

**PART IIIA**

**STUDY FINDINGS  
INJECTABLE HEROIN TRIAL**

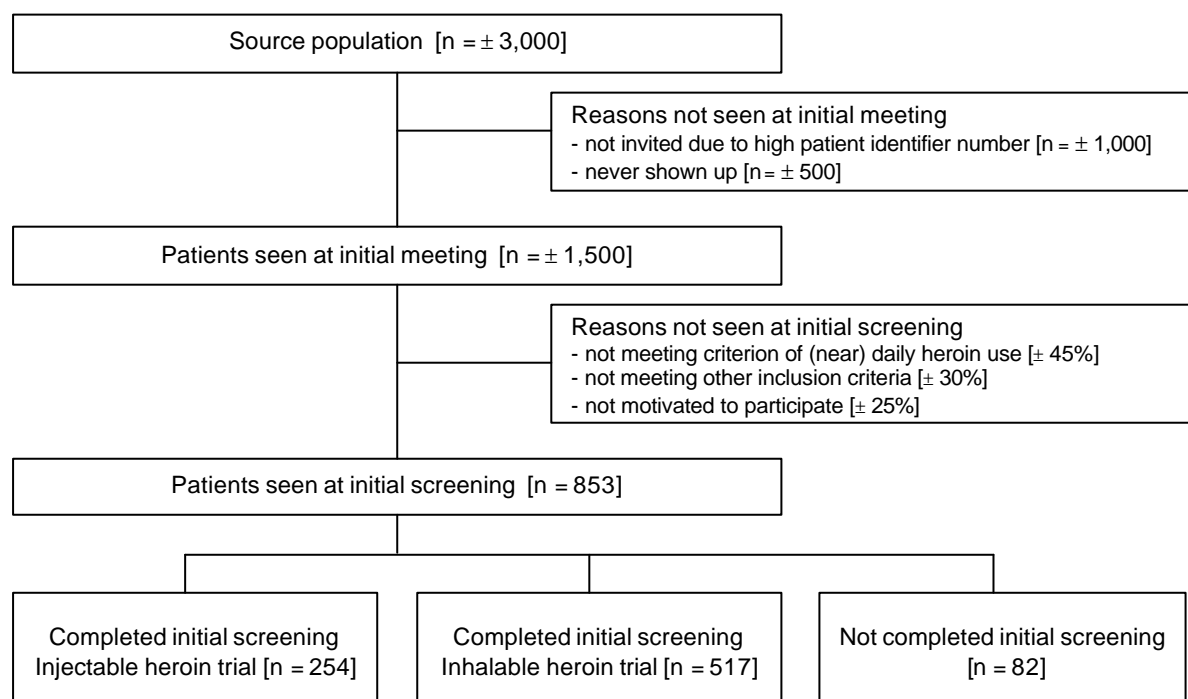


## Chapter 5<sup>A</sup>

### Selection and disposition of patients

As has been described in chapter 2, patients were recruited through an extensive selection procedure. The results of this selection process are described in this chapter. The first two steps of the selection process, the preselection of a source population on the basis of the treatment registration system, followed by the *initial meeting* with the physician, did not distinguish between heroin addicts that injected or inhaled heroin. During the *initial screening*, the third step of the recruitment process, the physician of the local treatment site decided whether the patient would participate in the trial on injectable heroin or the trial on inhalable heroin. Therefore, it was only from the initial screening that a distinction could be made between candidates for the trial on injectable heroin and the trial on inhalable heroin. Finally, since the first two steps of the selection process could not be fully documented, the results of these steps can only be presented by approximation. Figure 6 summarizes these first two steps of the selection process.

Figure 6. Flow diagram of first two steps of selection process



#### 5<sup>A</sup>.1 Selection procedure

##### *Step 1. Registration system*

In the first step of the selection procedure, the available information from the local methadone maintenance treatment registration data bases was analyzed in order to define the source population, which served as the basis for subsequent steps of the recruitment process. The source population amounted to approximately 3,000 methadone patients. These potential candidates were at least 25 years old and were registered in the city area of the local treatment site for at least three years. In addition, they were heroin dependent for at least five years, had been prescribed an

effective methadone dose for at least four consecutive weeks in the past five years and had had regular contact with the methadone maintenance program in the preceding six months. All potential candidates in the source population received a randomly assigned patient identifier number from the independent monitoring organization.

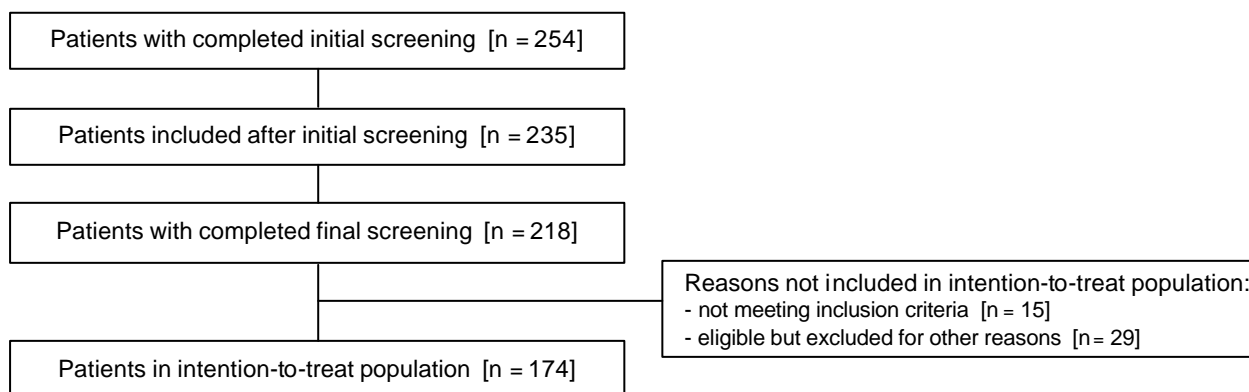
**Step 2. Initial meeting**

In each local treatment site, potential candidates were invited by the local study co-ordinator in the order of the patient identifier number for an initial meeting with the physician. Given the closing date of the randomization and the low prevalence of injecting in the remaining source population, approximately 1,000 potential candidates with a high patient identifier number were not invited anymore for the initial meeting of the selection procedure. Approximately 2,000 methadone clients from the source population were invited for this initial meeting. Around 500 of the invited candidates were never seen at the initial meeting. The major reasons for not attending the initial meeting were that potential candidates did not use heroin on a (near) daily basis, had left the methadone (maintenance) program, were incarcerated or hospitalized, had left the city or region, or had died. Almost half of all the methadone clients seen in the initial meeting ( $\pm 1,500$  of the  $\pm 2,000$  candidates invited), did not meet the inclusion criteria or were barred by one of the exclusion criteria. Of the candidates that were excluded at this phase of the selection process, 45% did not meet the criterion of (near) daily heroin use. After this first initial meeting, 853 candidates were eligible for the next step in the selection procedure, the initial screening by the local research team and the physician.

**Step 3. Initial screening**

All 853 candidates that passed the screening at the initial meeting were assessed by the local research team. Eighty-two potential candidates did not meet one or more of the inclusion criteria of poor functioning in the area of physical health, mental health or social functioning that were assessed in the interview by the research team or decided themselves not to continue the selection process and were not screened by the local physician. From the remaining 771 candidates, 254 were eligible for the trial on injectable heroin and 517 for the trial on inhalable heroin. In the remaining of this chapter the focus will be on the 254 candidates that were eligible for further screening in the injectable heroin trial (see Figure 7).

Figure 7. Flow diagram of selection process of patients in the trial on injectable heroin



Of the 254 candidates for whom the initial screening was completed, the majority met the criteria for inclusion and was not barred by any of the exclusion criteria (92.5%). The most common reason for not including candidates at this step of the selection procedure was that candidates did not meet at least one of the inclusion thresholds indicative of poor functioning in the area of

physical health, mental health or social functioning. Thus, 235 patients passed the initial screening and entered the qualification phase at the end of which they were invited for the second and final screening.

#### *Step 4. Final screening*

Four to eight weeks after the initial screening candidates were invited for their final screening. Sixteen potential patients did not show up for their final screening and one did not complete the final screening. Of the 218 candidates with a completed final screening the vast majority was eligible for randomization in the trial (93.1%). The major reason for not being included, was again related to not meeting the thresholds of poor functioning.

Two-hundred-and-three candidates were eligible for the trial investigating the effectiveness of injectable heroin. However, 29 eligible candidates were excluded from the intention-to-treat population. Most of these patients (23) were included in the treatment condition C of the injectable heroin trial in which patients received methadone alone during the first six months, followed by co-prescribed heroin and methadone during the second six months of the experimental phase. As has been described in chapter 4, this treatment condition was omitted from the trial due to the declining prevalence of injecting heroin use in the Netherlands. Five patients were not randomized into the study because they were partner of candidates that were randomized into the trial already. Instead, they were offered to participate in the same type of treatment condition as their randomized partner (see also chapter 4). Finally, one patient had been randomized, but was never informed about the result of the randomization, because he was expelled from the country. Thus, the intention-to-treat population for the injectable heroin trial consisted of 174 injecting heroin dependent patients meeting all criteria for inclusion in the trial.

#### *Step 5. Randomization and ITT-sample*

In Table 6, an overview is given of the randomization of all 174 patients in the intention-to-treat population, divided by treatment site. Ninety-eight injecting heroin addicts were randomized in the control group (A), receiving an offer of 12 months treatment with oral methadone alone, and 76 heroin addicts were randomized in the experimental group (B) receiving an offer of 12 months treatment with injectable heroin plus oral methadone.

Table 6. Intention-to-treat population and number of randomized patients per site (injectable heroin)

<i>Group</i>	<i>Amsterdam *</i>		<i>Rotterdam *</i>		<i>The Hague</i>	<i>Groningen</i>	<i>Heerlen</i>	<i>Utrecht</i>	<i>Total</i>
	<i>I</i>	<i>II</i>	<i>I</i>	<i>II</i>					
A	18	11	18	11	7	12	12	9	98
B	11	8	15	8	6	11	9	8	76
Total	29	19	33	19	13	23	21	17	174

\* In Amsterdam and Rotterdam two groups of patients were recruited and included in the trial. Given that the study was conducted in two stages (see paragraph 2.4), these two groups could be treated in the already existing treatment sites.

## 5<sup>A</sup>.2 Treatment participation and treatment completion

In this paragraph the treatment participation of patients will be described. Patients were defined as 'treatment completer' if they were still participating in the intended treatment condition in month 12 of the study as evidenced by the drug accountability data. Thus, patients in the control group A

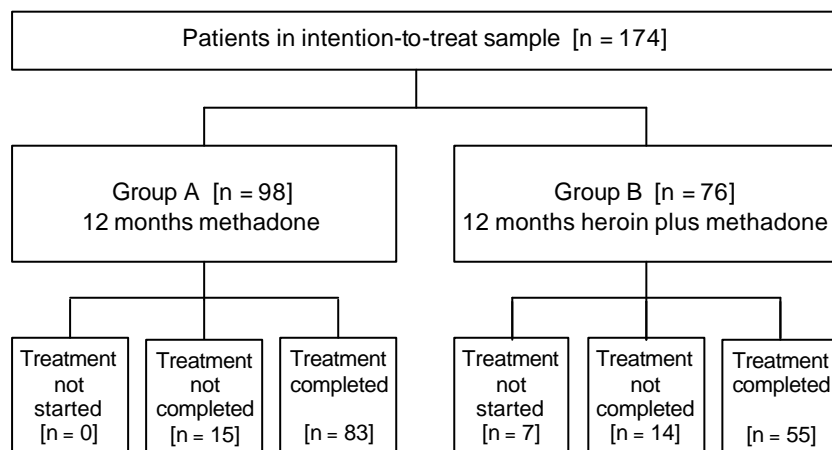
were considered to be treatment completers if they still received oral methadone in month 12. Similarly, patients in the experimental group B were considered to be treatment completers if they still received medically co-prescribed heroin in month 12.

As is shown in Figure 8 all patients in the methadone group started their methadone treatment offer. This is because these patients were already taking part in a methadone maintenance treatment program at the time of randomization. In the 12th month after baseline, 15 patients were no longer receiving methadone maintenance treatment, i.e., 15.3% of the patients in the control condition had 'dropped out' the treatment regimen offered at the beginning of the trial. The remaining 84.7% of the control patients had completed treatment.

It can be seen from Figure 8 that seven patients (9.2%) never started the co-prescribed heroin treatment. In the 12th month after baseline, 14 more patients (18.4%) were no longer treated with co-prescribed heroin. For the majority of patients the termination of the heroin treatment was non-voluntary. They were expelled from the program (five patients), had become incarcerated (one patient), had died (one patient) or were forced to stop the treatment for medical reasons (one patient) or because of problems with a residence permit (one patient). The other five patients ended the treatment with co-prescribed heroin voluntary for various personal reasons. The remaining 55 patients in group B were still treated with co-prescribed heroin at the end of the study and hence were considered as 'treatment completers' (72.4%).

The difference in treatment completion between the 12 months methadone condition (84.7%) and the 12 months co-prescribed heroin condition (72.4%) is not statistically significant (Odds-Ratio=0.48; 95% -CI: 0.22-1.02; p=0.0575).

Figure 8. Disposition of randomized patients



Treatment completing patients in the control condition had been prescribed methadone on 336 days (median) during the experimental treatment year. The mean dosage of methadone prescribed to treatment completers in the control group was 71 mg (sd=23.6 mg).

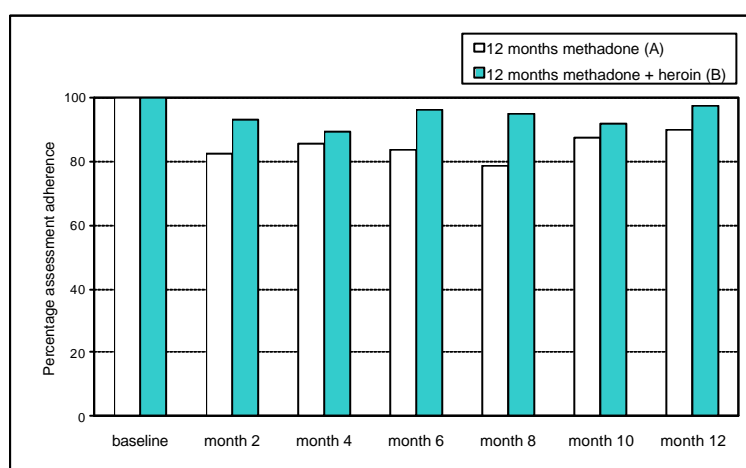
The mean methadone dosage in the experimental group was 60 mg (sd=17.0 mg), which is significantly lower compared to the control group (t-value=3.12; df=135; p=0.002). In addition, treatment completing patients in the experimental group visited the heroin dispensing units on 352 days (median) and 2.1 times per day (median). The mean heroin dosage prescribed was 254 mg per visit (sd=62.5 mg) and 549 mg per day (sd=193 mg).

Patients in the trial on injectable heroin had the opportunity to switch to medically prescribed inhalable heroin (see paragraph 2.2.2). Of the 55 treatment completers in the trial on injectable heroin, 18 had switched from injectable heroin to inhalable heroin by the end of the experimental study period (32.7%). The patients who switched to inhalable heroin did not differ significantly from the patients who stayed on injectable heroin with respect to their frequency of visiting the heroin dispensing units (2.1 versus 2.2 visits per day, respectively) or the heroin dosage prescribed (575 mg versus 536 mg per day, respectively). Lastly, it should be emphasized that patients remained in the trial they were assigned to at the start of the trial, regardless possible switches in their route of heroin administration. Thus, patients in the injectable heroin trial who had switched to co-prescribed inhalable heroin, were still analyzed as participants in the injectable heroin trial.

### 5<sup>A</sup>.3 Adherence at two-monthly assessments

During the experimental phase of the study, patients were assessed by the local research team and physician every two months. Thus, in the period from randomization to the primary endpoint at month 12, six assessments were scheduled.

Figure 9. Adherence at two-monthly assessments



The majority of patients had participated in all six assessments. In control group A 61.2% of the patients adhered to all six assessments, while 76.2% of the patients in the experimental group B adhered to all six assessments. The number of patients without any post baseline assessment is negligible: two patients in group A (2.0%), and none in group B. Adherence at the month 12 end-

point amounted to 89.8% for group A and 97.4% for group B. This implied that the 'Last Observation Carried Forward' procedure at month 12 was conducted for ten patients in group A and for only two patients in group B. In Figure 9, the adherence at the six successive assessment-points is graphically displayed.

- The majority of eligible patients (86%) was included in the intention-to-treat population;  $n=174$ .
- Twelve months treatment completion amounted to 85% in the control condition and to 72% in the experimental condition.
- Adherence at the month 12 endpoint-assessment amounted to 90% for patients in the methadone condition and to 97% for patients in the co-prescribed heroin condition.



## Chapter 6<sup>A</sup>

### Characteristics of the study population at baseline

#### 6<sup>A</sup>.1 Intention-to-treat population

##### 6<sup>A</sup>.1.1 Baseline characteristics

As described in the previous chapter, the intention-to-treat population in the injectable heroin trial consisted of 174 subjects. The demographic background and other relevant baseline characteristics of these patients are displayed in Table 7.

