relationship	2	1	5	0	8
	Relationship	5	17	**19**	2	43
2-y heroin phase 2	No relationship	4	2	1	-	7
	Relationship	3	15	**12**	-	30
Switchers phase 1	No relationship	-	2	-	-	2
	Relationship	-	-	-	-	
Switchers phase 2	No relationship	1	1	-	-	2
	Relationship	1	5	-	-	6

Table 7.14 presents the 85 AEs of the 2-year heroin group and the 8 AEs of the methadone-heroin switchers in terms of symptoms. The medical investigators assessed these AEs as severe and with a relationship to the study medication.

Table 7.14
Frequency of severe symptoms related to the study medication according to the study group

	2-y heroin		M-H switchers	
	1st year	2nd year	1st year	2nd year
Respiratory depression/resp. insufficiency/dazed state	10	3	-	1
Allergic reaction, skin (e.g. tingling, edemas)	6	1	-	-
Circulatory disorders with skin infection	1	-	-	-
Arterial application	2	-	-	1
Abdominal pain/ obstipation/ diarrhea	5	1	-	2
Mixed intoxication/ withdrawal	5	2	-	-
Fall/ accident	4	-	-	-
Grippal infection	1	-	-	-
Hepatitic episode/ icterus	2	-	-	-
Infection of a cardiac valve	1	-	-	-
Headache	3	-	1	-
Fit of perspiration	2	-	-	-
Sleep disturbances	2	-	1	-
Development of heat	1	-	-	-
Depression/ anxiety/ psychosis/ agitation	1	1	1	1

Convulsions as well as respiratory depression, respiratory insufficiency and dazed state are not considered as unexpected due to the intravenous form of application. They most often occurred in connection with not reported co-use of benzodiazepines (respiratory depression, respiratory insufficiency and dizziness) and alcohol and/or cocaine (convulsions). As patients are 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 as a major safety risk for the study participants, as these events were not assessed as un-

expected. The Safety Board explicitly confirmed this view at a meeting on 21.10.2003 (Minutes of the Safety Board meeting on 21.10.2003).

7.2 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 laid down in a study-specific SOP. The currently valid definition of SAE for this study (in the framework of the Amendment ZIS-HA9/7 of 28.4.2003) precisely states that a *planned hospitalisation for the treatment of a chronic condition* is not a SAE.
SAEs were reported and followed-up using a specially developed form assessing the *relationship with the study medication* as "certain", "likely", "possible", "unlikely" or "none" and the *outcome of the SAE* 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, likely or certain. The Safety Board received a copy of all the reported SAEs.

7.2.1 Safety Board

The Safety Board inspects and assesses all the AEs/SAEs at regular intervals. They check the compliance with notifying obligations, verify the classification of AEs/SAEs as severe or not severe and assess the relationship with the study medication. The Safety Board meets twice a year. Each member of the Safety Board may convene a special meeting, e.g. if an SAE leads to the assumption that the safety of 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. Dieter Naber; PD Dr. Christian Haasen, safety manager; Dr. Peter Degkwitz, study coordinator

- *Principal monitor:* Dr. Andreas Kolt.

7.2.2 Description of the severe adverse events

114 SAEs were documented in the second study phase. Related to the patients treated for 2 years, heroin patients and methadone-heroin switchers, 282 SAEs were reported in the entire period (see table 7.15). In the first and second study phase, 210 SAEs of heroin patients were described: 123 in the first study phase and 87 in the second phase. The 210 cases refer to 121 of the 344 patients. For the MH switchers, 45 SAEs were documented in the first study phase and 27 in the second phase. They occurred in 37 of the 90 MH switchers.

Table 7.15
Patients with SAEs in the first and second study phase, number and percentage

	Phase 1	**Phase 2**	**Total**
2-year heroin	123 (58.6%)	87 (41.4%)	210 (100%)
Methadone-heroin switchers	45 (62.5%)	27 (37.5%)	72 (100%)
Total	**168 (59.6%)**	**114 (40.4%)**	**282 (100%)**

Table 7.16 presents the relation with the study medication. In both groups, an unlikely or no relationship was found in most cases. A causal relationship (possible, likely or certain) between the SAE and the study medication was found more often in the 2-year heroin group than in the group of switchers: 57 cases in the heroin group and 6 cases in the group of switchers. No increase of causal relationship was found if methadone patients switched to heroin-assisted treatment.
If these cases are related to the individual treatment days, a SAE related to the study medication occurred every 4,227 treatment days in the 2-year heroin group and every 10,518 days among methadone-heroin switchers, who were treated with heroin for a shorter period.