Table 7. Characteristics intention-to-treat population at baseline ( $n = 174$ )

Domain	Variable	% / mean (sd)
Background	- gender: male	82.2 %
	- age	38.5 years (5.7)
	- ethnicity: Dutch/ western	95.4 %
	other	4.6 %
	- education: low	69.9 %
	middle	25.4 %
Physical health	high	4.6 %
	- living arrangements, past 2 months: alone	63.8 %
	with partner/ child(ren)	20.7 %
	other	15.5 %
	- MAP-HSS score (0 – 40)	11.5 (7.6)
Psychiatric status	- lifetime number of hospitalizations: 0	11.5 %
	1 – 5	70.1 %
	> 5	18.4 %
	- HIV -status positive (self report)	13.3 %
	- % receiving prescribed medication for physical problems	21.3 %
	- additional need for treatment: no	62.1 %
yes	37.9 %	
Psychiatric status	- SCL-90 total score (0 – 360)	74.3 (65.1)
	- lifetime number of hospitalizations: 0	81.5 %
	1 – 5	17.3 %
	> 5	1.2 %
	- ever attempted to commit suicide	38.2 %
	- % receiving prescribed medication for psychiatric problems	35.3 %
	- DSM-IV diagnosis, lifetime: any mood disorder	22.5 %
	any anxiety disorder	21.4 %
	any psychotic disorder	2.9 %
	any of these lifetime disorders	38.7 %
	- DSM-IV diagnosis, past six months: any mood disorder	17.9 %
	any anxiety disorder	19.7 %
	any psychotic disorder	2.9 %
	any of these recent disorders	33.0 %
- additional need for treatment: no	69.4 %	
yes	30.6 %	

(continued on next page)

Table 7. *Continued*

Domain	Variable	% / mean (sd)		
Social functioning	- usual employment status, past 3 years:	part-/ full-time employed unemployed other (e.g. incarcerated)	12.1 % 77.6 % 10.3 %	
	- major source of income, past month:	employment welfare/ public assistance illegal activities other	8.1 % 57.6 % 28.5 % 5.8 %	
	- debts (in €) (63,9%) *		2,950 (median)	
	- usual housing arrangement, past month:	home environment outside, public place, shelter	86.2 % 13.8 %	
	- lifetime number of charges for crimes against property:	0 1 – 10 11 – 50 > 50	13.2 % 37.9 % 33.9 % 14.9 %	
	- number of years ever incarcerated:	0 (years) 0 – 1 2 – 5 > 5	11.5 % 34.5 % 39.1 % 14.9 %	
	- days engaged in illegal activities, past month:	0 (days) 1 – 5 6 – 30	29.9 % 12.1 % 58.1 %	
	- days contact with non-drug-using person, past month:	0 (days) 1 – 5 6 – 30	24.7 % 22.4 % 52.9 %	
	Substance use	- years of regular use:	heroin (100 %) methadone (100 %) cocaine (93.7 %) amphetamines (47.7 %) benzodiazepines (70.1 %) alcohol ( $\geq$ 5 gl./day) (74.0 %) poly drug use (100 %)	15.9 years (5.7) 12.1 years (6.3) 10.5 years (6.3) 5.6 years (6.9) 10.4 years (7.6) 8.7 years (7.6) 17.3 years (6.7)
		- days of substance use, past month:	heroin (98.9 %) methadone (100 %) cocaine (90.2 %) amphetamines (10.9 %) benzodiazepines (71.8 %) alcohol ( $\geq$ 5 gl./day) (40.2 %) poly drug use (99.4 %)	25.9 days (6.0) 29.1 days (3.2) 18.7 days (10.2) 2 days (median) 19.5 days (11.2) 16.8 days (11.8) 28.9 days (3.0)
		- lifetime number of drug overdoses:	0 1 – 5 > 5	51.7 % 37.4 % 10.9 %
		- number of earlier addiction treatments:	outpatient methadone (100 %) detoxification (55.8 %) outpatient drug-free (3.5 %) inpatient drug-free (33.3 %) any drug-free treatment (66.5%) other drug treatments (28.7 %) any alcohol treatment (8.1 %)	2 (median) 2 (median) 1 (median) 2 (median) - 2 (median) 2 (median)
		- money (in €) spent in past month on:	drugs alcohol	995 (826) 56 (53)
		- additional need for treatment:	no yes	39.1 % 60.9 %

\* The percentages between parentheses in the middle column represent subjects with a positive value on the variable in question (e.g. subjects with debts).

### *Sociodemographic background*

The subjects in the intention-to-treat population (see Table 7) were predominantly male and from a Dutch/western background, with only few patients coming from a Surinamese (1.2%), Dutch Antillian (0.6%) or Moroccan (0.6%) background, no participants with a Turkish background, and 2.3% other<sup>1</sup>. The mean age in the sample amounted to 38.5 years (range: 27-52 years). The participants had typically received lower level education only, and were living alone.

### *Physical health*

On the MAP-HSS, 65.5% had a score of 8 or higher, the inclusion-threshold used in the study for the area of physical health. The mean MAP-HSS score amounted to 11.5 (range: 0-31). Based on self-report, 13.3% had a positive HIV-status, and more than one-fifth currently received prescribed medication for a physical health problem. Subjectively, more than one-third of the participants reported to experience a (moderate, considerable or extreme) need for additional treatment in this domain.

### *Psychiatric status*

SCL-90 total scores in the sample ranged from 2-331, with a mean of 74.3. Among the males and females, 58.7% and 64.5% reached the inclusion threshold score of 41 and 60, respectively. In the sample, 18.5% of the patients had at least once in their lives received inpatient treatment for a psychiatric problem. In addition, more than one-third had ever committed a suicide attempt, and one-third currently received prescribed medication for a psychiatric problem. DSM-IV mood and anxiety disorders were common on both lifetime and recent (i.e. past six months) basis. Lastly, almost one-third of the sample subjectively reported a (moderate, considerable or extreme) need for additional treatment for psychiatric problems.

### *Social functioning*

Most subjects had been unemployed during the (three) years prior to the baseline interview, and currently received income primarily from public assistance or from illegal activities. Among those with financial debts (63.9%), the median debts amounted to €2,950. In the month prior to the interview, 13.8% of the subjects had usually slept outside, in a public place or in a homeless shelter.

Among those who had ever (at least once) been charged for a crime against property, the number of charges ranged from 1 to more than 100, with a median of 15 charges (not in table). For those ever incarcerated, the years in detention ranged from 1 to more than 8 years, with a median of nearly 2 years (23 months). In the month prior to the interview, 58.1% had engaged in illegal activities to obtain money for 6 or more days, one of the inclusion thresholds in the social area. Lastly, almost half of the participants had had personal contact (of at least half an hour duration) less than 6 days in the previous month with a non-drug-using person (excluding treatment staff), the other inclusion threshold in the social area.

### *Substance use*

In addition to heroin and methadone (both 100%), most participants had ever in their lives used cocaine (93.7%), large quantities of alcohol (i.e. at least five standard glasses a day) (74.0%), benzodiazepines (70.1%), and amphetamines (47.7%) on a regular (i.e. three or more days a week) basis. The mean number of years of regular heroin use amounted to 15.9 years. In addition, among those with "lifetime" regular cocaine use, cocaine had been used on a regular basis for 10.5

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<sup>1</sup> To determine ethnicity, the definition of the Central Bureau of Statistics of the Netherlands (CBS, 1999) was used.

years. All participants were poly drug users. On the average, they had used more than one substance a day on a regular basis for 17.3 years.

All subjects had at least once in their lives been in outpatient substitution treatment (including the present methadone maintenance program they were recruited from), and had done so with a median of 2 times (i.e. two uninterrupted series of methadone maintenance treatment). On average, participants had used methadone on a regular basis for 12.1 years. In addition, more than half had ever participated in a detoxification program, and one-third in an inpatient drug-free program. Approximately one in twelve subjects had ever received treatment specifically for alcohol problems.

In the month preceding the baseline interview, all participants had used methadone, 98.9% heroin, and 90.2% cocaine. Among the cocaine users, both injecting (56.5%) and smoking (chasing/basing) (43.5%) were common routes of cocaine administration. Heroin and methadone had been used on a daily or nearly daily basis, and cocaine on slightly more than half the days (mean: 18.7 days). Subjects who had used illicit drugs in the previous month had spent an average of €995 on drugs. Among the patients with considerable alcohol use, the money spent on alcohol amounted to an average of €56. Lastly, almost two-thirds of the sample subjectively reported a (moderate, considerable or extreme) need for additional treatment for drug problems.

### 6<sup>A</sup>.1.2 Inclusion profiles

As described in the first chapter, a patient could be included in the study on the basis of his physical health status, psychiatric functioning, and/or social functioning. From the 174 patients in the injectable heroin trial, 65.5%, 59.8% and 75.3% were included on the basis of their functioning in these problem areas, respectively. Combining these three outcome areas into seven types of inclusion, each patient was admitted to the study according to a specific inclusion profile.

Table 8. Inclusion profile of the participants ( $n = 174$ )

<i>Inclusion profile</i>	
Health <sup>+</sup>	65.5 %
Psychiatric <sup>+</sup>	59.8 %
Social <sup>+</sup>	75.3 %
Health <sup>+</sup> Psychiatric <sup>+</sup> Social <sup>+</sup>	34.5 %
Health <sup>+</sup> Psychiatric <sup>+</sup> Social <sup>-</sup>	13.2 %
Health <sup>+</sup> Psychiatric <sup>-</sup> Social <sup>+</sup>	8.6 %
Health <sup>+</sup> Psychiatric <sup>-</sup> Social <sup>-</sup>	9.2 %
Health <sup>-</sup> Psychiatric <sup>+</sup> Social <sup>+</sup>	9.8 %
Health <sup>-</sup> Psychiatric <sup>+</sup> Social <sup>-</sup>	2.3 %
Health <sup>-</sup> Psychiatric <sup>-</sup> Social <sup>+</sup>	22.4 %

As can be seen in Table 8, the largest subgroup (34.5%) consisted of patients included on all three domains, followed by patients included on the social domain only (22.4%). Patients were rarely admitted to the study on the basis of their health status only (9.2%) or their psychiatric status only (2.3%). In nearly half the cases (47.7%), combined physical health and psychiatric problems were responsible for inclusion.

### 6<sup>A</sup>.1.3 Comparability of the treatment groups

To investigate the comparability of the treatment groups, the baseline characteristics of the subjects randomized to the methadone alone and the co-prescribed heroin treatment conditions were compared on key variables in the areas of demographic background (gender, age, ethnicity), components of the primary outcome measure (MAP-HSS, SCL-90, days illegal activities, days contact non-drug-using person), and lifetime and current substance use variables (years of use, and days of use in past month for heroin, methadone, cocaine, amphetamines, benzodiazepines, alcohol, and poly drug use). No significant differences (Bonferroni correction; overall  $p$ -value  $<0.10$ ) between the treatment groups were found on any of these key variables.

### 6<sup>A</sup>.1.4 Baseline characteristics across the six study sites

Similarly, the baseline characteristics were compared between the study populations in the six study sites involved in the study. No significant differences (Bonferroni correction; overall  $p$  value  $<0.10$ ) occurred on any of the investigated key variables.

### 6<sup>A</sup>.1.5 Comparison of the study populations in the injectable and inhalable heroin trials

The similarities and differences in baseline characteristics between the study populations in the two trials of the study are described in the corresponding paragraph 6<sup>B</sup>.1.5 of Part IIIB, concerning the study findings with regard to the inhalable heroin trial.

## 6<sup>A</sup>.2 Treatment completers

As described in chapter 5<sup>A</sup>, the population of treatment completers in the trial on injectable heroin consisted of 138 subjects (79.3% of the 174 subjects in the intention-to-treat population). These 138 subjects were compared with the remaining 36 subjects in the intention-to-treat population who did not complete the (methadone alone or co-prescribed heroin) treatment, utilizing the same set of baseline variables as displayed in paragraph 6<sup>A</sup>.1.1. With the exception of mean number of days that cocaine was used in the previous month (treatment completers: 17.3 days; non-completers: 23.6 days;  $t$ -value 3.32;  $df=155$ ;  $p=0.0011$ ), none of the baseline characteristics in the areas of demographic background, physical health status, psychiatric status, social functioning, and substance use showed significant differences (Bonferroni correction; overall  $p$ -value for each domain separately:  $p<0.10$ ) between the two sub-populations. Hence, overall, the baseline characteristics of the treatment completers in the intention-to-treat population did not differ from those who did not complete treatment.

- As intended, the study population consisted of chronically poor functioning, treatment-resistant heroin dependent patients. The participants had a long history of poly drug use, and participation in addiction treatments, including long-term methadone maintenance treatment. Despite earlier treatment efforts, patients had serious problems and experienced treatment needs with regard to their physical health, psychiatric status, and social functioning.
- Within each of these domains of functioning, approximately two-thirds of the patients were included in the study. Inclusion occurred most often on the basis of poor functioning in more than one problem domain.
- Randomization was successful, as indicated by the similarity in background characteristics, addiction history, additional problems, and inclusion profiles between the subjects in the two treatment groups.



## Chapter 7<sup>A</sup>

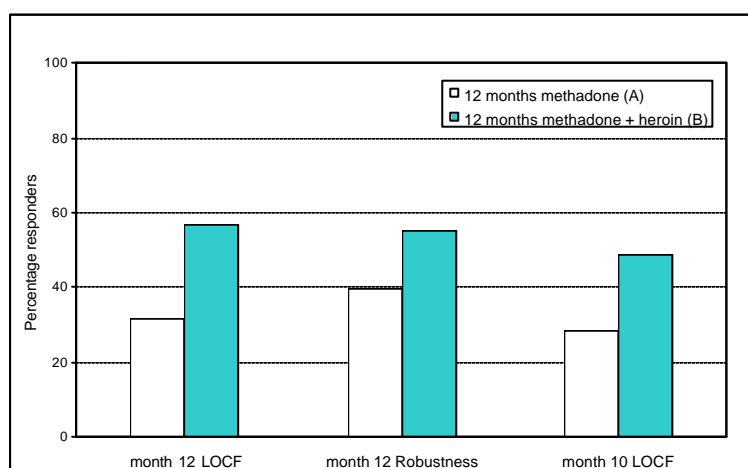
# Effectiveness of co-prescribed injectable heroin versus methadone alone treatment

### 7<sup>A</sup>.1 Treatment response after 12 months

#### 7<sup>A</sup>.1.1 Treatment response after 12 months in the intention-to-treat population

As described in paragraph 2.9.3, patients were considered as responders if they showed at least 40% improvement at the month 12 outcome assessment, compared to their situation at baseline, in at least one of the areas in which they functioned poorly at the start of the study (i.e. on the basis of which they were included at baseline), while these improvements should not have gone at the expense of similar (40% or more) deterioration in functioning in any of the other outcome domains. The primary study question, into the effectiveness of co-prescribed heroin versus methadone alone treatment after 12 months, was investigated by testing the difference in percentage responders between the experimental and control condition in the intention-to-treat population, using a logistic regression model, with "treatment site" as the only covariate, and applying the last observation carried forward method to deal with missing endpoint-assessments.

Figure 10. Effectiveness of co-prescribed injectable heroin versus methadone alone treatment ( $n = 174$ )



Note: LOCF = Last Observation Carried Forward.

In the heroin group<sup>1</sup>, the percentage responders amounted to 56.6%, compared to 31.6% in the methadone group (see Figure 10: left-hand bars). Controlling for differences in response between the treatment sites, the difference of 25.0% corresponded with an adjusted Odds-Ratio of 2.99 (95%-CI: 1.58-5.65;  $p=0.0008$ ). Neither "treatment site", nor the treatment-by-site interaction were significantly related to treatment response in the logistic

regression model. As indicated by the Hosmer and Lemeshow goodness-of-fit test, the data fitted the regression model ( $\chi^2=2.84$ ;  $df=7$ ;  $p=0.90$ ).

To illustrate the clinical meaning of the observed response rates, Table 9 shows the changes in mean scores from baseline to month 12 on the scales and items used as components of the multi-domain outcome index of response in the trial.

<sup>1</sup> For reasons of readability, the term "heroin group" is used in this chapter to refer to the treatment group receiving co-prescribed heroin and methadone, whereas the term "methadone group" refers to the methadone alone treatment group.

Table 9. Changes in patient status from baseline to month 12 (mean scores)

Outcome domain	Group	ITT-population (n = 174)		Non-responders (n = 100)		Responders (n = 74)	
		baseline	month 12	baseline	month 12	baseline	month 12
MAP-HSS (0-40)	Group A *	11.1	10.5	10.2	11.8	13.0	7.6
	Group B *	12.1	8.6	11.6	12.0	12.5	5.9
SCL-90 (0-360)	Group A	72.7	62.1	69.4	72.1	79.7	40.3
	Group B	76.3	55.1	74.4	76.4	77.8	38.8
Days illegal activities (0-30)	Group A	11.5	8.7	10.3	9.6	14.1	6.8
	Group B	12.9	2.9	10.6	3.9	14.7	2.1
Days without personal contact with non-drug users (0-30)	Group A	16.3	12.7	17.7	14.8	13.1	8.2
	Group B	17.9	14.0	18.8	17.1	17.2	11.6
Days cocaine use (0-30)	Group A	18.0	15.4	16.7	14.6	20.7	17.1
	Group B	15.5	12.8	13.4	13.7	17.0	12.1
Days amphetamine use (0-30)	Group A	1.2	0.6	1.6	0.9	0.3	0.0
	Group B	0.9	0.4	1.9	1.0	0.1	0.0
Days controlled environment **	Group A		4.1		5.8		0.3
	Group B		1.0		1.9		0.3

\* Group A: ITT-population n=98; non-responders n=67; responders n=31; Group B: ITT-population n=76; non-responders n=33; responders n=43.

\*\* No baseline data are presented, because patients with more than seven days in a controlled environment in the month prior to baseline were – for reasons of validity – excluded from the baseline assessments.

Among the responders (right-hand column), considerable changes from baseline to month 12 were observed for most scales and items. For example, the mean MAP-HSS score decreased in the methadone alone group (A) from 13.0 at baseline to 7.6 at the month 12 assessment, and in the co-prescribed heroin group (B) from 12.5 at baseline to 5.9 at month 12. The mean score of 5.9 on the MAP is quite comparable to the mean score of 4.8 found for the general population in the Netherlands (see paragraph 2.9.1). Similarly, the SCL-90 total scores among responders decreased to mean values (40.3 and 38.8), comparable to those found in the general Dutch population (males: 27.2; females: 38.9). In the social domain, a decrease from baseline to month 12 was observed for both the number of days of illegal activities, and – to a lesser extent – for the number of days without personal contact with non-drug-users. A similar decrease occurred for number of days of cocaine use among the responders in the heroin group (B). Amphetamine use at baseline was rare (10.9%), and among the responders limited to an average of less than one day a month.

Among the non-responders (middle column), on the other hand, changes from baseline to month 12 were absent on nearly all scales and items. The only exception occurred with regard to the number of days of illegal activities in the previous month. This variable showed a decrease not only among the responders in both treatment groups, but also among the non-responders in the co-prescribed heroin group.

### *Robustness of the findings*

At the month 12 assessment-point, data were obtained from 97.4% of the patients in the heroin group, and from 89.8% in the control group. To investigate the robustness of the observed 25% difference in percentage responders between the two groups, the (2.6%) missing endpoint-assessments in the heroin group were considered as non-responders, and those in the control group (10.2%) as responders. In this most conservative scenario, treatment response decreased from 56.6% to 55.3% in the heroin group, and increased from 31.6% to 39.8% in the methadone group (see Figure 10: middle bars). Hence, the difference in response decreased from 25.0% to

15.5%. This difference was still significant in the logistic regression model, with an adjusted Odds-Ratio for treatment group of 1.93 (95%-CI: 1.04-3.58;  $p=0.037$ ), and no significant treatment-by-site interaction. Also in this analysis, the data fitted the model ( $\chi^2=1.27$ ;  $df=7$ ;  $p=0.99$ ).

### *Anticipation effects*

In the follow-up phase of the study, the treatment with heroin could only be reinstated in patients who had responded to the heroin treatment at the end of the experimental phase. To investigate the influence of the anticipation of such a reinstatement (see paragraph 3.2.6) on the results of the study, the month 12 analysis described above was similarly conducted for the month 10 assessment-point. After 10 months, the percentage responders in the heroin group, utilizing LOCF, amounted to 48.7%, and in the methadone group to 28.6% (see Figure 10: right-hand bars). As in the main analysis of the month 12 effects, the difference in percentage responders between the treatment groups of 20.1%, when controlled for "treatment site", and given non-significant relationships between treatment site and response, and between the treatment-by-site interaction and response, was significant at the month 10 assessment-point (adjusted OR=2.46; 95%-CI: 1.30-4.65;  $p=0.0056$ ). Again, the goodness-of-fit test indicated that the data fitted the regression model ( $\chi^2=0.50$ ;  $df=7$ ;  $p=0.99$ ).

### 7<sup>A</sup>.1.2 Treatment response after 12 months among the treatment completers

The 138 treatment completers in the trial on injectable heroin – consisting of patients who still participated in treatment (i.e. received methadone in the control condition, and co-prescribed heroin in the experimental condition) in month 12 – involved 83 subjects in the methadone alone treatment group, and 55 subjects in the co-prescribed heroin group (see Chapter 5<sup>A</sup>). Analogous to the primary outcome analysis in the intention-to-treat population – applying LOCF for the missing endpoint-assessments – the percentage responders after 12 months was determined among the treatment completers. The response rate among the treatment completers in the co-prescribed heroin group amounted to 58.2%, compared to 34.9% in the methadone alone group. The difference of 23.3% was statistically significant in a good fitting logistic regression model, in which "treatment site" was the only covariate, and in which neither treatment site, nor treatment-by-site interaction were significantly related to response (adjusted OR=2.95; 95%-CI: 1.41-6.18;  $p=0.00041$ ).

- After twelve months of treatment, the experimental treatment with co-prescribed injectable heroin was significantly more effective than the control treatment with methadone alone. The observed difference in percentage responders between the experimental group and the control group amounted to 25.0%.
- The observed difference in percentage responders decreased from 25.0% to 15.5% when a worst-case scenario was applied for the missing endpoint-assessments. However, the difference was still statistically significant.
- The observed difference found after twelve months of treatment was also statistically significant two months earlier, after ten months of treatment. Hence, anticipation effects, with regard to a possible reinstatement of the heroin treatment after the experimental phase for responders in the heroin condition, can not be held responsible for the observed effect after twelve months of treatment.
- In the sub-population of treatment completers, the difference in percentage responders between the treatment groups was similar to the difference observed in the intention-to-treat population.
- The observed difference in percentage responders between the treatment groups after twelve months of treatment was not significantly different across the six participating sites.

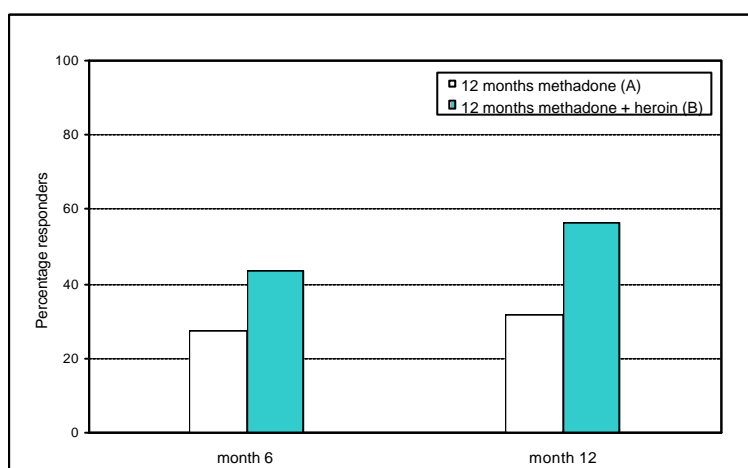
## 7<sup>A</sup>.2 Treatment response after six months

The six months effectiveness was investigated in the trial on injectable heroin by comparing the percentage responders among the patients in the co-prescribed heroin and methadone alone group halfway their intended treatment period, i.e. six months after baseline. The underlying study question pertained to the six months effectiveness of ongoing treatment with co-prescribed heroin, compared to that of ongoing methadone alone treatment. Analogous to the investigations into the month 12 effects described in the previous paragraph, the analysis was conducted in the intention-to-treat population, applying LOCF, and using a logistic regression model.

### *Effectiveness of co-prescribed heroin versus methadone alone treatment after six months*

At the month 6 assessment-point, 43.4% of the participants in the heroin group were responders, compared to 27.6% in the methadone group (see Figure 11: left-hand bars). Compared to the response percentages which were reported earlier for month 12 (right-hand bars), the difference in response between the heroin and methadone group increased from 15.8% after six months to 25.0% after twelve months.

Figure 11. Effectiveness of co-prescribed injectable heroin versus methadone alone treatment after six and twelve months ( $n = 174$ )



Adjusted for differences in response between the treatment sites, the Odds-Ratio corresponding with this difference of 15.8% was 2.03 (95%-CI: 1.07-3.85;  $p=0.0296$ ). Treatment response at month 6 was not significantly related to either treatment site or treatment-by-site interactions. According to the Hosmer and Lemeshow goodness-of-fit test, the data fitted the regression model ( $\chi^2=2.55$ ;  $df=7$ ;  $p=0.92$ ).

- After six months of treatment, i.e. halfway the intended twelve months treatment period, the experimental treatment with co-prescribed injectable heroin was significantly more effective than the control treatment with methadone alone.
- The observed difference in percentage responders between the experimental group and the control group amounted to 15.8% after six months and further increased to 25.0% after twelve months of treatment.
- As with the results after twelve months, the observed difference after six months of treatment was not significantly different across the six participating sites.

## 7<sup>A</sup>.3 Exploratory analyses of effectiveness

### 7<sup>A</sup>.3.1 Improvement and deterioration as components of treatment outcome

In the present trial, patients were considered as responders if they showed at least 40% improvement after twelve months of treatment, compared to their situation at baseline, in at least one of the areas in which they functioned poorly at the start of the study (i.e. on the basis of which they were included at baseline), and these improvements should not have gone at the expense of similar deterioration in functioning in any of the other outcome domains (see paragraph 2.9.3). Hence, non-responders in the trial could consist of (1) subjects who had improved 40% or more on at least one of the outcome domains, but had concurrently deteriorated on at least one of the other outcome domains, (2) subjects who had neither improved, nor deteriorated according to the criteria, and (3) subjects who had not shown improvement (of 40% or more) on any of the outcome domains, but who had deteriorated on at least one of the outcome domains. Table 10 provides an overview of the percentage of patients in the treatment groups A and B in each of these categories.

Table 10. Types of non-responders in terms of improvement and deterioration ( $n = 174$ )

<i>Treatment group</i>	<i>Responders (%)</i>	<i>Non-responders (%)</i>		
	Improved + not deteriorated	Improved + deteriorated	Not improved + not deteriorated	Not improved + deteriorated
12 months methadone (A)	31.6 %	15.3 %	22.5 %	30.6 %
12 months methadone + heroin (B)	56.6 %	10.5 %	18.4 %	14.5 %

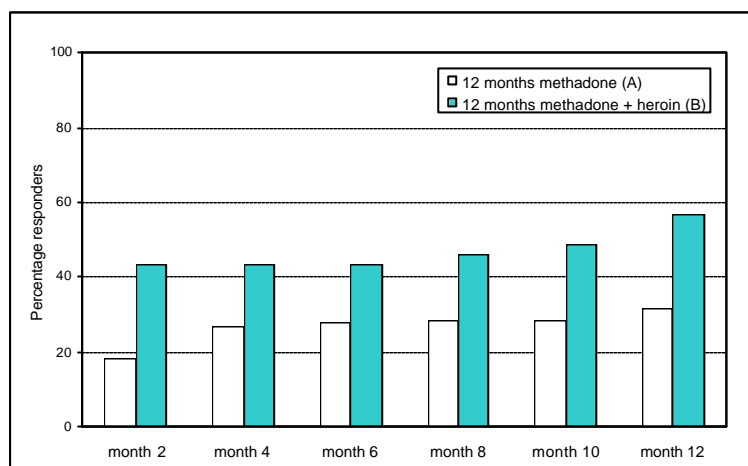
As indicated by Table 10, the observed effect in terms of percentage responders in the co-prescribed heroin group (56.6% versus 31.6% in the methadone alone group) did not go at the expense of an increased percentage of non-responders who did not improve and deteriorated (14.5% versus 30.6% in the methadone alone group).

### 7<sup>A</sup>.3.2 Response at subsequent assessments

To investigate the occurrence of response in the course of the experimental phase of the trial, the percentage responders in the intention-to-treat population was calculated for each assessment-point, using LOCF for each missing assessment during the trial. The results are displayed in Figure 12.

Two months after baseline, at the first assessment-point, response occurred in 43.4% of the participants in the heroin group, compared to 18.4% in the methadone group. In the heroin group, response remained stable in the following four months, and subsequently gradually increased from 43.4% at month 6 to 46.1% at month 8, 48.7% at month 10, and to 56.6% at the endpoint at month 12.

Figure 12. Percentage responders at subsequent assessments



In the methadone group, on the other hand, following the initial 18.4% response at month 2, and a subsequent increase to 26.5% at month 4, the response rate remained largely unchanged during the subsequent eight months of the trial, amounting to 31.6% at month 12.

### 7<sup>A</sup>.3.3 Relative contribution of the outcome domains to response

Given the response rates in the course of the trial, displayed in Figure 12, and particularly considering the substantial response rate in the heroin group present at the month 2 assessment-point, subsequent exploratory analyses were conducted to investigate the relative contribution of the outcome domains to the percentage responders at subsequent assessments during the trial. First, the type(s) of outcome domains on which the patients responded in the course of the trial ("response profiles") were investigated. Second, the number of response domains were investigated.

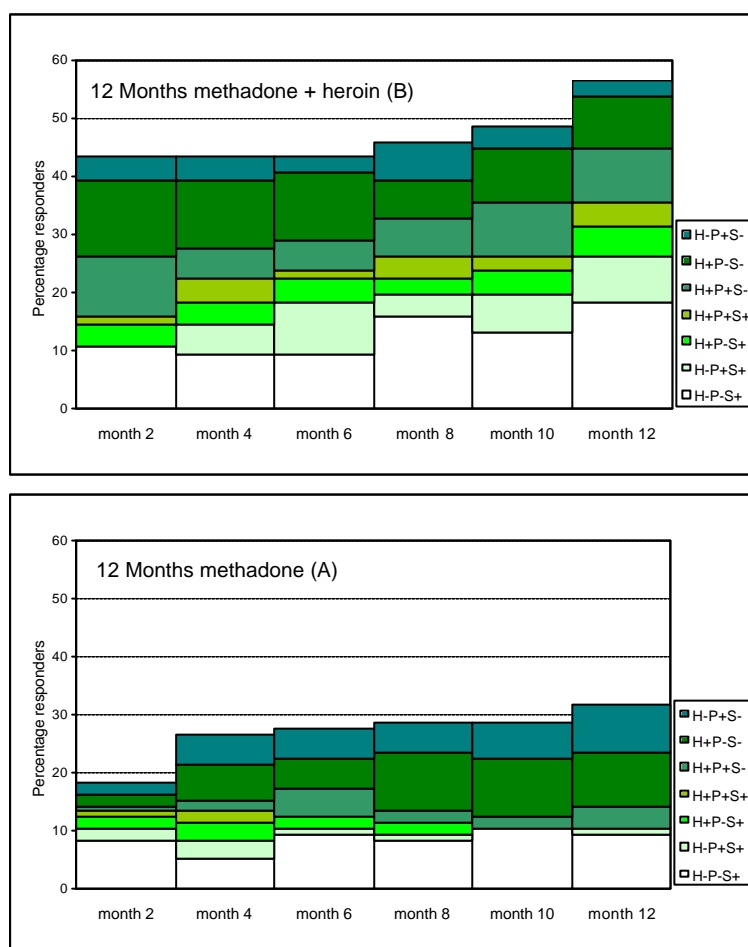
#### *Response profiles in the course of the trial*

Analogous to the inclusion profiles described earlier in paragraph 6<sup>A</sup>.1.2, the three outcome domains of physical health, psychiatric status, and social functioning were combined into seven types of response, each representing a unique and mutually exclusive response profile. In Figure 13, the resulting bar charts are displayed for the heroin group and methadone group separately. Notably, the total values of each column for the heroin and methadone group in Figure 13 are identical to the response rates of the treatment groups at each corresponding assessment-point, displayed earlier in Figure 12.

As indicated by the upper bar chart in Figure 13, response in the heroin group – both at the start, during the course, and at the end of the trial – was based on contributions from all three outcome domains. For example, with response rates at month 12 of 35.5%, 27.6%, and 23.7% respectively, the social, physical health and psychiatric domain each contributed considerably to the occurrence of overall (56.6%) response after twelve months of treatment. In addition, as suggested by the 18.4% response due to the social domain alone at month 12, response in the heroin group could not be attributed to a dominating influence of decreased illegal activities by the participants.

This limited influence on response of the social domain alone is also illustrated when subjects, who were included in the trial on the basis of their poor functioning in the social domain alone (22.4% of the intention-to-treat population), are left out of the analysis (not shown in Figure 13). In this case, overall response at month 12 still amounted to 56.5% in group B ( $n=62$ ), and increased from 31.6% to 39.7% in group A ( $n=73$ ). Using the same logistic regression model as

Figure 13. Contribution of the outcome domains to response at subsequent assessments



Note: H = physical health; P = psychiatric status; S = social functioning.

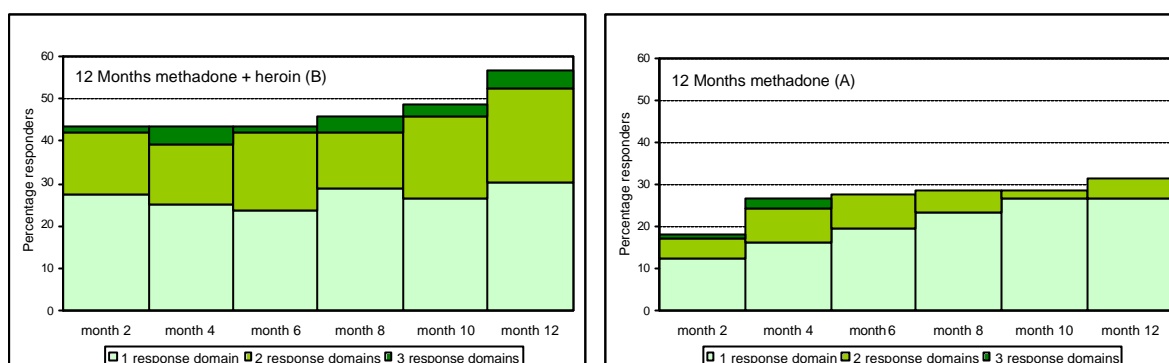
described earlier, the difference in percentage responders remained significant (adjusted OR=2.18; 95% -CI: 1.06-4.45; p=0.0333).

In the methadone group (lower chart in Figure 13), the three outcome domains contributed to the occurrence of response as well. Here, however, response at month 12 (31.6%) often occurred on the social domain alone (9.2%), physical health domain alone (9.2%), and psychiatric domain alone (8.2%). Hence, response in the methadone group was often based on improvements in one single domain.

**Single-domain versus multi-domain response**

The difference in comprehensiveness of response between the methadone alone and the co-prescribed heroin group is further illustrated in Figure 14. As before, it should be noted that the total values of each column for the heroin and methadone group in Figure 14 are identical to the response rates of the treatment groups at each corresponding assessment-point, displayed in the earlier figures in this paragraph.

Figure 14. Comprehensiveness of response at subsequent assessments



In the heroin group, at the primary assessment-point at month 12 (left-hand chart in Figure 14), 30.3% of the participants had responded on one domain only, 22.4% on two domains, and 4.0% on three domains simultaneously. Expressed as a percentage of the total response rate at month 12, 46.5% of the response in the heroin group occurred on more than one domain. In addition, Figure 14 shows that treatment comprehensiveness in the heroin group increased with time-in-treatment.

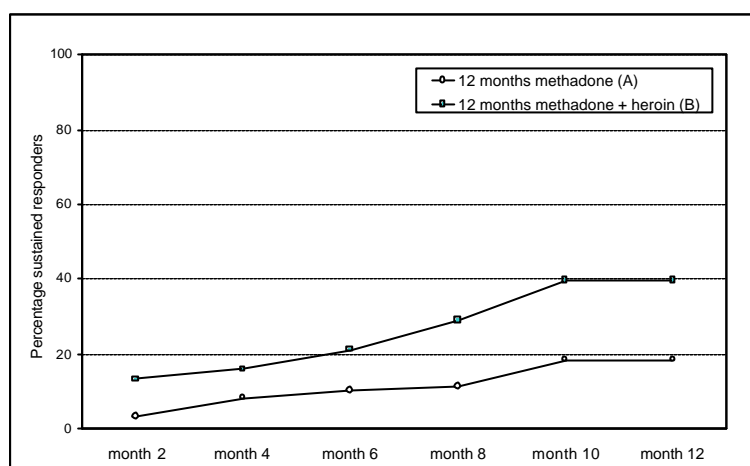
In contrast, in the methadone group (right-hand chart in Figure 14), 26.5% of the subjects had responded on one domain only, 5.1% on two domains combined, and none of the subjects had responded on three domains simultaneously. Hence, given the total response rate of 31.6% at month 12 in this group, 83.9% of the response in the methadone group was limited to improvements on one single domain, and – conversely – only 16.1% of the total response occurred on more than one domain. The difference in percentage multi-domain response between the two treatment groups (30.4%) was tested in a logistic regression model, with treatment site as the only covariate, and with non-significant relationships between multi-domain response and both treatment site and treatment-by-site interaction. In the model, the difference in percentage multi-domain responders was significant (adjusted OR=4.80; 95% -CI: 1.48-15.59; p=0.009).

### 7<sup>A</sup>.3.4 Sustained response

To gain further insight into the development of response over time, the percentage of "stable" or "sustained" responders in the treatment groups was determined at each assessment-point, as before using LOCF for the missing assessments during the trial. Sustained responders were defined as patients who (1) became responder prior to the month 12 assessment, and (2) remained a responder during the course of the trial, once they had become responder for the first time. For the month 12 assessment, this definition implied that patients who became responder for the first time at month 12, were considered as non- (sustained) responders. Similarly, patients who were responder at some earlier assessment-point, but non-responder at a later assessment, were considered as non- (sustained) responders at all assessment-points. Hence, the analysis represents a very conservative approach of response. Figure 15 shows the results of the analysis.

After 12 months of treatment, the percentage sustained responders amounted to 39.5% in the co-prescribed heroin group, and to 18.4% in the methadone alone group. In a logistic regression model, with percentage sustained responders as the dependent variable, and treatment site as covariate, the observed difference of 21.1% between the treatment groups corresponded with an

Figure 15. Percentage sustained responders at subsequent assessments



adjusted Odds-Ratio of 2.94 (95% -CI: 1.47-5.87; p=0.002).