Table 7.16
SAEs and relationship with study medication, number and percentages

Relationship with study medication	**2-year heroin**			**Methadone-heroin switchers**		
	Phase 1	**Phase 2**	**Total**	**Phase 1**	**Phase 2**	**Total**
None	62 (50.4%)	47 (54.0%)	109 (51.9%)	24 (53.3%)	15 (55.6%)	39 (54.2%)
Unlikely	21 (17.1%)	23 (26.4%)	44 (21.0%)	18 (40.0%)	9 (33.3%)	27 (37.5%)
Possible	24 (19.5%)	5 (5.7%)	29 (13.8%)	2 (4.4%9	2 (7.4%)	4 (5.6%)
Likely	11 (8.9%)	4 (4.6%)	15 (7.1%)	1 (2.2%)	1 (3.7%)	2 (2.89
Certain	5 (4.1%)	8 (9.25)	13 (6.2%)	-	-	-
Total	**123 (100%)**	**87 (100%)**	**210 (100%)**	**45 (100%)**	**27 (100%)**	**72 (100%)**

The listing of actions taken with respect to the study medication shows that the occurrence of an SAE did not necessary result in a change of the study medication, neither among M-H switchers nor among 2-year heroin patients. In the heroin group, an SAE led more frequently to a reduction, temporary discontinuation or complete discontinuation of the study medication (see table 7.17). Temporary discontinuation of the study medication is most often related to

hospitalisation, where heroin maintenance cannot be continued. In two cases of the group of switchers, the study medication was raised. In only a few cases (heroin group: 5, M-H switchers: 2), it was necessary to discontinue the study medication.

Table 7.17
Measures related to the study medication, number and percentages[a)]

Measures	2-year heroin			Methadone-heroin switchers		
	Phase 1	**Phase 2**	**Total**	**Phase 1**	**Phase 2**	**Total**
No change	28 (23.0%)	24 (27.6%)	52 (24.9%)	30 (66.7%)	9 (33.3%)	39 (55.7%)
Reduced	23 (18.9%)	13 (14.9%)	36 (17.2%)	1 (2.2%)	1 (3.7%)	2 (2.9%)
Raised	-	-		1 (2.2%)	1 (3.7%)	2 (2.9%)
Temp. discontinued	52 (42.6%)	42 (48.3%)	94 (44.8%)	8 (17.8%)	12 (44.4%)	20 (28.6%)
Discontinued	4 (3.3%)	1 (1.1%)	5 (2.4%)	1 (2.2%)	1 (3.7%)	2 (2.8%)
Not applicable	15 (12.3%)	7 (8.0%)	22 (10.5%)	2 (4.7%)	3 (11.1%)	5 (2.9%)
Total	**122 (100%)**	**87 (100%)**	**209 (100%)**	**43 (100%)**	**27 (100%)**	**70 (100%)**

a) For 3 of the 282 SAEs (one heroin group and two switchers) no data on measures taken related to the study medication are available.

As to the outcome or the consequences of the SAEs, table 8.16 shows that the condition prior to the SAE could be restored in both treatment groups in most cases (see table 7.18). In a smaller proportion, the initial condition could be restored “with consequences”. Overall, four patients died. The circumstances leading to their death are explained in detail in paragraph 7.2.4.

Table 7.18
Outcome of severe adverse events, number and percentages[a)]

Outcome/ consequences	2-year heroin			Methadone-heroin switchers		
	Phase 1	**Phase 2**	**Total**	**Phase 1**	**Phase 2**	**Total**
Restored	101 (82.1%)	58 (66.7%)	159 (75.7%)	28 (62.2%)	13 (48.1%)	41 (56.9%)
Restored with consequences	18 (14.6%)	24 (27.6%)	42 (20.0%)	13 (28.9%)	12 (44.4%)	25 (34.7%)
Ongoing	2 (1.6%)	1 (1.1%)	3 (1.4%)	2 (4.4%)	1 (3.7%)	3 (4.2%)
Died	-	3 (3.4%)	3 (1.4%)	-	1 (3.7%)	1 (1.4%)
Not known	2 (1.6%)	1 (1.1%)	3 (1.4%)	1 (2.2%)	-	1 (1.4)
Total	**123 (100%)**	**87 (100%)**	**210 (100%)**	**44 (100%)**	**27 (100%)**	**71 (100%)**

a) No data exist on outcome/consequences for one SUE of the methadone-heroin switcher group.

7.2.3 Severe adverse events classified according to ICD-10

Analogous to the AEs, the SAEs were coded according to the ICD-10. The ICD diagnoses were again combined according to the diagnosis categories described in paragraph 7.1.3 and the frequency of their occurrence (see tables 7.19 and 7.20).

Table 7.19
Frequency of SAEs in the in the higher-ranking ICD-10 categories for n=282 (cf. paragraph 7.1.3, table 7.8)

Category	2-year heroin		M-H switchers		Total	
	Number	%	Number	%	Number	%
2	8	3.8	1	1.4	9	3.2
4	2	1.0	-	-	2	0.7
5	2	1.0	3	4.2	5	1.8
7	2	1.0	-	-	2	0.7
8	4	1.9	1	1.4	5	1.8
9	1	0.5	-	-	1	0.4
10	2	1.0	1	1.4	3	1.1
11	-	-	1	1.4	1	0.4
12	38	18.1	9	12.5	47	16.7
13	3	1.4	2	2.8	5	1.8
14	12	5.7	3	4.2	15	5.3
15	5	2.4	1	1.4	6	2.1
18	14	6.7	2	2.8	16	5.7
19	2	1.0	-	-	2	0.7
20	2	1.0	-	-	2	0.7
22	-	-	1	1.4	1	0.4
23	14	6.7	3	4.2	17	6.0
24	3	1.4	-	-	3	1.1
25	15	7.1	10	13.9	25	8.9
26	2	1.0	1	1.4	3	1.1
27	4	1.9	7	9.7	11	3.9
29	4	1.9	2	2.8	6	2.1
31	6	-	5	6.9	11	3.9
32	16	7.6	4	5.6	20	7.1
33	5	2.4	-	-	5	1.8
34	2	1.0	-	-	2	0.7
35	-	-	3	4.2	3	1.1
36	3	1.4	1	1.4	4	1.4
37	1	0.5	-	-	1	0.4
38	6	2.9	1	1.4	7	2.5
39	2	1.0	1	1.4	3	1.1
43	1	0.5	1	1.4	2	0.7
44	7	3.3	1	1.4	8	2.8
45	2	1.0	-	-	2	0.7
46	14	6.7	4	5.6	18	6.4
47	1	0.5	-	-	1	0.4
48	3	1.4	1	1.4	4	1.4
49	2	1.0	2	2.8	4	1.4
Total	**210**	**100.0**	**72**	**100.0**	**282**	**100.0**

Table 7.20
Frequency of SAEs in the higher-ranking ICD-10 categories in terms of relationship[a)] with the study medication for n=282

Category	2-year heroin		M-H switchers		Total	
	No relationship	With relationship	No relationship	With relationship	No relationship	With relationship
2	**8**		**1**		**9**	
4	**1**	**1**			**1**	**1**
5	**2**		**3**		**5**	
7	**2**				**2**	
8	**4**		**1**		**5**	
9	**1**				**1**	
10	**2**		**1**		**3**	
11			**1**			
12	**10**	**28**	**7**	**2**	**17**	**30**
13	**3**		**2**			
14	**11**	**1**	**2**	**1**	**13**	**2**
15	**5**		**1**		**6**	
18	**3**	**11**	**2**		**5**	**11**
19	**2**				**2**	
20	**2**				**2**	
22			**1**			
23	**11**	**3**	**2**	**1**	**13**	**4**
24	**3**				**3**	
25	**15**		**9**	**1**	**26**	**1**
26	**2**		**1**		**3**	
27	**3**	**1**	**7**		**10**	**1**
29	**4**		**2**		**6**	
31	**5**	**1**	**5**		**10**	**1**
32	**14**	**2**	**4**		**18**	**2**
33	**5**				**5**	
34	**1**	**1**			**1**	**1**
35			**3**		**3**	
36	**3**		**1**		**4**	
37	**1**				**1**	
38	**1**	**5**	**1**		**2**	**5**
39	**1**	**1**	**1**		**2**	**1**
43	**1**			**1**	**1**	**1**
44	**7**		**1**		**8**	
45	**2**					
46	**12**	**2**	**4**		**16**	**2**
47	**1**				**1**	
48	**3**		**1**		**4**	
49	**2**		**2**		**2**	
Total	**153**	**57**	**66**	**6**	**219**	**63**

a) "No relationship" describes the assessment categories: no or unlikely relationship. "With relationship" describes the assessment categories: possible, likely or certain relationship.