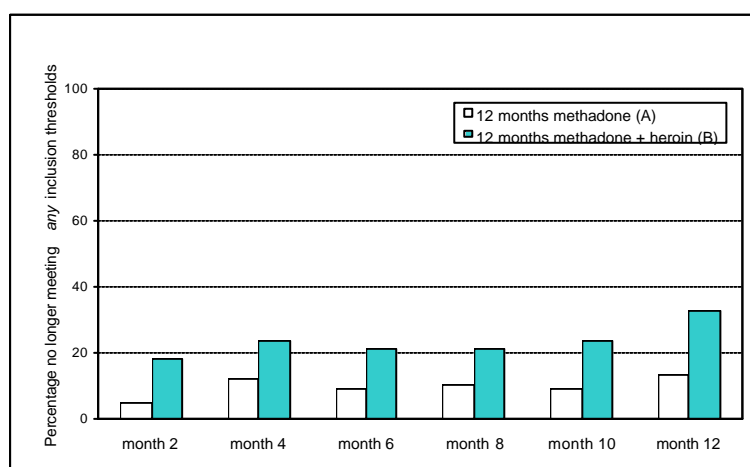
At the month 2 assessment, the percentage sustained responders amounted to 13.2% in the co-prescribed heroin group, and to 3.1% in the methadone alone group. These early response percentages for the sustained responders are considerably lower than those found for the responders at this assessment-point (43.4% and

18.4%, respectively; see paragraph 7<sup>A</sup>.3.2).

### 7<sup>A</sup>.3.5 Patients no longer meeting inclusion thresholds of the trial

In order to be included in the trial, patients had to function poorly in at least one of the areas of physical health, psychiatric status and social functioning, according to specific threshold values on the corresponding instruments in these domains. To investigate the extent to which patients improved in such a way that they did not function poorly anymore according to these inclusion thresholds, this measure of "poor functioning" was used as an alternative dichotomous index of treatment outcome in the trial. Figure 16 shows the development in percentage of patients who did not meet any of the inclusion thresholds for "poor functioning" anymore in the course of the trial. As before, these percentages were calculated for the intention-to-treat population, using LOCF for each missing assessment during the trial.

Figure 16. Percentage of patients no longer meeting the inclusion thresholds of the trial



Two months after baseline, 18.4% of the patients in the heroin group had improved above the level of "poor functioning", compared to 5.1% in the methadone group. After 12 months of treatment, 32.9% of the patients in the heroin group, and 13.3% of the patients in the methadone group, no longer met any of the inclusion thresholds for "poor functioning".

Similar to the analyses conducted earlier for "response", the difference of 19.6% between the treatment groups at month 12 was tested for significance in a logistic regression model, with "poor functioning" as the dependent variable, and treatment site as the only covariate. With non-

significant relationships between "poor functioning" and both treatment site, and treatment-by-site interaction, and with a good fit of the data to the logistic regression model ( $\chi^2=0.80$ ;  $df=7$ ;  $p=0.99$ ), the observed difference of 19.6% corresponded with an adjusted Odds-Ratio of 3.27 (95%-CI: 1.52-7.03;  $p=0.0024$ ).

- The observed effect in terms of percentage responders in the co-prescribed injectable heroin group did not go at the expense of an increased percentage of non-responders who did not improve and deteriorated.
- In the group with co-prescribed heroin, a considerable response rate could be observed two months after the start of this treatment. This response rate gradually increased during the last six months of the trial. In the methadone alone treatment group, on the other hand, the early response rate of 20-25% remained largely unchanged until the end of the trial.
- Response in the co-prescribed heroin group was based on considerable contributions from each of the outcome domains of physical health, psychiatric status, and social functioning. The effect of heroin treatment could not be attributed to a dominating influence of decreased illegal activities by the participants. The effect of methadone alone treatment, in contrast, was largely accounted for by contributions from the physical health domain alone, psychiatric domain alone, or social domain alone.
- The co-prescribed injectable heroin treatment did not only result in a higher percentage of responders than the methadone alone treatment, but also yielded a significantly higher percentage of multi-domain responders.
- Co-prescribed injectable heroin treatment resulted in a significantly higher percentage of stable, sustained responders than methadone alone treatment.
- Co-prescribed injectable heroin treatment resulted in significantly more participants who no longer met the inclusion thresholds for the trial, indicative of "poor functioning", than methadone alone treatment.

#### 7<sup>A</sup>.4 Consequences of discontinuing the co-prescribed heroin treatment

According to the analysis plan (see paragraph 3.3), the effects of discontinuing the experimental treatment with co-prescribed heroin after 12 months were investigated by determining the percentage responders in the 12 months co-prescribed heroin condition who had subsequently deteriorated considerably – i.e. at least 20% of the baseline value on at least one of the outcome domains on which the patient had responded – two months after termination of the heroin treatment. This analysis was conducted only for treatment completers who were responders at the month 12 assessment.

From the 76 patients in the intention-to-treat population in the co-prescribed heroin group, 55 patients completed the experimental treatment period (see chapter 5<sup>A</sup>). Among this subgroup of treatment completers, 32 patients were responders (58.2%). Among these responders, the percentage of patients, who had deteriorated two months after discontinuing the co-prescribed heroin treatment, amounted to 84.4%.

The clinical meaning of the observed rate of deterioration is illustrated in Table 11, which shows the changes in mean scores from month 12 to month 14 on the scales and items used as components of the primary outcome measure in the trial, among the deteriorated responders ( $n=27$ ).

Table 11. Changes in patient status from month 12 to month 14 (mean scores;  $n = 27$ )

<i>Outcome domain</i>	<i>Deteriorated responders group B</i>		
	<i>baseline</i>	<i>month 12</i>	<i>month 14</i>
MAP-HSS (0-40)	12.0	4.3	13.2
SCL-90 (0-360)	74.2	30.6	62.1
Days illegal activities (0-30)	13.5	0.3	16.0
Days without personal contact with non-drug users (0-30)	17.3	11.9	19.5
Days cocaine use (0-30)	12.6	8.1	12.8
Days amphetamine use (0-30)	0.1	0.0	0.7
Days in controlled environment *		0.1	0.1

\* *No baseline data are presented, because patients with more than seven days in a controlled environment in the month prior to baseline were – for reasons of validity – excluded from the baseline assessments.*

As can be seen in Table 11, marked changes occurred from month 12 to month 14 on most variables. The mean MAP-HSS score increased from month 12 to month 14 from 4.3 to 13.2, and the mean SCL-90 total score from 30.6 to 62.1. The mean number of days of illegal activities in the month prior to the assessment increased from less than one day to 16 days. In addition, increases were observed for the number of days without contact with a non-drug-using person, and for the number of days of cocaine use in the previous month. On all variables, the changes from month 12 to month 14 indicate a return to the baseline values observed at the start of the trial.

- Two months after discontinuation of the co-prescribed injectable heroin treatment at the end of the intended treatment period, the majority (84%) of responders had deteriorated considerably.
- The level of deterioration indicated a return to the baseline values observed at the start of the trial.



## Chapter 8<sup>A</sup>

# Safety of co-prescribed injectable heroin treatment

### 8<sup>A</sup>.1 Focus of the evaluation

To evaluate the medical safety of co-prescription of injectable heroin in the present trial, all clinically significant adverse events (AEs), serious adverse events (SAEs) and unexpected adverse events were documented by the treating physician on a continuous basis during the trial. Adverse events and serious adverse events were defined, registered and reported in accordance with the ICH/EU guidelines. In addition, drug overdoses, psychoses and (epileptic) seizures were documented separately throughout the trial.

For the purpose of the present report, the evaluation of the medical safety of co-prescribed heroin focussed on the occurrence of SAEs, and separately on the occurrence of drug overdoses, psychoses and seizures. Other types of AEs were not included in the present evaluation. The observation period used for the evaluation was limited to the experimental treatment phase of the trial, i.e. the first twelve months following randomization. The evaluation was limited to the intention-to-treat population ( $n=174$ ).

An additional safety topic concerned the evaluation of SAEs, drug overdoses, psychoses and (epileptic) seizures following the discontinuation of co-prescribed heroin treatment at the end of the experimental treatment phase. This evaluation was limited to the patients who had received and completed the experimental treatment with co-prescribed heroin (i.e. the treatment completers in group B). The observation period of this – separate – evaluation concerned the two months following the discontinuation of the co-prescribed heroin treatment (i.e. before a possible reinstatement of the heroin treatment in phase III; see paragraph 2.2.1).

### 8<sup>A</sup>.2 Serious adverse events in the experimental treatment phase of the trial

According to the standard ICH/EU definition, serious adverse events are events which result in death, are life-threatening, require inpatient hospitalization or prolongation of existing hospitalization, result in persistent or significant disability or incapacity, or represent a congenital anomaly or birth defect. Table 12 provides an overview of the SAEs.

During the twelve months experimental study phase, a total of 18 SAEs occurred among 174 patients. From these, seven SAEs (involving seven patients; 7.1%) occurred among the 98 patients in the methadone alone treatment group (A), and 11 SAEs (involving nine patients; 11.8%) among the 76 patients in the co-prescribed heroin group (B). The percentage of patients with at least one SAE was not significantly different between the treatment groups A and B (Fisher's Exact Test;  $p=0.30$ ).

In the methadone alone treatment group (A), one fatal event occurred. The patient died in a traffic accident. Since the patient participated in the methadone alone control treatment, this fatal event was considered to be not related to the experimental medication. For the same reason, all other SAEs in this group were registered as not related to the heroin medication.

Table 12. Overview of SAEs during the experimental treatment phase of the trial

<i>Treatment group</i>	<i># SAEs</i>	<i># Patients with SAE(s)</i>
A (12 months methadone; <i>n</i> = 98) - death - life-threatening adverse event - (prolongation of) hospital admission	1 2 4	1 2 4
B (12 months methadone + heroin; <i>n</i> = 76) - death - life-threatening adverse event - (prolongation of) hospital admission	1 2 8	1 * 2 * 8 *
Total ( <i>n</i> = 174)	18	16

\* *The 11 SAEs in group B occurred in nine subjects. One subject had three SAEs: one in each of the described categories.*

The 11 SAEs in the co-prescribed heroin treatment group (B) occurred among nine patients (right-hand column in Table 12). One patient in this treatment group had three SAEs. The first of these SAEs concerned a hospital admission for a seizure, due to the combination of (non-prescribed) heroin and cocaine use. This seizure was considered to be possibly related to the experimental medication (heroin). The second event of this individual concerned a life-threatening grand mal epileptic seizure, which occurred approximately one hour after the self-administration of the co-prescribed heroin. Also this event was considered possibly related to the heroin medication. The third event was again a hospitalization for an epileptic seizure. The patient was treated with the opioid antagonist naloxone, and was subsequently discharged. Several hours later the patient died. Section was conducted, which revealed no specific cause of death. The cause of death was therefore designated as natural. This fatal SAE was considered to be not related to the heroin medication.

Table 13 provides an overview of the relationship between each of the 18 SAEs and the heroin medication. Four SAEs were judged to be possibly related to the intake of co-prescribed heroin. Besides the two SAEs of the (one) patient discussed above, these included one drug overdose and one case of pneumonia. The overdose case, classified as a life-threatening SAE, is described in paragraph 8<sup>A</sup>.3. The pneumonia case involved a patient who felt severely ill for three days, had a high body temperature, and was subsequently hospitalized. Notably, none of the SAEs in the injectable heroin trial were considered to be probably or definitely related to the heroin medication.

#### *Context of the observed SAEs*

The observed total number of 11 SAEs in the co-prescribed heroin group, and four possibly related SAEs occurred among the 76 patients in group B of the intention-to-treat population. From these, 69 patients started the treatment in group B (see chapter 5<sup>A</sup>). Hence, the 11 SAEs in group B correspond with an average of 0.16 SAE per patient per treatment-year, compared to an average of 0.07 SAE per patient per year in the methadone alone treatment group. In addition, the observed SAEs in group B occurred in a context in which approximately 45,000 heroin prescriptions were dispensed.

Table 13. Relationship of SAEs with heroin medication during the experimental treatment phase of the trial

<i>Relationship with heroin medication</i>	<i># SAEs</i>
Not related	14
Possibly related - pneumonia (hospital admission) - seizure, due to combination of heroin and cocaine use (hospital admission) - grand mal epileptic seizure (life-threatening) - drug overdose, due to combination of heroin and cocaine use (life-threatening)	1 1 1 1
Probably related	0
Definitely related	0
Not known	0
Total	18

### 8<sup>A</sup>.3 Drug overdoses, psychoses and seizures during the experimental phase

Drug overdoses, psychoses and (epileptic) seizures were registered separately throughout the trial. In total, 13 such events occurred during the 12 months experimental treatment phase of the study.

#### *Drug overdoses*

A drug overdose was defined as an intentional or unintentional intake of a drug dose in a much larger quantity than normal for the individual, or than normal in the context of treating a disease, which is likely to result in a severe toxic reaction or death. A severe toxic reaction was evident in case of a considerably diminished level of consciousness, ranging from clouded consciousness to coma, and in case of respiratory depression, which are life-threatening and/or require treatment with an antagonist.

Four drug overdoses were registered, all occurring in the co-prescribed heroin treatment group. The severity of one overdose event was considered as mild. Three overdoses were considered moderate in severity. One of the overdoses was considered to be an SAE (see Table 14). This overdose was registered in the SAE-category "life-threatening event". Due to an overdose of (non-prescribed) heroin and cocaine, the patient lost consciousness, and was admitted to a hospital. The same day, the patient left the hospital on his own initiative, without notifying the hospital staff. Later that day, the patient restarted the treatment with co-prescribed heroin. This SAE was judged to be not related to the heroin medication. Two other drug overdoses – involving two other patients – were considered to be definitely related to the co-prescribed heroin medication (right-hand column in Table 14). These were not registered as SAEs.

#### *Psychoses*

A psychosis was defined in terms of the diagnosis psychosis/hallucinosi, involving signs and symptoms which are observed during an acute schizophrenic episode, like hallucinations and delusions.

One psychosis was reported during the 12 months treatment period. The psychosis occurred in a patient who participated in the methadone alone treatment group, and – hence – was unrelated to the heroin medication. The psychosis was not registered as SAE.

Table 14. Relationship of drug overdoses, psychoses and seizures with heroin medication during the experimental treatment phase of the trial

<i>Type of event / treatment group</i>	<i># Events</i>	<i># SAEs</i>	<i># Definitely related events</i>
Drug overdose - treatment group A - treatment group B	0 4	0 1	0 2
Psychosis - treatment group A - treatment group B	1 0	0 0	0 0
(Epileptic) seizure - treatment group A - treatment group B	4 4	0 2	0 0
Total	13	3	2

### Seizures

An (epileptic) seizure was present (1) in case of a grand mal attack, or epileptic state which met the criteria usually applied in the treatment of epilepsy, and (2) in case of an epileptiform seizure, including all other types of seizures with contractions and diminished level of consciousness, which did not meet the criteria mentioned under (1).

Five patients reported a total of eight (epileptic) seizures. The four seizures in the methadone group involved three patients; one patient reported two seizures. The four seizures in the co-prescribed heroin group involved two patients, who each reported two seizures. Two of these seizures were registered as SAE. None were considered to be definitely related to the heroin medication.

### 8<sup>A</sup>.4 SAEs, drug overdoses, psychoses and seizures following the discontinuation of co-prescribed heroin treatment

As described earlier in chapter 5<sup>A</sup>, a total of 55 patients completed the 12 months treatment with co-prescribed injectable heroin. During the two months following the discontinuation of this treatment, one SAE was documented. The SAE was classified as a hospital admission, not related to the (discontinuation of the) heroin medication. The hospitalization occurred for a complicated cruris fracture (an open wound, involving wound infection and requiring skin transplant).

Among the 55 treatment completers in group B, no drug overdoses, psychoses or seizures were documented during the two months following the discontinuation of the co-prescribed heroin treatment.

- The incidence of serious adverse events during the twelve months treatment period was comparable between the co-prescribed heroin treatment group and the methadone alone group.
- The observed total of 11 serious adverse events in the co-prescribed heroin group, of which four events were considered to be possibly related to the study medication, occurred in the context of approximately 45,000 heroin dispensations.
- No serious adverse events were observed that were related to the discontinuation of the co-prescribed heroin treatment at the end of the experimental treatment period.

## PART IIIB

# STUDY FINDINGS INHALABLE HEROIN TRIAL

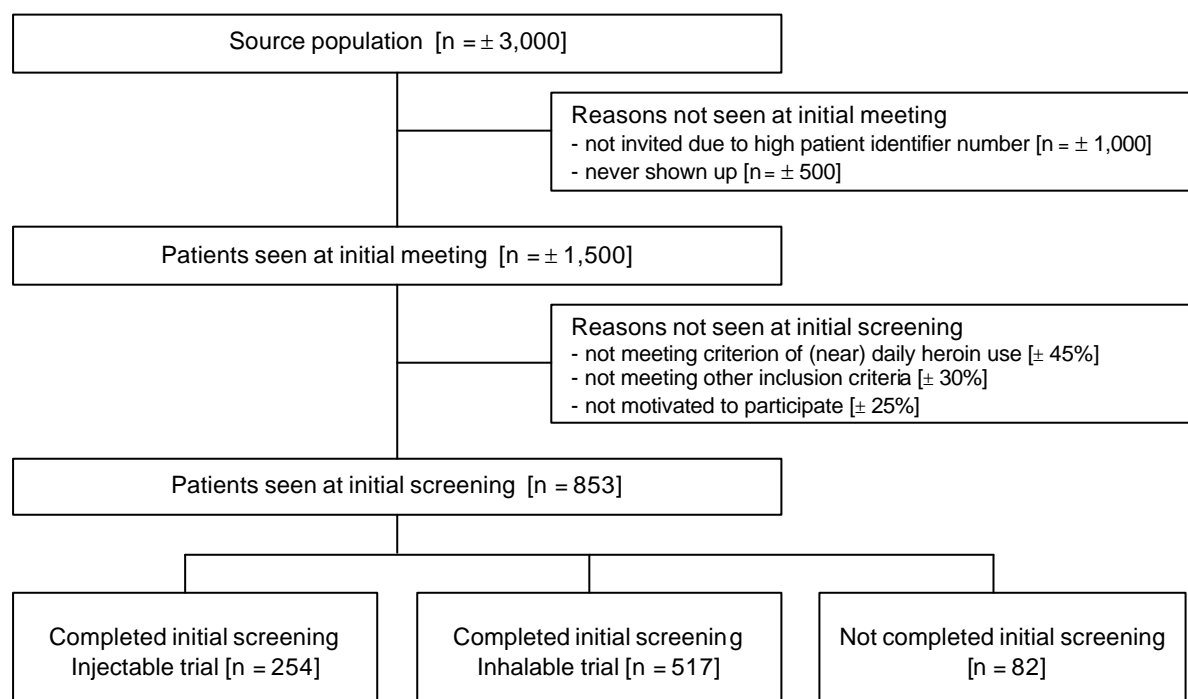


## Chapter 5<sup>B</sup>

### Selection and disposition of patients

As has been described in chapter 2, patients were recruited through an extensive selection procedure. The results of this selection process are described in this chapter. The first two steps of the selection process, the preselection of a source population on the basis of the treatment registration system, followed by the *initial meeting* with the physician, did not distinguish between heroin addicts that injected or inhaled heroin. During the *initial screening*, the third step of the recruitment process, the physician of the local treatment site decided whether the patient would participate in the trial on injectable heroin or the trial on inhalable heroin. Therefore, it was only from the initial screening that a distinction could be made between candidates for the trial on injectable heroin and the trial on inhalable heroin. Finally, since the first two steps of the selection process could not be fully documented, the results of these steps can only be presented by approximation. Figure 17 summarizes these first two steps of the selection process.