Table 7.20 shows that, in the 2-year heroin group, the most frequent event with a relationship to the study medication is related to the basic illness opioid dependency ("F1 diagnosis") (in 28 of 57 cases, corresponding to 49%). Only two cases (6%) occurred in the group of switchers. In these cases, the descriptions and diagnoses on the SAE report sheet most often state "respiratory depression after intravenous heroin application with unclear co-use".
Co-use is also involved in cerebral convulsions, the second most frequent events with a relationship to the study medication. 11 cases were described in the 2-year heroin group (19%). Two convulsions occurred in the M-H switchers, however not related to the study medication. In all the cases, the initial condition was restored after the SAE.

7.2.4 Deaths

Deviant from the previous procedure, where only patients were considered, who completed the first as well as the second study phase, this paragraph considers all the deaths of both study phases.
12 deaths were described in the first study phase (5 of the heroin group, 7 of the methadone group (see table 7.21). 4 deaths (3 of the 2-year heroin group, 1 of the group of methadone-heroin switchers) occurred in the second study phase.

Table 7.21
Deaths occurring in the first and second study phase according to gender

Study medication		**Women**	**Men**	**Total**
Heroin	Phase 1	1	4	5
Heroin	Phase 2		3	3
Methadone	Phase 1	1	6	7
Heroin	Phase 2		1	1
Total		**2**	**14**	**16**

Seven of the 12 deaths of the first study phase (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. In the second study phase, 3 of the 4 deaths occurred during treatment.
A causal relationship with the study medication was excluded in 9 cases and considered unlikely in 7 cases. The causes of death are presented in table 7.22.
Five autopsies were performed, in four cases the results did not go beyond the presumption diagnosis. In the case of the 44-year old woman with the randomisation no. 40046, four expert opinions were procured. All the death reports, including postmortem reports and expert opinions, were reported to the BfArM.

Table 7.22
Causes of death during the first and second study phase

Cause of death	**In treatment**	**Not in treatment**	**Total**
Mixed intoxication	1	2	3
Accident	1	-	1
Complications of basic disease	1	2	3
Suicide	3	-	3
Not known	2	4	6
Total	**8**	**8**	**16**

Table 7.23 presents a short overview of all the deaths of the first and second study phase. A detailed description of the deaths occurring in the first study year is included in the report of the first study phase (Naber & Haasen 2006). Below is a description of the deaths occurring in the second study phase.

Table 7.23
Overview of deaths occurring in the first and second study phase

Rd nr.	Study group	Gender/ age	Date of occurrence	Treatment initiated	Time of death	Cause of death
1st study phase						
10061	Heroin	Male/46	23.04.2003	Yes	After dropout	Sepsis
10129	Methadone	Male/34	09.06.2003 (found dead)	No	-	Not known
10133	Methadone	Male/36	05.02.2004 (found dead)	Yes	During treatment (245 days)	Not known
30025	Methadone	Male/45	03.10.2003	Yes	After dropout (194 days)	Not known
30067	Heroin	Male/41	14.12.2002	Yes	During treatment (77 days)	Myocarditis, pneumonia
30087	Methadone	Male/35	06.07.2003	No	-	Not known
40046	Heroin	Female/44	15.08.2003	Yes	During treatment	Fall on rails
40076	Methadone	Male/35	23.08.2004 (found dead)	No	-	Not known
50065	Heroin	Male/31	13.11.2003 (found dead)	Yes	After dropout (226 days)	Not known, presumed intox.
50077	Methadone	Male/38	21.10.2003	Yes	During treatment (344 days)	Pericardial tamponade
60099	Heroin	Male/38	30.03.2003 (found dead)	Yes	During treatment (2 days)	intoxication
80057	Methadone	Female/40	No	No	-	Presumed intox.
2nd study phase						
1010	2-year heroin	Male/37	17.07.2004	Yes	During treatment (660 days)	Suicide
1117	M-H switcher	Male/36	26.11.2004 (found dead)	Yes	During treatment (424 days)	Suicide
3026	2-year heroin	Male/45	31.01.20005	Yes	During treatment (457 days)	Suicide
4078	2-year heroin	Male/43	13.07.2005	Yes	After dropout (734 days)	AIDS

7.2.4.1 Individual description of the cases of death in the second study phase

Random no.:	**1010**
Gender:	Male
Initiation of treatment/	
Change to second study phase:	23.09.2002 / 24.09.2003
Daily dose:	240 mg diaphine
Date of event:	17.07.2004
Study medication immediately before event:	240 mg diaphine
Symptoms, course, final condition:	Found hanged on a bridge
Presumption diagnosis:	Suicide

Emergency measures:	Not applicable
Causal relationship with study medication:	Unlikely
Relevant examination results:	None
Simultaneously administered medication:	Amitryptilin when required
Comments:	Patient was in psychiatric treatment

Random no.:	**1117**
Gender:	Male
Initiation of treatment/	
Change to second study phase:	09.10.2003 / 15.10.2004
Daily dose:	120 mg d,l methadone
Date of event:	26.11.2004 (found dead)
Study medication immediately before event:	120 mg d,l methadone
Symptoms, course, final condition:	Found dead in appartment
Presumption diagnosis:	Suicide
Emergency measures:	Not applicable
Causal relationship with study medication:	Unlikely
Relevant examination results:	None
Simultaneously administered medication:	Rivotril 1 mg/d, doxepin 100 mg/dl
Comments:	Patient switched from control group to heroin group on 15.10.2003 and received last 2x220 mg DAM + 2 ml d,l methadone take-home on 27.10.2004

Random no.:	**3026**
Gender:	Male
Initiation of treatment/	
Change to second study phase:	31.10.2002 / 02.11.2003
Daily dose:	400 mg diaphine, 6 ml d,l methadone take-home
Date of event:	01.02.2004
Study medication immediately before event:	200 mg diaphine (31.01.2004)
Symptoms, course, final condition:	Jumped from high-rise building
Presumption diagnosis:	Suicide
Emergency measures:	Not applicable
Causal relationship with study medication:	Unlikely
Relevant examination results:	None
Simultaneously administered medication:	

Comments:

Random no.:	**4078**
Gender:	Male
Initiation of treatment/	
Change to second study phase:	11.11.2003 / 12.11.2004
Daily dose:	240 mg diaphine (from 26.9.05: 40 mg d,l methadone)
Date of event:	30.11.2005
Study medication immediately before event:	40 mg d,l methadone
Symptoms, course, final condition:	HIV disease
Presumption diagnosis:	Death related to AIDS disease
Emergency measures:	Not applicable
Causal relationship with study medication:	None
Relevant examination results:	None
Simultaneously administered medication:	
Comments:	Patient died in nursing home for HIV patients

8. Conclusions

The clinical study report of the first phase of the German model project for heroin-assisted treatment of opioid dependent patients found a statistically significant superiority of heroin treatment over methadone treatment (Naber & Haasen 2006); the course of long-term effects of heroin treatment was explored in the second study phase. Overall, there is a stabilisation and further improvement of the effects achieved in the first year of treatment. The group of methadone-heroin switchers in particular benefited from heroin-assisted treatment initiated in the second year.

434 patients initiated the second study phase; 344 continued heroin treatment (79.3%) and 90 patients switched from methadone treatment (20.7%). According to the study design of the second phase, the 434 patients were distributed to four groups of approximately equal size according to target group stratum and type of psychosocial treatment. Four fifths of the patients regularly concluded the study treatment of the second phase (and most of them changed to the follow-up phase). As expected, the retention rate is thus higher in the second year of treatment. Related to the 2-year study period – and considering all the 515 patients randomised to heroin treatment – 55% were still in heroin treatment after 24 months. The retention rate is therefore similar to that of the Swiss study after two years (Rehm et al. 2001).[54] This is remarkable, considering that the Swiss project was a naturalistic cohort study (and not a clinical randomised "experiment"),[55] whose recruitment procedure could be better adapted to the natural conditions of admission. Apparently, the participants of the German study became accustomed to the (high-threshold) study and treatment conditions, not least because of the positive effects. More than half of the patients, who discontinued heroin treatment, changed to a different addiction treatment, most often maintenance treatment with methadone or buprenorphine. 10% embarked on abstinence treatment. It is conspicuous that after two years, a difference emerges between the target groups "methadone treatment failures" and "not reached". Among patients previously treated with methadone, the retention rate is 10% higher after 24 months. Moreover, more MTF dropouts took up subsequent treatment than patients, who had not been in treatment prior to the study treatment. This can be interpreted to the effect that previous experience of methadone maintenance makes it easier for patients to comply with the conditions of study treatment (or subsequent treatment). But it also points out that the group of "not reached" are a particular challenge for the treatment services and that it is necessary to think about adequate (low-threshold) treatment offers.

The results of the second study phase are evidence of the importance of long-term heroin maintenance, which enables patients to slowly initiate positive processes of change after many years of opioid dependency. If the primary outcome criteria of the first study phase (health improvement and decline of illicit drug use) are taken as outcome parameters, the level continues to be high after 24 months. Determined by the methods used, slightly lower

[54] Related to study patients, who actually initiated heroin treatment, the proportion is 56%, rather comparable to the Swiss results. 24-month data of the Dutch project are not available. Because of the 2-month discontinuation experiment after one year, they could not be directly compared with the German and Swiss results.