Figure 17. Flow diagram of first two steps of selection process



#### 5<sup>B</sup>.1 Selection procedure

##### *Step 1. Registration system*

In the first step of the selection procedure, the available information from the local methadone maintenance treatment registration data bases was analyzed in order to define the source population, which served as the basis for subsequent steps of the recruitment process. The source population amounted to approximately 3,000 methadone patients. These potential candidates were at least 25 years old and were registered in the city area of the local treatment site for at least three

years. In addition, they were heroin dependent for at least five years, had been prescribed an effective methadone dose for at least four consecutive weeks in the past five years and had had regular contact with the methadone maintenance program in the preceding six months. All potential candidates in the source population received a randomly assigned patient identifier number from the independent monitoring organization.

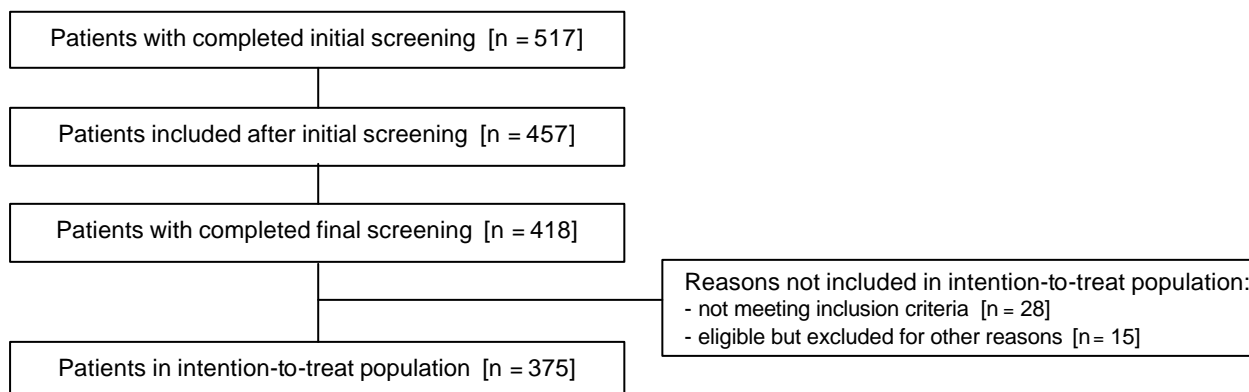
**Step 2. Initial meeting**

In each local treatment site, potential candidates were invited by the local study co-ordinator in the order of the patient identifier number for an initial meeting with the physician. Given the closing date of the randomization and the low prevalence of injecting in the remaining source population, approximately 1,000 potential candidates with a high patient identifier number were not invited anymore for the initial meeting of the selection procedure. Approximately 2,000 methadone clients from the source population were invited for this initial meeting. Around 500 of the invited candidates were never seen at the initial meeting. The major reasons for not attending the initial meeting were that potential candidates did not use heroin on a (near) daily basis, had left the methadone (maintenance) program, were incarcerated or hospitalized, had left the city or region, or had died. Almost half of all the methadone clients seen in the initial meeting ( $\pm 1,500$  of the  $\pm 2,000$  candidates invited), did not meet the inclusion criteria or were barred by one of the exclusion criteria. Of the candidates that were excluded at this phase of the selection process, 45% did not meet the criterion of (near) daily heroin use. After this first initial meeting, 853 candidates were eligible for the next step in the selection procedure, the initial screening by the local research team and the physician.

**Step 3. Initial screening**

All 853 candidates that passed the screening at the initial meeting were assessed by the local research team. Eighty-two potential candidates did not meet one or more of the inclusion criteria of poor functioning in the area of physical health, mental health or social functioning that were assessed in the interview by the research team or decided themselves not to continue the selection process and were not screened by the local physician. From the remaining 771 candidates, 254 were eligible for the trial on injectable heroin and 517 for the trial on inhalable heroin. In the remaining of this chapter the focus will be on the 517 candidates that were eligible for further screening in the inhalable heroin trial (see Figure 18).

Figure 18. Flow diagram of selection process of patients in the trial on inhalable heroin



Of the 517 candidates for whom the initial screening was completed, the majority met the criteria for inclusion and was not barred by any of the exclusion criteria (88.4%). The most common

reason for not including candidates at this step of the selection procedure was that candidates did not meet at least one of the inclusion thresholds indicative of poor functioning in the area of physical health, mental health or social functioning. Thus, 457 patients passed the initial screening and entered the qualification phase at the end of which they were invited for the second and final screening.

**Step 4. Final screening**

Four to eight weeks after the initial screening candidates were invited for their final screening. Thirty potential patients did not show up for their final screening and nine did not complete the final screening. Of the 418 candidates with a completed final screening the majority was eligible for randomization in the trial (85.3%). The major reason for not being included, was again related to not meeting the thresholds of poor functioning.

Three-hundred-and-ninety candidates were eligible for the trial investigating the effectiveness of inhalable heroin. However, 15 eligible candidates were excluded from the intention-to-treat population. At the beginning of the study, four patients were transferred from the control group (A) to the experimental group (B) in order to have a sufficient number of patients in the treatment site to be treated with co-prescribed heroin. These four patients were therefore excluded from the intention-to-treat population (CCBH, 1999b). Eleven patients were not randomized into the study because they were partner of candidates that were randomized into the trial already. Instead, they were offered to participate in the same type of treatment condition as their randomized partner (see also chapter 4). Thus, the intention-to-treat population for the inhalable trial consisted of 375 inhaling heroin dependent patients meeting all criteria for inclusion in the trial.

**Step 5. Randomization and ITT-sample**

In Table 15, an overview is given of the randomization of all 375 patients in the intention-to-treat population, divided by treatment site. One-hundred-and-thirty-nine inhaling heroin addicts were randomized in the control group (A), receiving an offer of 12 months treatment with methadone alone, 117 heroin addicts were randomized in the experimental group (B) receiving an offer of 12 months treatment with inhalable heroin plus oral methadone, and 119 patients were randomized into the group (C) receiving an offer of an initial period of six months treatment with methadone alone followed by six months treatment with inhalable heroin plus oral methadone.

Table 15. Intention-to-treat population and number of randomized patients per site (inhalable heroin)

Group	Amsterdam *		Rotterdam *		The Hague	Groningen	Heerlen	Utrecht	Total
	I	II	I	II					
A	22	16	18	13	21	13	18	18	139
B	19	13	16	13	17	11	14	14	117
C	16	14	18	10	20	12	15	14	119
Total	57	43	52	36	58	36	47	46	375

\* In Amsterdam and Rotterdam two groups of patients were recruited and included in the trial. Given that the study was conducted in two stages (see paragraph 2.4), these two groups could be treated in the already existing treatment sites.

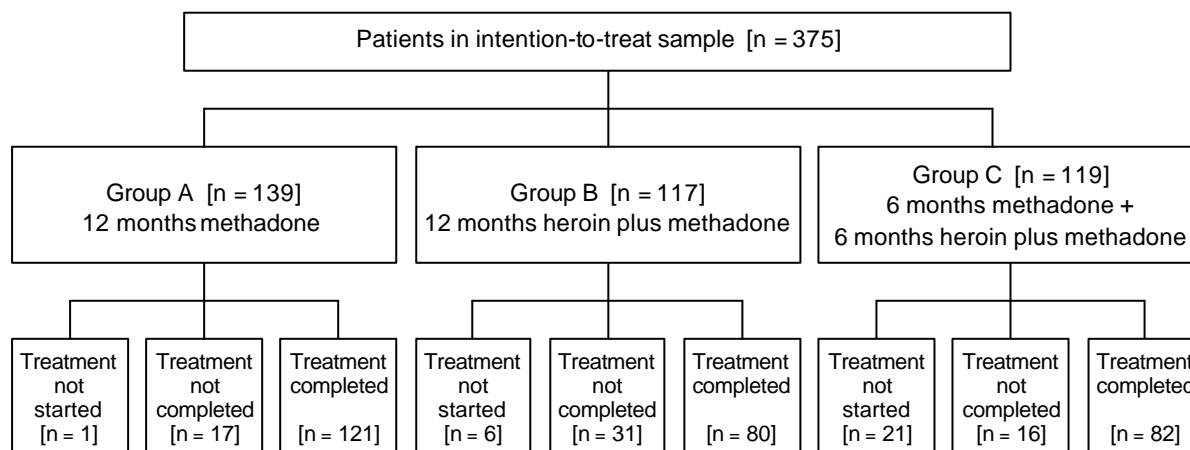
## 5<sup>B</sup>.2 Treatment participation and treatment completion

In this paragraph the treatment participation of patients will be described. Patients were defined as 'treatment completer' if they were still participating in the intended treatment condition in month 12 of the study as evidenced by the drug accountability data. Thus, patients in the control group A were considered to be treatment completer if they still received oral methadone in month 12. Similarly, patients in the experimental groups B and C were considered to be treatment completer if they still received medically co-prescribed heroin in month 12.

As is shown in Figure 19 all but one patients in the methadone group started their methadone treatment offer. This is because these patients were already taking part in a methadone maintenance treatment program at the time of randomization. In the 12th month after baseline, 17 additional patients were no longer receiving methadone maintenance treatment, i.e., 12.9% of the patients in the control condition had 'dropped out' the treatment regimen offered at the beginning of the trial. The remaining 87.1% of the control patients had completed treatment.

It can be seen from Figure 19 that six patients (5.1%) never started the co-prescribed heroin treatment for 12 months (group B). In the 12th month after baseline, 31 more patients (26.5%) were no longer treated with co-prescribed heroin. For almost half of the patients the termination of the heroin treatment was non-voluntary. They were expelled from the program (six patients), had become incarcerated (two patients), or were forced to stop the treatment for medical reasons (three patients) or because of problems with the alcohol policy of the treatment site (one patient). Fifteen patients ended the treatment with co-prescribed heroin voluntary for various personal reasons and for four persons the reasons why they did not complete treatment is unknown. The remaining 80 patients in group B were still treated with co-prescribed heroin at the end of the study and hence were considered as 'treatment completer' (68.4%).

Figure 19. Disposition of randomized patients



In a similar way it can be seen that 21 patients in group C (17.7%), who were treated with oral methadone for the first six months, did not start the treatment with co-prescribed heroin six months after baseline. For a minority this was due to non-voluntary reasons (four patients). Twelve patients did not start the heroin treatment for a variety of personal reasons and for five patients it is unknown why they did not start the treatment with heroin. In addition, another 16 patients were no longer treated with heroin in the 12th month after baseline (13.5%). Again, for almost half of the patients the termination of the heroin treatment was non-voluntary. They were

expelled from the program (two patients) or had become incarcerated (four patients). Seven patients ended the treatment with co-prescribed heroin voluntary for various personal reasons and for three persons the reasons why they did not complete treatment is unknown. The remaining 82 patients in group C were still treated with co-prescribed heroin at the end of the study and hence were considered as 'treatment completer' (68.9%).

The differences in treatment completion between on the one hand the 12 months methadone condition (87.1%) and on the other hand the 12 months co-prescribed heroin condition (68.4%) and the six months co-prescribed heroin condition (68.9%) are statistically significant (Treatment completion group A versus group B: Odds-Ratio=0.32; 95%-CI: 0.17-0.60; p=0.0004, and treatment completion group A versus group C: Odds-Ratio=0.33; 95%-CI: 0.17-0.61; p=0.0005).

Treatment completing patients in the control condition had been prescribed methadone on 330 days (median) during the experimental treatment year. The mean dosage of methadone prescribed to treatment completers in the control group was 67 mg (sd=23.2 mg).

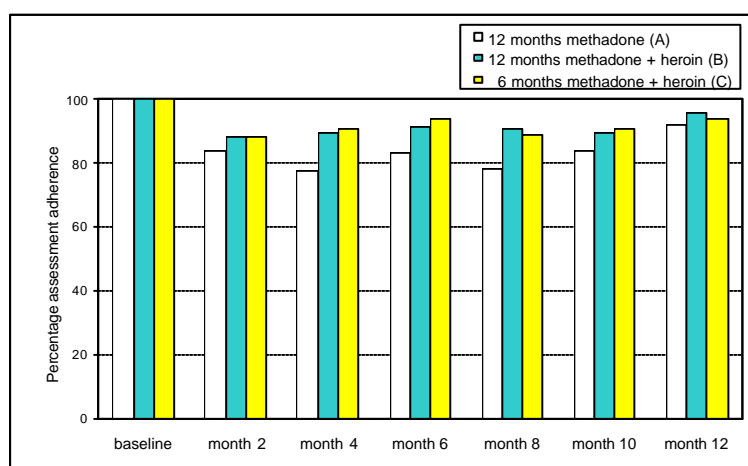
The mean methadone dosage in the experimental group B was 57 mg (sd=18.1 mg), which is significantly lower compared to the control group (t-value=3.23; df=193; p=0.001). In addition, treatment completing patients in the experimental group B visited the heroin dispensing units on 353 days (median) and 2.1 times per day (median). The mean heroin dosage prescribed was 263 mg per visit (sd=59.0 mg) and 547 mg per day (sd=173.5 mg).

Similarly, for treatment completing patients in group C the mean methadone dosage prescribed amounted to 66 mg (sd=27.4 mg) during the six months that co-prescribed heroin was offered. This methadone dosage does not differ from the dosage prescribed in the methadone control condition (67 mg) (t-value=0.26; df=201; p=0.80). In addition in this six months period, treatment completers in group C visited the heroin dispensing units on 169 days (median) and 2.1 times per day (median). The average heroin dosage prescribed was 252 mg per visit (sd=68.0 mg) and 539 mg per day (sd=151.2 mg).

### 5<sup>B</sup>.3 Adherence at two-monthly assessments

During the experimental phase of the study, patients were assessed by the local research team and physician every two months. Thus, in the period from randomization to the primary endpoint at month 12, six assessments were scheduled.

Figure 20. Adherence at two-monthly assessments



The majority of patients had participated in all six assessments. In control group A 61.2% of the patients adhered to all six assessments, while in the experimental groups B and C, 77.8% and 74.0% of the patients adhered to all six assessments, respectively. The number of patients without any post baseline assessment is low: five patients in group A (3.6%),

three patients in group B (2.6%), and one patient in group C (0.8%). Adherence at the month 12 endpoint amounted to 92.1% for group A, 95.7% for group B, and 94.1% for group C. This implied that the 'Last Observation Carried Forward' procedure at month 12 was conducted for eleven patients in group A, for five patients in group B, and for seven patients in group C. In Figure 20, the adherence at the six successive assessment-points is graphically displayed.

- The majority of eligible patients (96%) was included in the intention-to-treat population; n=375.
- Twelve-month treatment completion amounted to 87% in the control condition and to 68% in the experimental condition. The treatment completion in the experimental condition that was offered co-prescribed heroin treatment for six months (69%) was similar to the treatment completion for the experimental condition that was offered co-prescribed heroin treatment for 12 months (68%).
- Adherence at the month 12 endpoint-assessment amounted to 92% for patients in the methadone condition, to 96% for patients in the 12 months co-prescribed heroin condition, and to 94% for patients in the six months heroin condition.

## Chapter 6<sup>B</sup>

### Characteristics of the study population at baseline

#### 6<sup>B</sup>.1 Intention-to-treat population

##### 6<sup>B</sup>.1.1 Baseline characteristics

As described in chapter 5, the intention-to-treat population in the inhalable trial consisted of 375 subjects. The demographic background and other relevant baseline characteristics of these patients are displayed in Table 16.

Table 16. Characteristics intention-to-treat population at baseline (*n* = 375)

<i>Domain</i>	<i>Variable</i>	<i>% / mean (sd)</i>	
Background	- gender: male	79.7 %	
	- age	39.6 years (5.7)	
	- ethnicity: Dutch/ western	81.2 %	
	other	18.8 %	
	- education: low	77.1 %	
	middle	16.8 %	
- living arrangements, past 2 months:	high	6.1 %	
	alone	50.8 %	
	with partner/ child(ren)	24.9 %	
	other	24.3 %	
Physical health	- MAP-HSS score (0 – 40)	11.3 (7.3)	
	- lifetime number of hospitalizations: 0	15.7 %	
	1 – 5	69.9 %	
	> 5	14.4 %	
	- HIV -status positive (self report)	6.8 %	
	- % receiving prescribed medication for physical problems	25.1 %	
- additional need for treatment:	no	69.9 %	
	yes	30.1 %	
Psychiatric status	- SCL-90 total score (0 – 360)	72.7 (59.9)	
	- lifetime number of hospitalizations: 0	87.5 %	
	1 – 5	12.3 %	
	> 5	0.3 %	
	- ever attempted to commit suicide	22.9 %	
	- % receiving p rescribed medication for psychiatric problems	34.7 %	
	- DSM-IV diagnosis, lifetime:	any mood disorder	21.5 %
		any anxiety disorder	23.9 %
		any psychotic disorder	5.1 %
		any of these lifetime disorders	37.3 %
	- DSM-IV diagnosis, past six months:	any mood disorder	17.4 %
		any anxiety disorder	19.6 %
		any psychotic disorder	4.3 %
any of these recent disorders		30.6 %	
- additional need for treatment:	no	71.8 %	
	yes	28.2 %	

*(continued on next page)*

Table 16. *Continued*

Domain	Variable	% / mean (sd)		
Social functioning	- usual employment status, past 3 years:	part-/ full-time employed unemployed other (e.g. incarcerated)	12.3 % 73.5 % 14.2 %	
	- major source of income, past month:	employment welfare/ public assistance illegal activities other	7.8 % 62.0 % 25.9 % 4.3 %	
	- debts (in €) (70.5%) *		2,730 (median)	
	- usual housing arrangement, past month:	home environment outside, public place, shelter	92.5 % 7.5 %	
	- lifetime number of charges for crimes against property:	0 1 – 10 11 – 50 > 50	18.9 % 36.5 % 27.6 % 17.0 %	
	- number of years ever incarcerated:	0 (years) 0 – 1 2 – 5 > 5	18.0 % 34.4 % 32.8 % 14.8 %	
	- days engaged in illegal activities, past month:	0 (days) 1 – 5 6 – 30	39.7 % 8.3 % 52.0 %	
	- days contact with non-drug-using person, past month:	0 (days) 1 – 5 6 – 30	21.9 % 15.7 % 62.4 %	
	Substance use	- years of regular use:	heroin (100 %) methadone (100 %) cocaine (91.2 %) amphetamines (33.6 %) benzodiazepines (64.2 %) alcohol ( $\geq$ 5 gl./day) (66.4 %) poly drug use (100 %)	16.7 years (5.9) 12.4 years (6.3) 9.2 years (6.1) 4.7 years (5.8) 8.2 years (7.1) 10.7 years (8.7) 17.3 years (6.6)
		- days of substance use, past month:	heroin (100 %) methadone (99.5 %) cocaine (84.3 %) amphetamines (3.7 %) benzodiazepines (59.1 %) alcohol ( $\geq$ 5 gl./day) (38.4 %) poly drug use (99.5 %)	25.8 days (6.4) 29.1 days (3.6) 17.4 days (10.4) 2 days (median) 19.5 days (11.7) 20.8 days (10.8) 28.8 days (3.5)
		- lifetime number of drug overdoses:	0 1 – 5 > 5	70.4 % 25.3 % 4.3 %
		- number of earlier addiction treatments:	outpatient methadone (100 %) detoxification (45.1 %) outpatient drug-free (8.3 %) inpatient drug-free (28.1 %) any drug-free treatment (57.8%) other drug treatments (24.0 %) any alcohol treatment (6.9 %)	2 (median) 2 (median) 1 (median) 2 (median) - 1 (median) 3 (median)
		- money (in €) spent in past month on:	drugs alcohol	871 (745) 68 (59)
		- additional need for treatment:	no yes	31.6 % 68.4 %

\* The percentages between parentheses in the middle column represent subjects with a positive value on the variable in question (e.g. subjects with debts).