[55] Which should not be misunderstood as methodological criticism of the Swiss study.

response rates can be mainly put down to lower rates of patients reached again and the coding of study dropouts as non-responders. The influence of heroin as an adequate maintenance substance is particularly apparent in the success of 90 patients, who changed from the control group treated with methadone to heroin treatment after one year. Contrary to the 12-month results, no significant differences are found between the 2-year heroin patients and the methadone-heroin switchers after 24 months. Therefore, the switchers succeed in catching up with the 2-year heroin patients in the second year of treatment under heroin maintenance. This special analysis of the "switcher group" thus provides a scientific-methodological independent contribution to confirm the superiority of heroin over methadone treatment. But the 2-year heroin patients also continue to benefit from the treatment: Statistically significant improvements of the physical and mental health are still found in the second year. The same applies to the decline of cocaine use. The ongoing heroin treatment leads to a significant reduction between month 12 and month 24. The average street heroin use does not change in the second study phase; the markedly low level already reached in the first year, is maintained in the second year. The most impressive change occurs in risk behaviour directly related to illicit drug use, i.e. the sharing of syringes or injection equipment. This high-risk behaviour is completely dropped in both groups after two years, in the group of switchers again with some delay. Therefore, heroin treatment proves to be extremely effective in (re-)infection prevention, which is important for the specific medical treatment of viral infections.

The second study phase focuses on the effects of the 2-year heroin treatment. 67% of the study participants, who had originally been randomised to the heroin branch, continued this treatment immediately subsequent to the first phase. The average daily dose of heroin for the entire 2-year period of both study phases is 452 mg. The mean daily dose of methadone additionally prescribed to heroin patients is 40 mg; related to all days of heroin application, it results in an "actual" daily average dose of 7.0 mg of methadone. While the overall heroin dose continuously declines over 24 months, the average daily dose of methadone slightly increases in the course of treatment. Apparently, a stealthy change or approximation to the structure of methadone treatment occurs, though heroin continues to be the primary maintenance substance. The individually adapted patterns of dosage contribute to withdrawal symptoms being reduced in the course of treatment and stabilising at a low, subjectively hardly impairing level. At the same time, the adverse (side) effects directly related to the heroin application, continuously decline in the course of treatment, probably due to increasing habituation to the heroin effects.

As a rule, the health of heroin patients rapidly improved within the first months of treatment. In the second year, slight improvements are still found in almost all areas such as physical symptoms, nutritional state, mental state, psychosocial level of functioning and symptoms of depressiveness and anxiety. But the high degree of mental disorders is still a matter of concern and requires particular attention during maintenance treatment. Health improvements that occurred in the heroin and methadone group at the beginning of the first study phase and even during the indication examinations in the course of the recruiting process suggest that these effects are not induced by the maintenance substance but by sufficient medical care in the

framework of (and prior to) the study treatment.[56] It was only in the later course that differentiated effects occurred displaying the superiority of heroin over methadone treatment. They hint already to the long-term success of heroin treatment, which was confirmed in the further course of the second year of treatment and points out the necessity of offering to the patient heroin-assisted treatment over a longer period. Short, temporary heroin treatment might produce (at least temporary) an effect of health recovery, but the strengths of this type of treatment are mainly long-term effects.

The latter is particularly true for changes regarding the patients' social situation. Their life situation is often characterised by marginalisation and criminalisation, and social and professional improvements need a lot of time. It is the more impressing that the housing situation of the heroin patients significantly stabilised during the first as well as the second study phase. Social contacts slightly increase, also to friends and acquaintances outside the drug context. Leisure occupations also develop positively. Nonetheless, some heroin patients still have a problem with loneliness. Two thirds have no steady partnership, at least one tenth have no reliable friends after 2 years, and one third of the friends of the other patients are still drug users. Even if these friends are probably mainly other patients of the drug unit, it shows the tedious process of social integration outside the drug and scene context familiar for many years.

The job situation developed more positively than expected. Against the background of the overall difficult situation on the employment market and considerable health impairments, 11% increase of regularly working patients reaching 27% after two years of heroin treatment are indeed a success. Heroin treatment has a positive effect in terms of health improvement and the related increase of medically attested ability to work. Among patients able to work, the proportion of wage earners even increases from 25% to 43%. Although it became common practice to apply modest success standards to the professional integration of opioid-dependent patients in maintenance treatment, and even more to the "most severely dependent patients", the results of heroin-assisted treatment show that challenging goals can be attained. The concomitant psychosocial treatment probably plays a central role in the industrial rehabilitation of opioid addicts.