### *Sociodemographic background*

The subjects in the intention-to-treat population (see Table 16) were predominantly male and from a Dutch/western background, with a sizeable subgroup with Surinamese background (12.6%) and only few participants from Dutch Antillian (1.1%), Moroccan (2.4%), Turkish (0.5%), and other (2.2%) background<sup>1</sup>. The mean age in the sample amounted to 39.6 years (range: 27-56 years). The participants had typically received lower level education only, and were living alone.

### *Physical health*

On the MAP-HSS, 66.1% had a score of 8 or higher, the inclusion-threshold used in the study for the area of physical health. The mean MAP-HSS score amounted to 11.3 (range: 0-40). Based on self-report, 6.8% had a positive HIV-status, and a quarter currently received prescribed medication for a physical health problem. Subjectively, nearly one-third of the participants reported to experience a (moderate, considerable or extreme) need for additional treatment in this domain.

### *Psychiatric status*

SCL-90 total scores in the sample ranged from 0-293, with a mean of 72.7. Among the males and females, 60.9% and 56.6% reached the inclusion threshold score of 41 and 60, respectively. In the sample, 12.5% of the patients had at least once in their lives received inpatient treatment for a psychiatric problem. In addition, nearly a quarter had ever committed a suicide attempt, and more than one-third currently received prescribed medication for a psychiatric problem. DSM-IV mood and anxiety disorders were common on both lifetime and recent (i.e. past six months) basis. Lastly, more than one quarter of the sample subjectively reported a (moderate, considerable or extreme) need for additional treatment for psychiatric problems.

### *Social functioning*

Most subjects had been unemployed during the (three) years prior to the baseline interview, and currently received income primarily from public assistance or from illegal activities. Among those with financial debts (70.5%), the median debts amounted to €2,730. In the month prior to the interview, 7.5% of the subjects had usually slept outside, in a public place or a homeless shelter.

Among those who had ever (at least once) been charged for a crime against property, the number of charges ranged from 1 to more than 100, with a median of 15 charges (not in table). For those ever incarcerated, the years in detention ranged from 1 to more than 8 years, with a median of nearly 2 years (22 months). In the month prior to the interview, 52.0% had engaged in illegal activities to obtain money for 6 or more days, one of the inclusion thresholds in the social area. Lastly, more than one-third of the participants had had personal contact (of at least half an hour duration) for less than 6 days in the previous month with a non-drug-using person (excluding treatment staff), the other inclusion threshold in the social area.

### *Substance use*

In addition to heroin and methadone (both 100%), most participants had ever in their lives used cocaine (91.2%), large quantities of alcohol (i.e. at least five standard glasses a day) (66.4%), benzodiazepines (64.2%), and amphetamines (33.6%) on a regular (i.e. three or more days a week) basis. The mean number of years of regular heroin use amounted to 16.7 years. In addition, among those with "lifetime" regular cocaine use, cocaine had been used on a regular basis for 9.2 years. All participants were poly drug users. On the average, they had used more than one substance a day on a regular basis for 17.3 years.

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<sup>1</sup> To determine ethnicity, the definition of the Central Bureau of Statistics of the Netherlands (CBS, 1999) was used.

All subjects had at least once in their lives been in outpatient substitution treatment (including the present methadone maintenance program they were recruited from), and had done so with a median of 2 times (i.e. two uninterrupted series of methadone maintenance treatment). On average, participants had used methadone on a regular basis for 12.4 years. In addition, nearly half had ever participated in a detoxification program, and more than a quarter in an inpatient drug-free program. Approximately one in fourteen subjects had ever received treatment specifically for alcohol problems.

In the month preceding the baseline interview, all participants had used heroin, 99.5% methadone, and 84.3% cocaine. Among the cocaine users, smoking (chasing/basing) (94.9%) was a much more common route of cocaine administration than injecting (4.8%). Heroin and methadone had been used on a daily or nearly daily basis, and cocaine on slightly more than half the days (mean: 17.4 days). Subjects who had used illicit drugs in the previous month had spent an average of €871 on drugs. Among the patients with considerable alcohol use, the money spent on alcohol amounted to an average of €68. Lastly, more than two-thirds of the sample subjectively reported a (moderate, considerable or extreme) need for additional treatment for drug problems.

### 6<sup>B</sup>.1.2 Inclusion profiles

As described in the first chapter, a patient could be included in the study on the basis of his physical health status, psychiatric functioning, and/or social functioning. From the 375 patients in the inhable trial, 66.1%, 60.0% and 70.4% were included on the basis of their functioning in these problem areas, respectively. Combining these three outcome areas into seven types of inclusion, each patient was admitted to the study according to a specific inclusion profile.

Table 17. Inclusion profile of the participants (*n* = 375)

<i>Inclusion profile</i>	
Health <sup>+</sup>	66.1 %
Psychiatric <sup>+</sup>	60.0 %
Social <sup>+</sup>	70.4 %
Health <sup>+</sup> Psychiatric <sup>+</sup> Social <sup>+</sup>	28.8 %
Health <sup>+</sup> Psychiatric <sup>+</sup> Social <sup>-</sup>	18.1 %
Health <sup>+</sup> Psychiatric <sup>-</sup> Social <sup>+</sup>	11.2 %
Health <sup>+</sup> Psychiatric <sup>-</sup> Social <sup>-</sup>	8.0 %
Health <sup>-</sup> Psychiatric <sup>+</sup> Social <sup>+</sup>	9.6 %
Health <sup>-</sup> Psychiatric <sup>+</sup> Social <sup>-</sup>	3.5 %
Health <sup>-</sup> Psychiatric <sup>-</sup> Social <sup>+</sup>	20.8 %

As can be seen in Table 17, the largest subgroup (28.8%) consisted of patients included on all three domains, followed by patients included on the social domain only (20.8%). Patients were rarely admitted to the study on the basis of their health status only (8.0%) or their psychiatric status only (3.5%). In nearly half the cases (46.9%), combined physical health and psychiatric problems were responsible for inclusion.

### 6<sup>B</sup>.1.3 Comparability of the treatment groups

To investigate the comparability of the treatment groups, the baseline characteristics of the subjects randomized to the treatment conditions A (12 months methadone alone), B (12 months co-prescribed heroin), and C (six months methadone alone, followed by six months co-prescribed heroin) were compared on key variables in the areas of demographic background (gender, age, ethnicity), components of the primary outcome measure (MAP-HSS, SCL-90, days illegal activities, days contact non-drug-using person), and lifetime and current substance use variables (years of use, and days of use in past month for heroin, methadone, cocaine, amphetamines, benzodiazepines, alcohol, and poly drug use). No significant differences (Bonferroni correction; overall  $p$ -value  $<0.10$ ) between the treatment groups were found on any of these key variables.

### 6<sup>B</sup>.1.4 Baseline characteristics across the six study sites

Similarly, the baseline characteristics were compared between the study populations in the six study sites involved in the study. Significant differences (Bonferroni correction; overall  $p$ -value  $<0.10$ ) were found for ethnicity and on several substance use variables. The proportion of subjects with a non-Dutch ethnic background was particularly low in the site of Heerlen (2.1%), and relatively high in Rotterdam (26.1%) and The Hague (25.9%). The mean number of years of regular (i.e. at least three days a week) methadone use was significantly higher in the site of The Hague (14.8 years) than in the other sites (10.5-13.7 years). In addition, the duration of cocaine use was longest in the site of Amsterdam (10.7 years), compared to the sites in other cities (6.1-9.8 years). With respect to recent substance use, the number of days of heroin use in the month prior to the baseline interview was significantly lower in the site of Groningen (21.7 days) than in the other sites (25.2-27.7 days). Similarly, recent cocaine use was less frequent in the sites of The Hague (13.4 days) and Heerlen (12.3 days) than in the other sites (18.6-20.8 days).

### 6<sup>B</sup>.1.5 Comparison of the study populations in the injectable and inhalable heroin trials

The same set of key variables was used to compare the baseline characteristics of the study population in the injectable and inhalable trial. The results are displayed in Table 18.

Table 18. Baseline characteristics of the study population: injectable vs. inhalable trial ( $n = 549$ )

Variable		Injectable trial ( $n = 174$ )	Inhalable trial ( $n = 375$ )	$P = *$
- gender:	male	82.2 %	79.7 %	0.50
- age		38.5 years	39.6 years	0.04
- ethnicity:	Dutch/ western	95.4 %	81.2 %	<u>0.00</u>
- MAP-HSS score (0 – 40)		11.5	11.3	0.75
- SCL-90 total score (0 – 360)		74.3	72.7	0.78
- days engaged in illegal activities, past month		12.1 days	10.4 days	0.10
- days contact with non-drug-using person, past month		13.0 days	15.5 days	0.04

(continued on next page)

Table 18. *Continued*

Variable		<i>Injectable trial</i> (n = 174)	<i>Inhalable trial</i> (n = 375)	P = *
- years of regular use: **	heroin	15.9 years	16.7 years	0.16
	methadone	12.1 years	12.4 years	0.58
	cocaine	10.5 years	9.2 years	0.02
	amphetamines	5.6 years	4.7 years	0.29
- days of substance use, past month: **	heroin	25.9 days	25.8 days	0.78
	methadone	29.1 days	29.1 days	0.38
	cocaine	18.7 days	17.4 days	0.17

\* The p-values represent values before Bonferroni correction; underlined values are significant after Bonferroni correction, utilizing an overall p-value of p<0.10 (14 tests).

\*\* The mean values across the substances were calculated with the exclusion of patients who had never used the substance on a lifetime basis or in the past month, respectively.

As can be seen in the table, the study populations in both trials were quite similar on nearly all key variables. The only significant difference (Bonferroni correction; overall p-value <0.10) occurred with regard to the ethnicity of the subjects. The inhalable trial included more subjects from a non-Dutch ethnic (particularly Surinamese) background than the injectable trial.

## 6<sup>B</sup>.2 Treatment completers

As described in chapter 5<sup>B</sup>, the population of treatment completers in the trial on inhalable heroin consisted of 283 subjects (75.5% of the 375 subjects in the intention-to-treat population). These 283 subjects were compared with the remaining 92 subjects in the intention-to-treat population who did not complete the (methadone alone or co-prescribed heroin) treatment, utilizing the same set of baseline variables as displayed in paragraph 6<sup>B</sup>.1.1. None of the baseline characteristics in the areas of demographic background, physical health status, psychiatric status, social functioning, and substance use showed significant differences (Bonferroni correction; overall p-value for each domain separately: p<0.10) between the two sub-populations. Hence, overall, the baseline characteristics of the treatment completers in the intention-to-treat population did not differ from those who did not complete treatment.

- As intended, the study population consisted of chronically poor functioning, treatment-resistant heroin dependent patients. The participants had a long history of poly drug use, and participation in addiction treatments, including long-term methadone maintenance treatment. Despite earlier treatment efforts, patients had serious problems and experienced treatment needs with regard to their physical health, psychiatric status, and social functioning.
- Within each of these domains of functioning, approximately two-thirds of the patients were included in the study. Inclusion occurred most often on the basis of poor functioning in more than one problem domain.
- Randomization was successful, as indicated by the similarity in background characteristics, addiction history, additional problems, and inclusion profiles between the subjects in the three treatment groups.
- The trial on inhalable heroin included more subjects from an ethnic non-Dutch background than the trial on injectable heroin. On all other investigated variables, the subjects in the two trials were comparable at the start of the study.

## Chapter 7<sup>B</sup>

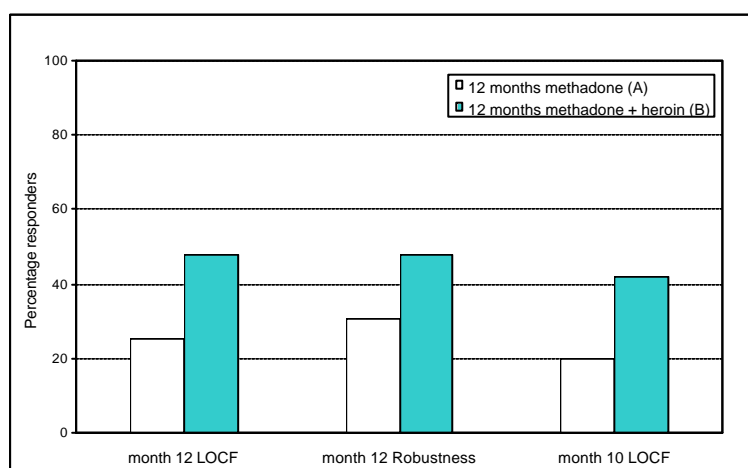
# Effectiveness of co-prescribed inhalable heroin versus methadone alone treatment

### 7<sup>B</sup>.1 Treatment response after 12 months

#### 7<sup>B</sup>.1.1 Treatment response after 12 months in the intention-to-treat population

As described in paragraph 2.9.3, patients were considered as responders if they showed at least 40% improvement at the month 12 outcome assessment, compared to their situation at baseline, in at least one of the areas in which they functioned poorly at the start of the study (i.e. on the basis of which they were included at baseline), while these improvements should not have gone at the expense of similar (40% or more) deterioration in functioning in any of the other outcome domains. The primary study question, into the effectiveness of co-prescribed heroin versus methadone alone treatment after 12 months, was investigated by testing the difference in percentage responders between the experimental and control condition in the intention-to-treat population, using a logistic regression model, with "treatment site" as the only covariate, and applying the last observation carried forward method to deal with missing endpoint-assessments.

Figure 21. Effectiveness of co-prescribed inhalable heroin versus methadone alone treatment ( $n = 256$ )



Note: LOCF = Last Observation Carried Forward.

In the heroin group<sup>1</sup>, the percentage responders amounted to 47.9%, compared to 25.2% in the methadone group (see Figure 21: left-hand bars). Controlling for differences in response between the treatment sites, the difference of 22.7% corresponded with an adjusted Odds-Ratio of 2.77 (95%-CI: 1.63-4.71;  $p=0.0002$ ). Neither "treatment site", nor the treatment-by-site interaction were significantly related to treatment response in the

logistic regression model. As indicated by the Hosmer and Lemeshow goodness-of-fit test, the data fitted the regression model ( $\chi^2=6.15$ ;  $df=7$ ;  $p=0.52$ ).

<sup>1</sup> For reasons of readability, the term "heroin group" is used in this chapter to refer to the treatment group receiving twelve months of co-prescribed heroin and methadone, whereas the term "methadone group" refers to the methadone alone treatment group. Where in this chapter the twelve and six months heroin groups are distinguished, the intended treatment duration of the treatment groups is explicitly mentioned.

Table 19. Changes in patient status from baseline to month 12 (mean scores)

Outcome domain	Group	ITT-population (n = 256)		Non-responders (n = 165)		Responders (n = 91)	
		baseline	month 12	baseline	month 12	baseline	month 12
MAP-HSS (0-40)	Group A *	11.6	11.3	10.9	12.1	13.4	9.0
	Group B *	10.6	9.3	10.4	12.7	10.9	5.6
SCL-90 (0-360)	Group A	70.7	66.7	70.3	75.7	71.6	40.0
	Group B	68.4	50.1	67.6	70.0	69.3	28.4
Days illegal activities (0-30)	Group A	11.2	7.8	10.2	8.5	14.1	6.0
	Group B	11.4	3.6	11.3	4.9	11.6	2.2
Days without personal contact with non-drug users (0-30)	Group A	13.7	12.2	14.0	14.0	12.7	6.8
	Group B	14.2	11.8	13.7	13.5	14.7	9.9
Days cocaine use (0-30)	Group A	15.2	16.5	14.5	17.2	17.2	14.5
	Group B	15.2	11.9	15.8	13.3	14.6	10.3
Days amphetamine use (0-30)	Group A	0.1	0.1	0.1	0.2	0.1	0.0
	Group B	0.1	0.4	0.1	0.6	0.1	0.1
Days controlled environment **	Group A		1.4		1.8		0.2
	Group B		1.9		3.5		0.3

\* Group A: ITT-population n=139; non-responders n=104; responders n=35; Group B: ITT-population n=117; non-responders n=61; responders n=56.

\*\* No baseline data are presented, because patients with more than seven days in a controlled environment in the month prior to baseline were – for reasons of validity – excluded from the baseline assessments.

To illustrate the clinical meaning of the observed response rates, Table 19 shows the changes in mean scores from baseline to month 12 on the scales and items used as components of the multi-domain outcome index of response in the trial.

Among the responders (right-hand column), considerable changes from baseline to month 12 were observed for most scales and items. For example, the mean MAP-HSS score decreased in the methadone alone group (A) from 13.4 at baseline to 9.0 at the month 12 assessment, and in the co-prescribed heroin group (B) from 10.9 at baseline to 5.6 at month 12. The mean score of 5.6 on the MAP is quite comparable to the mean score of 4.8 found for the general population in the Netherlands (see paragraph 2.9.1). Similarly, the SCL-90 total scores among responders decreased to mean values (40.0 and 28.4), comparable to those found in the general Dutch population (males: 27.2; females: 38.9). In the social domain, a decrease from baseline to month 12 was observed for both the number of days of illegal activities, and – to a lesser extent – for the number of days without personal contact with non-drug-users. A similar decrease occurred for number of days of cocaine use among the responders in the heroin group (B). Amphetamine use at baseline was rare (3.7%), and among the responders limited to an average of less than one day a month.

Among the non-responders (middle column), on the other hand, changes from baseline to month 12 were absent on nearly all scales and items. The only exception occurred with regard to the number of days of illegal activities in the previous month. This variable showed a decrease not only among the responders in both treatment groups, but also among the non-responders in the co-prescribed heroin group.

### *Robustness of the findings*

At the month 12 assessment-point, data were obtained from 95.7% of the patients in the heroin group, and from 92.1% in the control group. To investigate the robustness of the observed 22.7% difference in percentage responders between the two groups, the (4.3%) missing endpoint-

assessments in the heroin group were considered as non-responders, and those in the control group (7.9%) as responders. In this most conservative scenario, treatment response remained 47.9% in the heroin group, and increased from 25.2% to 30.9% in the methadone group (see Figure 21: middle bars). Hence, the difference in response decreased from 22.7% to 17.0%. This difference, however, was still significant in the logistic regression model, with an adjusted Odds-Ratio for treatment group of 2.07 (95%-CI: 1.24-3.45;  $p=0.0056$ ), and no significant treatment-by-site interaction. Also in this analysis, the data fitted the model ( $\chi^2=3.66$ ;  $df=8$ ;  $p=0.89$ ).

### *Anticipation effects*

In the follow-up phase of the study, the treatment with heroin could only be reinstated in patients who had responded to the heroin treatment at the end of the experimental phase. To investigate the influence of the anticipation of such a reinstatement (see paragraph 3.2.6) on the results of the study, the month 12 analysis described above was similarly conducted for the month 10 assessment-point. After 10 months, the percentage responders in the heroin group, utilizing LOCF, amounted to 41.9%, and in the methadone group to 20.1% (see Figure 21: right-hand bars). As in the main analysis of the month 12 effects, the difference in percentage responders between the treatment groups of 21.8%, when controlled for "treatment site", and given non-significant relationships between treatment site and response, and between the treatment-by-site interaction and response, was significant at the month 10 assessment-point (adjusted OR=2.95; 95%-CI: 1.68-5.16;  $p=0.0002$ ). Again, the goodness-of-fit test indicated that the data fitted the regression model ( $\chi^2=7.96$ ;  $df=8$ ;  $p=0.44$ ).

### 7<sup>B</sup>.1.2 Treatment response after 12 months among the treatment completers

The 234 treatment completers in the trial on inhalable heroin – consisting of patients who still participated in treatment (i.e. received methadone in the control condition, and co-prescribed heroin in the experimental condition) in month 12 – involved 121 subjects in the 12 months methadone alone treatment group, 80 subjects in the 12 months co-prescribed heroin group, and 82 subjects in the six months co-prescribed heroin group (see Chapter 5). Analogous to the primary outcome analyses in the intention-to-treat population – applying LOCF for the missing endpoint-assessments – the percentage responders after 12 months was determined among the treatment completers in the treatment groups A and B. The response rate among the treatment completers in the 12 months co-prescribed heroin group amounted to 51.3%, compared to 27.3% in the 12 months methadone alone group. The difference of 24.0% was statistically significant in a good fitting logistic regression model, in which treatment site was the only covariate, and in which neither "treatment site", nor treatment-by-site interaction were significantly related to response (adjusted OR=2.82; 95%-CI: 1.55-5.13;  $p=0.0007$ ).

- After twelve months of treatment, the experimental treatment with co-prescribed inhalable heroin was significantly more effective than the control treatment with methadone alone. The observed difference in percentage responders between the experimental group and the control group amounted to 22.7%.
- The observed difference in percentage responders decreased from 22.7% to 17.0% when a worst-case scenario was applied for the missing endpoint-assessments. However, the difference was still statistically significant.

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- The observed difference found after twelve months of treatment was also statistically significant two months earlier, after ten months of treatment. Hence, anticipation effects, with regard to a possible reinstatement of the heroin treatment after the experimental phase for responders in the heroin condition, can not be held responsible for the observed effect after twelve months of treatment.
- In the sub-population of treatment completers, the difference in percentage responders between the treatment groups was similar to the difference observed in the intention-to-treat population.
- The observed difference in percentage responders between the treatment groups after twelve months of treatment was not significantly different across the six participating sites.

## 7<sup>B</sup>.2 Treatment response after six months

The six months effectiveness was investigated in the trial on inhalable heroin by (1) comparing the percentage responders in the 12 months co-prescribed heroin group (B) and 12 months methadone alone treatment group (A) halfway their intended treatment period, i.e. six months after baseline, and (2) comparing the percentage responders in the 12 months co-prescribed heroin group (B) and six months co-prescribed heroin group (C) at the end of their intended treatment period, ie. 12 months after baseline. As argued before, the first type of investigation informed about the effects after six months of ongoing heroin treatment, compared to those of ongoing methadone treatment, whereas the second type of investigation pertained to the question whether the month 12 effects of heroin treatment could already be achieved after six months. Analogous to the investigations into the month 12 effects described in the previous paragraph, both analyses were conducted in the intention-to-treat population, applying LOCF, and using a logistic regression model.

### *Effectiveness of co-prescribed heroin versus methadone alone treatment after six months*

Halfway the intended treatment period, at the month 6 assessment-point, 38.5% of the participants in the heroin group were responders, compared to 27.3% in the methadone group (see Figure 22: left-hand bars).

Figure 22. Effectiveness of co-prescribed inhalable heroin versus methadone alone treatment after six and twelve months ( $n = 256$ )



Compared to the response percentages which were reported earlier for month 12 (right-hand columns), the difference in response between the heroin and methadone group increased from 11.2% after six months to 22.7% after twelve months.

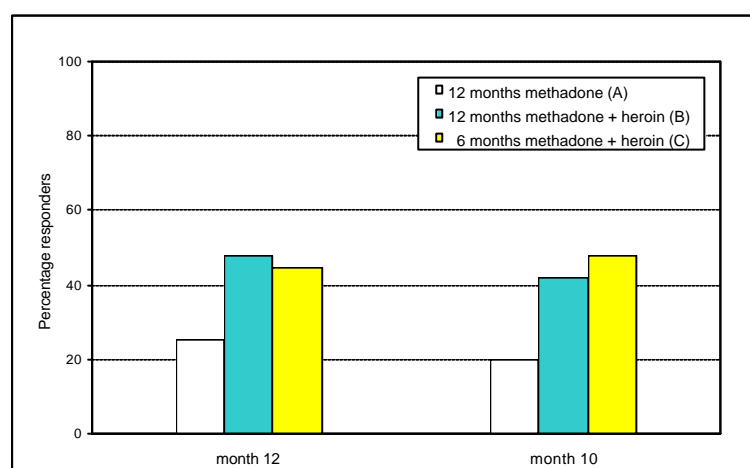
Adjusted for differences in response between the treatment sites, the Odds-Ratio corresponding with this difference of 11.2% was 1.68 (95% -CI: 0.99-

2.86;  $p=0.0547$ ). Hence, the difference in treatment response at month 6 between the treatment groups did not reach statistical significance. In addition, treatment response at month 6 was not significantly related to either treatment site or treatment-by-site interactions. According to the Hosmer and Lemeshow goodness-of-fit test, the data fitted the regression model ( $\chi^2=7.94$ ;  $df=8$ ;  $p=0.44$ ).

#### *Effectiveness of twelve versus six months of co-prescribed heroin treatment*

At the end of the intended six months co-prescribed heroin treatment period, 44.5% of the subjects in group C were responders, compared to 47.9% in group B, the group receiving 12 months of co-prescribed heroin treatment (see Figure 23: left-hand bars). The difference of 2.4% between the groups was not significant (adjusted OR=1.12; 95%-CI: 0.67-1.89;  $p=0.66$ ). As in the previous analyses, neither treatment site nor treatment-by-site interactions were significantly related to response, whereas the data fitted the logistic regression model ( $\chi^2=1.84$ ;  $df=8$ ;  $p=0.99$ ).

Figure 23. Effectiveness of twelve versus six months of co-prescribed heroin treatment ( $n = 236$ )



Compared to group A at month 12 (25.2% responders; left-hand bars in Figure 23), the response rate in group C at month 12 was significantly higher (adjusted OR=2.43; 95%-CI: 1.43-4.14;  $p=0.0011$ ). In the logistic regression model, there was a good fit of the data ( $\chi^2=4.37$ ;  $df=8$ ;  $p=0.82$ ), and the model did not yield significant relationships between response and treatment site or treatment-by-site interaction.

#### *Anticipation effects*

To investigate whether the lack of difference between the treatment groups B and C at the month 12 assessment-point may have been caused by anticipation effects in both groups (see paragraph 3.2.6), the difference in percentage responders between both groups was also investigated at the month 10 assessment-point (Figure 23: right-hand columns). With a response percentage of 47.9% in group C, and of 41.9% in group B, using treatment site as covariate, and in the absence of significant relationships between response, treatment site and treatment-by-site interaction term, the difference in response between group B and C was again not significant (adjusted OR=0.76; 95%-CI: 0.45-1.28;  $p=0.30$ ).

#### *Effectiveness of six months of co-prescribed heroin treatment among treatment completers*

Among the treatment completers in group C ( $n=82$ ), the response rate amounted to 51.2%, compared to 51.3% among the treatment completers in group B ( $n=80$ ), and 27.3% among the completers in group A ( $n=121$ ). The difference of 0.1% between the treatment groups C and B was not statistically significant. Between the treatment completers in groups C and A, the difference in percentage responders of 23.9% was statistically significant. The difference corresponded with an adjusted Odds-Ratio of 2.80 (95%-CI: 1.55-5.08;  $p=0.0007$ ) in a logistic

regression model with treatment site as covariate, no significant relationships between response and treatment site or treatment-by-site interaction, and good fitting data ( $\chi^2=5.17$ ;  $df=7$ ;  $p=0.64$ ).

- After six months of treatment, i.e. halfway the intended twelve months treatment period, the effectiveness of the experimental treatment with co-prescribed inhalable heroin was not statistically significantly different from that of the control treatment with methadone alone.
- The observed difference in percentage responders between the experimental group and the control group amounted to 11.2% after six months and further increased to 22.7% after twelve months of treatment.
- Comparing the co-prescribed heroin groups with an intended duration of six months and twelve months at the end of the treatment period, the six months group was just as effective as the twelve months group.
- This lack of difference in percentage responders between the six and twelve months treatment groups was already present two months earlier, after ten months of treatment, and, hence, could not be attributed to anticipation effects with regard to a possible reinstatement of the heroin treatment after the experimental phase for responders in the heroin condition.
- The lack of difference between the six and twelve months treatment groups was observed for both the intention-to-treat population and among the treatment completers.
- Both halfway the intended twelve months treatment, and at the end of the twelve months treatment period, the results did not significantly differ across the six participating sites.

### 7<sup>B</sup>.3 Exploratory analyses of effectiveness

#### 7<sup>B</sup>.3.1 Improvement and deterioration as components of treatment outcome

In the present trial, patients were considered as responders if they showed at least 40% improvement after twelve months of treatment, compared to their situation at baseline, in at least one of the areas in which they functioned poorly at the start of the study (i.e. on the basis of which they were included at baseline), and these improvements should not have gone at the expense of similar deterioration in functioning in any of the other outcome domains (see paragraph 2.9.3). Hence, non-responders in the trial could consist of (1) subjects who had improved 40% or more on at least one of the outcome domains, but had concurrently deteriorated on at least one of the other outcome domains, (2) subjects who had neither improved, nor deteriorated according to the criteria, and (3) subjects who had not shown improvement (of 40% or more) on any of the outcome domains, but who had deteriorated on at least one of the outcome domains. Table 20 provides an overview of the percentage of patients in the three treatment groups in each of these categories.

As indicated by Table 20, the observed effect in terms of percentage responders in the co-prescribed heroin groups (47.9% and 44.5%, versus 25.2% in the methadone alone group) did not go at the expense of an increased percentage of non-responders who did not improve and deteriorated (17.1% and 15.1%, versus 34.5% in the methadone alone group).

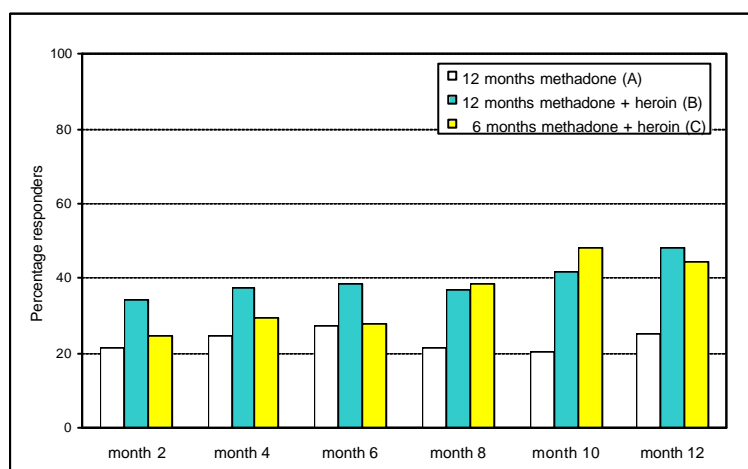
Table 20. Types of non-responders in terms of improvement and deterioration ( $n = 375$ )

Treatment group	Responders (%)	Non-responders (%)		
	Improved + not deteriorated	Improved + deteriorated	Not improved + not deteriorated	Not improved + deteriorated
12 months methadone (A)	25.2 %	20.1 %	20.1 %	34.5 %
12 months methadone + heroin (B)	47.9 %	14.5 %	20.5 %	17.1 %
6 months methadone + heroin (C)	44.5 %	12.6 %	27.7 %	15.1 %

### 7<sup>B</sup>.3.2 Response at subsequent assessments

To investigate the occurrence of response in the course of the experimental phase of the trial, the percentage responders in the intention-to-treat population was calculated for each assessment-point, using LOCF for each missing assessment during the trial. The results are displayed in Figure 24.

Figure 24. Percentage responders at subsequent assessments



Two months after baseline, at the first assessment-point, response occurred in 34.2% of the participants in group B, compared to 21.6% in group A. Response in group B remained stable around 34-38% in the following six months, and subsequently increased from month 8 (36.8%), through month 10 (41.9%) to the endpoint at month 12 (47.9%).

In group A, the 12 months methadone group, on the other hand, following the initial 21.6% response at month 2, the response rate remained largely unchanged during the subsequent ten months of the trial, amounting to 25.2% at month 12.

Notably, during the first six months in the trial, i.e. at the time that subjects in group C received methadone alone, the response rates observed in group C were very similar to those found in group A. Following the transition in group C to co-prescribed heroin as of month 6, on the other hand, the response rates in group C were comparable to those during the last six months in group B, the 12 months heroin group.

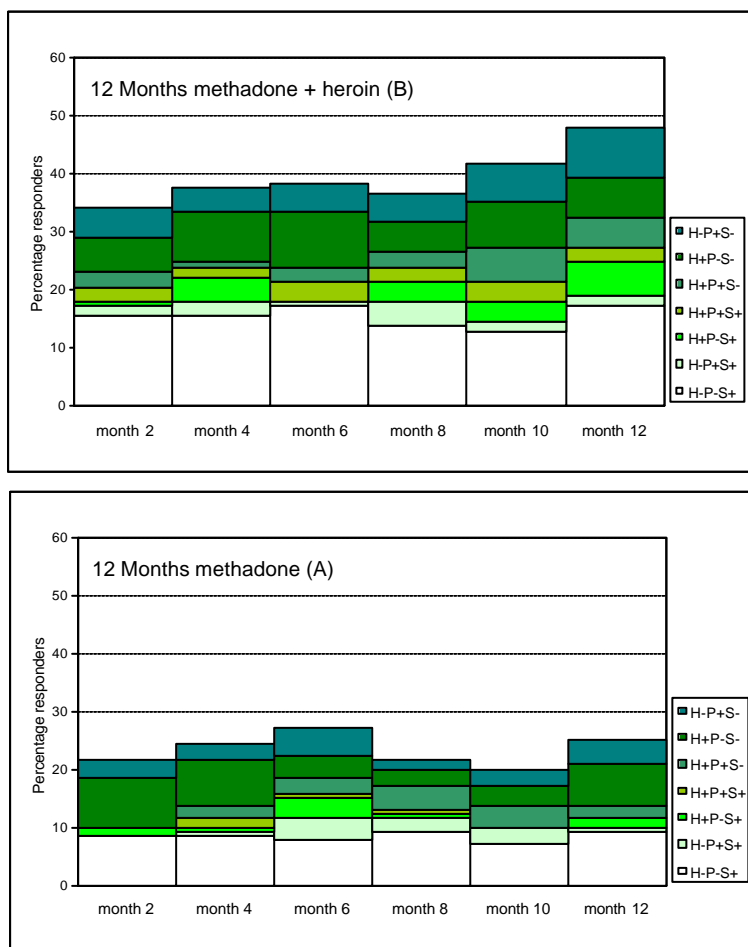
### 7<sup>B</sup>.3.3 Relative contribution of the outcome domains to response

Given the response rates in the course of the trial, displayed in Figure 24, and particularly considering the substantial response rate in the 12 months heroin group present at the month 2 assessment-point, subsequent exploratory analyses were conducted to investigate the relative contribution of the outcome domains to the percentage responders at subsequent assessments during the trial. First, the type(s) of outcome domains on which the patients responded in the course of the trial ("response profiles") were investigated. Second, the number of response domains were investigated.

#### *Response profiles in the course of the trial*

Analogous to the inclusion profiles described earlier in paragraph 6<sup>B</sup>.1.2, the three outcome domains of physical health, psychiatric status, and social functioning were combined into seven types of response, each representing a unique and mutually exclusive response profile. In Figure 25, the resulting bar charts are displayed for the 12 months heroin group and 12 months methadone group separately. Notably, the total values of each column for the heroin and methadone group in Figure 25 are identical to the response rates of the treatment groups at each corresponding assessment-point, displayed earlier in Figure 24.

Figure 25. Contribution of the outcome domains to response at subsequent assessments



Note: H = physical health; P = psychiatric status; S = social functioning.

As indicated by the upper bar chart in Figure 26, response in the 12 months heroin group – both at the start, during the course, and at the end of the trial – was based on contributions from all three outcome domains. For example, with response rates at month 12 of 27.3%, 20.5%, and 18.0% respectively, the social, physical health and psychiatric domain each contributed considerably to the occurrence of overall (47.9%) response after twelve months of treatment. In addition, as suggested by the 17.1% response due to the social domain alone at month 12, response in the heroin group could not be attributed to a dominating influence of decreased illegal activities by the participants.

This limited influence on response of the social domain alone is also illustrated when subjects, who were included in the trial on the basis of their poor functioning in the social domain alone (20.8% of the intention-to-treat population), are left out of the analysis (not shown in Figure 26). In this case, overall response at month 12 still amounted to 46.1% in group B ( $n=89$ ), and increased from 25.2% to 29.0% in group A ( $n=114$ ). Using the same logistic regression model as described earlier, the difference in percentage responders remained significant (adjusted OR=2.12; 95%-CI: 1.18-3.80;  $p=0.012$ ).