The development of delinquent behaviour is analysed in detail in the context of the criminological collateral study (Löbmann 2006; Köllisch & Kreuzer 2006). If the corresponding ASI-Composite-Score is taken as global measure of change, a marked decline of criminal behaviour is found in the first year of treatment and a slight improvement or stabilisation in the second study phase. Without anticipating the results of the collateral studies, clearly positive effects of heroin treatment are found in the field of legal probation. They are probably mostly due to the decline of illicit drug use and the separation from the drug context. But the decline of delinquency is probably also influenced by the settlement of the income situation (in particular the utilisation of public funds) and by jobs in part of the patients. According to the existing results, the decline of criminal activities is the area with the greatest economic benefit due to heroin-assisted treatment (Uchtenhagen et al. 2000; Dijkgraaf et al. 2005).

[56] Of course, the well-proved effect of methadone maintenance on health improvement has to be considered (e.g. Ball & Ross 1991; Gossop et al. 2001; Verthein et al. 1998; Ward et al. 1998).

The central objective – apart from health improvement – of heroin-assisted treatment, the reduction of illicit drug use, is reached to a considerable extent: Although the decline of street heroin, cocaine and crack use and intravenous use is highest at the beginning of the first year of treatment, further success is achieved in the second year of treatment. The 30-day prevalence rates of cocaine, crack and i.v. use further decline in the second study phase. Moreover, urinalyses attest a (continuous) decline of cannabis and benzodiazepine use. The intensity of use, i.e. the average number of days of use in the last month, stabilises at a low level compared to baseline. The decline of prevalence indicates that, even after 2 years, a group of heroin patients uses hard drugs more or less regularly. If the criterion is drug use at least once a week, one fifth of the patients continue using street heroin and/or cocaine with a certain regularity. A greater part of them are treatment dropouts, and their health condition is worse. These problematic patients are in particularly great need of treatment and support and should receive particular consideration in the context of heroin-assisted treatment to prevent them from dropping out.
Utilisation of psychosocial treatment is very high for both types (psychoeducation with drug counselling and case management with motivational interviewing) during the second study phase. This was expected, as the study group was composed only by regular concluders of the first study phase. Patients' acceptance and satisfaction with PST is also good; the method of case management scores higher than the combination of group and individual counselling. According to the results of the first study phase, the type of psychosocial concomitant treatment had no (statistically detectable) influence on the treatment effect; the situation is different after 24 months. Treatment success is significantly higher in patients treated with drug counselling and psychoeducative groups, which is not in accordance with the higher acceptance and treatment satisfaction of case management. A possible influencing factor might be the higher retention rate in patients treated with psychoeducation and drug counselling. The difference of success is independent of centre effects and raises questions regarding the optimisation of the psychosocial treatment offer. It is possible that longer treatment duration positively influences the group effect allowing a better deployment of general therapeutic active principles such as problem coping, motivational clarification and resource activation (following Grawe et al. 1993; Grawe 1998). In combination with individual counselling, an optimised treatment process adapted to the individual patient should evolve and contribute to the treatment results.

The safety of medication related to the second phase was again evaluated on the basis of (severe) adverse events. Considering the adverse events for the entire 2-year study period, the decline of AEs in the second year is remarkable. In the group of patients, who received heroin continuously for 2 years as well as in the group of methadone-heroin switchers, two thirds of all the reported AEs occurred in the first year. The reasons are presumably, on the one hand, the greatly improved health of patients, on the other hand developments on the part of doctors and treating staff. They might have become more confident in their contact with patients and the dispensing of the medication, in particular heroin.
Switching from methadone to heroin does not involve new complications for the patient. Heroin-typical AEs such as convulsions, respiratory depression, application problems etc. are

reported only to a very low degree by methadone-heroin switchers in the second study year; these complications still occur more frequently in the 2-year heroin group. The reason is probably patients' stabilisation in the first year, mainly regarding decreased co-use, but also selection effects: In the original methadone control group, regular concluders of the first phase were rather patients with high compliance and (assumedly) fewer treatment complications. After the (desired) switching to heroin, these patients reach greater effects in the second study phase compared to the two-year heroin patients, and the probability of adverse events tends to be reduced due to heath improvement and decrease of illicit drug use.

Severe adverse events also markedly decrease in the course of treatment across the two study phases. In the second year of treatment, the number of SAEs was lower both in the 2-year heroin group and in the group of switchers. This is also most probably due to health improvement and the marked decrease of illicit drug use. Of course, habituation effects in patients and professionals and selection effects also play a part, as patients prone to complications are more likely to have dropped out earlier.

Concerning the safety of the study medication, mainly those SAEs have to be considered, where a relationship with the study medication is likely, possible or certain. These SAEs with a causal relationship also markedly decreased in both study groups in the second study year. It has to be emphasised that switching the maintenance substance did not increase the number of SAEs.

In the first study year, the majority of SAEs related to the study medication were cerebral convulsions and respiratory depressions (Naber & Haasen 2006). As such complications are probably frequent outside of the treatment setting after using street heroin, the documentation of these SAEs can be considered as a reflection of the degree of peril that heroin users are exposed to as a rule. In the second study phase, diagnoses related to causal adverse events change. In addition to cerebral convulsions and respiratory depressions, affections of the cardio-vascular system and the digestive system increased. In the switcher group, three SAEs with certain relationship to the study medication occurred after switching from methadone to heroin. But no convulsion or respiratory depression occurred in these cases.

The mortality rate in the second study phase is again 1%, which corresponds to the result of the first study phase and is in general comparable to the mortality rate of opioid dependent patients in maintenance treatment (Rehm et al. 2005). Also in the second study phase, no death had a causal relationship with the study medication. However, the frequency of suicides is conspicuous. It is necessary to evaluate in the further course of the study whether this accumulation is accidental or whether it is a latent suicidality of long-term opioid addicts, which possibly becomes apparent only in the course of long-term maintenance treatment.

The methodological approach of the second phase was different from the first phase, as it was restricted to the evaluation of the course of heroin treatment. The analyses were mainly longitudinal and less concerned with group comparisons. As the design required that only regular concluders of the first phase were admitted to the second phase, the phase-2 sample represents a certain selection of the initially randomised patients. However, patient characteristics at baseline hardly differed from the patients, who did not initiate the second year of treatment – apart from a somewhat more stable housing and working situation. This indicates that the

sample of the second study phase is really representative of all the heroin addicts ever randomised. After 12 months, i.e. at the initiation of the second study phase, the response rate among the 2-year heroin patients was slightly higher, which correlates with the regular conclusion of the first year of treatment.
The overall follow-up rates were high also for the surveys of the second phase (at T_{18} and T_{24}) indicating a valid data base. Due to the low degree of characteristics differences and comparable results in the primary analysis of the first study phase, the target group strata "methadone treatment failures" (MTF) and "not reached" (NR) were again analysed jointly. The long-term lower retention rate among the "not reached" indicates that this problematic user group should receive particular attention in the future.
As a rule, the course of certain characteristics was described across all patients or groups and analysed descriptively. Significance tests were performed every year (between T_{12} and T_{24}) for characteristics less sensitive to change (social situation), and every six months (between T_{12} and T_{18} and between T_{18} and T_{24}) for health and use related data. It is possible that the latter criteria show statistical significance in the yearly intervals but not in the 6-month intervals. But here, too, changes in the course are interpreted descriptively.
In terms of effect power, heroin-assisted treatment is assessed to be a highly efficient treatment of opioid addiction (which will be analysed in more detail in the collateral study on treatment services). In the long run, only small additional steps towards the improvement of heroin patients' overall situation can be expected. The target is long-term stabilisation to enable patients step by step to successfully conclude the heroin-assisted treatment.

The results of the second study phase confirm and substantiate the findings of the comparative study of the first phase in an impressive way. Heroin-assisted treatment proves to be a very successful treatment of severely dependent heroin users with long-term effects. If this treatment were introduced into the catalogue of accepted treatment options, an even higher acceptance is expected, due to the absence of study related "selection mechanisms" and less elaborate examinations. The inclusion criteria and quality standards of heroin treatment proved to be effective and should be maintained in regular treatment, unless modifications are suggested by more recent findings.
Meanwhile, various studies provided scientific evidence of the positive effects of heroin-assisted treatment, and, therefore, health policy steps should prepare without delay the legal conditions required for the implementation. Deferments create an unclear situation for all those concerned – in particular patients and the staff of the treatment units –, which hampers ethically responsible treatment activities and caring support. In accordance with the evaluations and demands of numerous national and international experts and the representatives of physicians, treatment institutions and associations of addiction services, the evaluation of the positive results of both study phases of the German model project results in the formal recommendation to incorporate this treatment type in the catalogue of accepted types of treatment for heroin addicted patients.

9. Literature

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