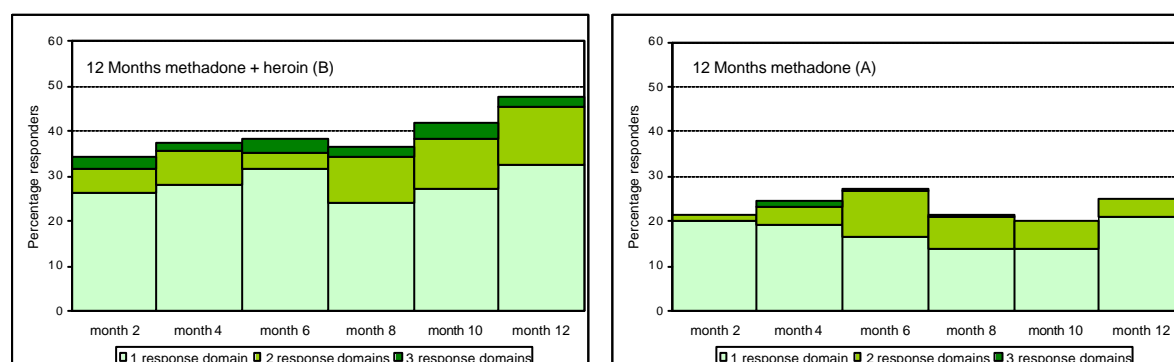
In the 12 months methadone group (lower chart in Figure 26), the three outcome domains contributed to the occurrence of response as well. Here, however, response at month 12 (25.2%) often occurred on the social domain alone (9.4%), physical health domain alone (7.2%), and psychiatric domain alone (4.3%). Hence, response in the 12 months methadone group was often based on improvements in one single domain.

The findings in the 12 months heroin group were paralleled by the results in the six months heroin group (not displayed in Figure 26). Also in the six months heroin group, there was a considerable contribution to response from all three outcome domains, and a lack of dominance of one single domain.

#### *Single-domain versus multi-domain response*

The difference in comprehensiveness of response between the methadone alone and the co-prescribed heroin group is further illustrated in Figure 27. As before, it should be noted that the total values of each column for the heroin and methadone group in Figure 27 are identical to the response rates of the treatment groups at each corresponding assessment-point, displayed in the earlier figures in this paragraph.

Figure 27. Comprehensiveness of response at subsequent assessments



In the 12 months heroin group, at the primary assessment-point at month 12 (left-hand chart in Figure 27), 32.5% of the participants had responded on one domain only, 12.8% on two domains,

and 2.6% on three domains simultaneously. Expressed as a percentage of the total response rate at month 12, 32.1% of the response in the heroin group occurred on more than one domain. In addition, Figure 27 shows that treatment comprehensiveness in the heroin group increased with time-in-treatment.

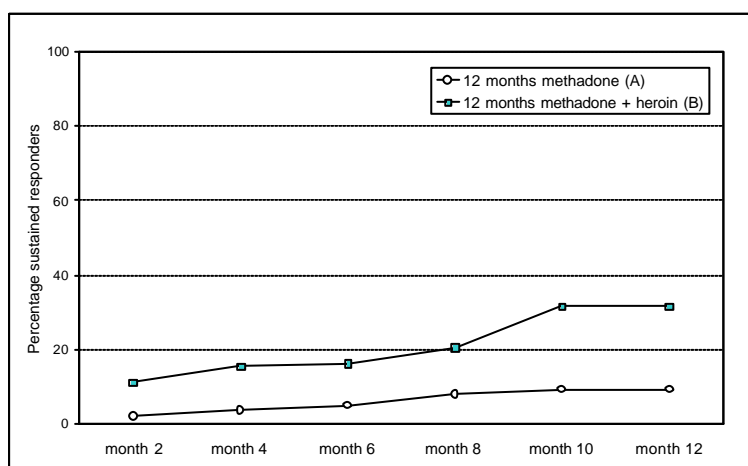
In contrast, in the 12 months methadone group (right-hand chart in Figure 27), 20.9% of the subjects had responded on one domain only, 4.3% on two domains combined, and none of the subjects had responded on three domains simultaneously. Hence, given the total response rate of 25.2% at month 12 in this group, 82.9% of the response in the methadone group was limited to improvements on one single domain, and – conversely – only 17.1% of the total response occurred on more than one domain. The difference in percentage multi-domain response between the two treatment groups (15.0%) was tested in a logistic regression model, with treatment site as the only covariate, and with non-significant relationships between multi-domain response and both treatment site and treatment-by-site interaction. In the model, the difference in percentage multi-domain responders was not significant (adjusted OR=2.27; 95% -CI: 0.74-6.89; p=0.1501).

With 37.8% of the response after twelve months of treatment occurring on more than one domain, the results of the six months heroin group (not displayed in Figure 27) were again very similar to those of the 12 months heroin group.

### 7<sup>B</sup>.3.4 Sustained response

To gain further insight into the development of response over time, the percentage of "stable" or "sustained" responders in the treatment groups was determined at each assessment-point, as before using LOCF for the missing assessments during the trial. Sustained responders were defined as patients who (1) became responder prior to the month 12 assessment, and (2) remained a responder during the course of the trial, once they had become responder for the first time. For the month 12 assessment, this definition implied that patients who became responder for the first time at month 12, were considered as non- (sustained) responders. Similarly, patients who were responder at some earlier assessment-point, but non-responder at a later assessment, were considered as non- (sustained) responders at all assessment-points. Hence, the analysis represents a very conservative approach of response. Figure 28 shows the results of the analysis.

Figure 28. Percentage sustained responders at subsequent assessments



After 12 months of treatment, the percentage sustained responders amounted to 31.6% in the 12 months heroin group, and to 9.3% in the 12 months methadone alone group. In a logistic regression model, with percentage sustained responders as the dependent variable, and treatment site as covariate, the observed difference of 22.3% between the treatment groups A and B corresponded with an

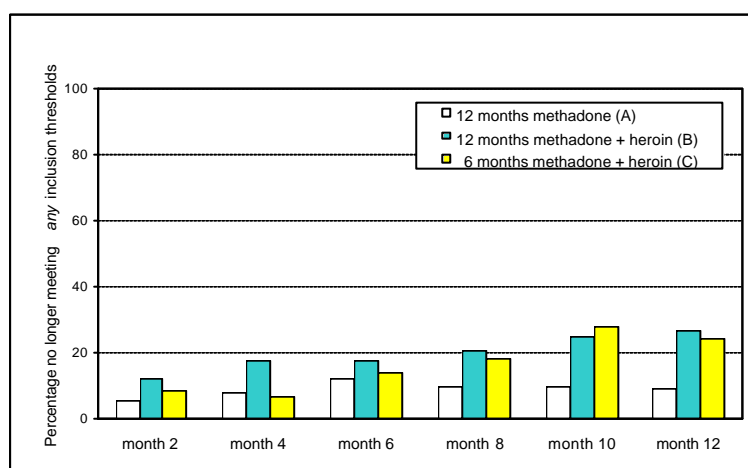
adjusted Odds-Ratio of 4.74 (95% -CI: 2.34-9.58; p=0.0001).

At the month 2 assessment, the percentage sustained responders amounted to 11.1% in the heroin group, and to 2.2% in the methadone group. These early response percentages for the sustained responders are considerably lower than those found for the responders at this assessment-point (34.2% and 21.6% , respectively; see paragraph 7<sup>B</sup>.3.2).

### 7<sup>B</sup>.3.5 Patients no longer meeting inclusion thresholds of the trial

In order to be included in the trial, patients had to function poorly in at least one of the areas of physical health, psychiatric status and social functioning, according to specific threshold values on the corresponding instruments in these domains. To investigate the extent to which patients improved in such a way that they did not function poorly anymore according to these inclusion thresholds, this measure of "poor functioning" was used as an alternative dichotomous index of treatment outcome in the trial. Figure 29 shows the development in percentage of patients who did not meet any of the inclusion thresholds for "poor functioning" anymore in the course of the trial. As before, these percentages were calculated for the intention-to-treat population, using LOCF for each missing assessment during the trial.

Figure 29. Percentage of patients no longer meeting the inclusion thresholds of the trial



Two months after baseline, 12.0% of the patients in the 12 months heroin group had improved above the level of "poor functioning", compared to 5.8% in the 12 months methadone group. After 12 months of treatment, 26.5% of the patients in the 12 months heroin group, and 9.4% in the 12 months methadone group no longer met any of the inclusion thresholds for "poor functioning". Parallel

to the changes observed in group C for response reported earlier, there was a transition in percentage of patients no longer meeting the "poor functioning" criteria as of month 6, from the rates observed in group A to those found in group B.

Similar to the analyses conducted earlier for "response", the difference of 17.1% between the treatment groups A and B at month 12 was tested for significance in a logistic regression model, with "poor functioning" as the dependent variable, and treatment site as the only covariate. With non-significant relationships between "poor functioning" and both treatment site, and treatment-by-site interaction, and with a good fit of the data to the logistic regression model ( $\chi^2=5.84$ ;  $df=7$ ;  $p=0.56$ ), the observed difference of 17.1% corresponded with an adjusted Odds-Ratio of 3.50 (95%-CI: 1.73-7.09;  $p=0.0005$ ). With respect to the comparison between the treatment groups A and C, the observed difference in percentage responders of 15.0% corresponded with an adjusted Odds-Ratio of 3.12 (95%-CI: 1.54-6.35;  $p=0.0017$ ), in a good fitting model ( $\chi^2=3.18$ ;  $df=7$ ;  $p=0.87$ ).

### 7<sup>B</sup>.3.6 Underreporting of illegal drug use and treatment effect

The self-report data pertaining to the patient's criminality and substance use were verified by investigation of registered data in the police records, and by analysis of urine samples, respectively (see paragraph 3.2.8). In the area of criminality, the data suggested acceptable agreement, and no systematic underreporting by the patients. In the area of substance use, the results of verification indicated acceptable agreement between self-reported substance use (i.e. cocaine and amphetamines) and the results of urinalysis for both trials, and some differential underreporting in the inhalable trial.

The potential effect of the observed differential underreporting of illegal drug use between the treatment groups on the occurrence of response in the inhalable trial was investigated by removing the substance use component from the primary outcome measure. Thus, the percentage responders was calculated, regardless the occurrence of deterioration in the area of illegal drug use (see paragraph 2.9.3).

Utilizing this variation of the response definition, 53.0% of the patients in the 12 months co-prescribed heroin group were responder at the month 12 assessment, compared to 32.4% of the patients in the 12 months methadone alone treatment group. In a logistic regression model, with treatment response at month 12 – as defined – as the dependent variable, and treatment site as covariate, the treatment group effect remained significant (adjusted OR=2.38; 95% -CI: 1.43-3.96; p=0.0009).

- The observed effect in terms of percentage responders in the two co-prescribed inhalable heroin groups did not go at the expense of an increased percentage of non-responders who did not improve and deteriorated.
- In the groups with six and twelve months co-prescribed heroin treatment, a considerable response rate could be observed two months after the start of this treatment. This response rate gradually increased during the last four to six months of the trial. In the methadone alone treatment group, on the other hand, the early response rate of 20-25% remained largely unchanged until the end of the trial.
- Response in both the six and twelve months co-prescribed heroin groups was based on considerable contributions from each of the outcome domains of physical health, psychiatric status, and social functioning. The effect of heroin treatment could not be attributed to a dominating influence of decreased illegal activities by the participants. The effect of methadone alone treatment, in contrast, was largely accounted for by contributions from the physical health domain alone, psychiatric domain alone, or social domain alone.
- The co-prescribed inhalable heroin treatment did not only result in a higher percentage of responders than the methadone alone treatment, but also yielded a higher percentage of multi-domain responders. The difference in multi-domain response between the treatment groups, however, did not reach statistical significance.
- Co-prescribed inhalable heroin treatment resulted in a higher percentage of stable, sustained responders than methadone alone treatment.
- Co-prescribed inhalable heroin treatment resulted in significantly more participants who no longer met the inclusion thresholds for the trial, indicative of "poor functioning", than methadone alone treatment.

## 7<sup>B</sup>.4 Consequences of discontinuing the co-prescribed heroin treatment

According to the analysis plan (see paragraph 3.3), the effects of discontinuing the six and twelve months experimental treatment with co-prescribed heroin were investigated by determining the percentage responders in conditions B and C who had subsequently deteriorated considerably – i.e. at least 20% of the baseline value on at least one of the outcome domains on which the patient had responded – two months after termination of the heroin treatment. This analysis was conducted only for treatment completers who were responders at the month 12 assessment.

From the 117 patients in the intention-to-treat population in the 12 months co-prescribed heroin group, 80 patients completed the experimental treatment period (see chapter 5<sup>B</sup>). Among this subgroup of treatment completers, 41 patients were responders (51.3%). Among these responders, the percentage patients, who had deteriorated two months after discontinuing the co-prescribed heroin treatment, amounted to 82.9%.

In the six months co-prescribed heroin group, the intention-to-treat population consisted of 119 patients, of whom 82 patients completed the experimental treatment period (see chapter 5<sup>B</sup>). From these, 42 patients were responders (51.2%). The percentage deteriorated patients among this subgroup of responders in group C amounted to 80.5% ( $n=41$ , since for one patient deterioration data was missing).

The clinical meaning of the observed rate of deterioration is illustrated in Table 21, which shows the changes in mean scores from month 12 to month 14 on the scales and items used as components of the primary outcome measure in the trial, among the deteriorated responders.

Table 21. Changes in patient status from month 12 to month 14 (mean scores)

<i>Outcome domain</i>	<i>Deteriorated responders group B (n = 34)</i>			<i>Deteriorated responders group C (n = 33)</i>		
	<i>baseline</i>	<i>month 12</i>	<i>month 14</i>	<i>baseline</i>	<i>month 12</i>	<i>month 14</i>
MAP-HSS (0-40)	10.9	5.4	13.0	13.6	6.9	16.2
SCL-90 (0-360)	70.0	22.3	75.6	80.8	32.7	86.0
Days illegal activities (0-30)	11.1	0.4	15.7	10.3	0.9	14.2
Days without personal contact with non-drug users (0-30)	15.2	11.2	21.2	17.3	8.8	18.7
Days cocaine use (0-30)	11.5	8.6	11.3	13.1	6.5	16.2
Days amphetamine use (0-30)	0.1	0.1	0.0	0.9	0.8	0.0
Days in controlled environment *		0.0	0.1		0.3	0.4

\* No baseline data are presented, because patients with more than seven days in a controlled environment in the month prior to baseline were – for reasons of validity – excluded from the baseline assessments.

As can be seen in Table 21, considerable changes on most variables occurred in the patients of the 12 months heroin group (B) from month 12 to month 14. The mean MAP-HSS score increased from month 12 to month 14 from 5.4 to 13.0, and the mean SCL-90 total score from 22.3 to 75.6. The mean number of days of illegal activities in the month prior to the assessment increased from less than one day to more than 15 days. In addition, increases were observed for the number of days without contact with a non-drug-using person, and for the number of days of cocaine use in the previous month. Table 21 also shows that the changes in scale-scores for the deteriorated responders in the six months heroin group (C) were similar to those in the 12 months heroin

group. In both treatment groups, the changes from month 12 to month 14 indicate a return to the baseline values observed at the start of the trial on all variables.

- Two months after discontinuation of the co-prescribed inhalable heroin treatment at the end of the intended treatment period, the majority (> 80%) of responders had deteriorated considerably.
- The level of deterioration indicated a return to the baseline values observed at the start of the trial.

## Chapter 8<sup>B</sup>

# Safety of co-prescribed inhalable heroin treatment

### 8<sup>B</sup>.1 Focus of the evaluation

To evaluate the medical safety of co-prescription of inhalable heroin in the present trial, all clinically significant adverse events (AEs), serious adverse events (SAEs) and unexpected adverse events were documented by the treating physician on a continuous basis during the trial. Adverse events and serious adverse events were defined, registered and reported in accordance with the ICH/EU guidelines. In addition, drug overdoses, psychoses and (epileptic) seizures were documented separately throughout the trial.

For the purpose of the present report, the evaluation of the medical safety of co-prescribed heroin focussed on the occurrence of SAEs, and separately on the occurrence of drug overdoses, psychoses and seizures. Other types of AEs were not included in the present evaluation. The observation period used for the evaluation was limited to the experimental treatment phase of the trial, i.e. the first twelve months following randomization. The evaluation was limited to the intention-to-treat population ( $n=375$ ).

An additional safety topic concerned the evaluation of SAEs, drug overdoses, psychoses and (epileptic) seizures following the discontinuation of co-prescribed heroin treatment at the end of the experimental treatment phase. This evaluation was limited to the patients who had received and completed the experimental treatment with co-prescribed heroin (i.e. the treatment completers in group B, and in group C). The observation period of this – separate – evaluation concerned the two months following the discontinuation of the co-prescribed heroin treatment (i.e. before a possible reinstatement of the heroin treatment in phase III; see paragraph 2.2.1).

### 8<sup>B</sup>.2 Serious adverse events in the experimental treatment phase of the trial

According to the standard ICH/EU definition, serious adverse events are events which result in death, are life-threatening, require inpatient hospitalization or prolongation of existing hospitalization, result in persistent or significant disability or incapacity, or represent a congenital anomaly or birth defect. Table 22 provides an overview of the SAEs.

During the twelve months experimental study phase, a total of 40 SAEs occurred among 375 patients. From these, 14 SAEs (involving 11 patients; 7.9%) occurred among the 139 patients in the methadone alone treatment group (A), 14 SAEs (involving 14 patients; 12.0%) among the 117 patients in the 12 months co-prescribed heroin group (B), and 12 SAEs (involving 11 patients; 9.2%) among the 119 patients in the six months co-prescribed heroin group (C). The percentage of patients with at least one SAE was not significantly different between the treatment groups A and B (Fisher's Exact Test;  $p=0.30$ ).

In the methadone alone treatment group (A), 14 SAEs occurred. Given that the patients participated in the methadone alone control treatment, these SAEs were all considered to be not related to the heroin medication. The 12 SAEs in group A, which were designated as (prolongation of) hospital admission, occurred among nine patients (right-hand column in Table 22). One patient in this treatment group had three SAEs, and one patient had two SAEs.

Table 22. Overview of SAEs during the experimental treatment phase of the trial

<i>Treatment group</i>	<i># SAEs</i>	<i># Patients with SAE(s)</i>
A (12 months methadone; <i>n</i> = 139) - life-threatening adverse event - (prolongation of) hospital admission	2 12	2 9
B (12 months methadone + heroin; <i>n</i> = 117) - life-threatening adverse event - (prolongation of) hospital admission	2 12	2 12
C (6 months methadone + heroin; <i>n</i> = 119) - death - life-threatening adverse event - (prolongation of) hospital admission	1 1 10	1 1 9
Total ( <i>n</i> = 375)	40	36

In the 12 months co-prescribed heroin treatment group (B), 14 SAEs occurred. From these, two SAEs were registered as life-threatening. Both were considered to be possibly related to the co-prescribed heroin medication. In one case, registered as drug intoxication, a patient was found unconscious on the street, with low body temperature, and under the influence of benzodiazepines. The patient was admitted to a hospital, and subsequently recovered from coma without residue. The same day, the patient was discharged from the hospital, and the following day he restarted the treatment with co-prescribed heroin. The second case of a life-threatening SAE in treatment group B, possibly related to the heroin medication, involved a patient with a history of psychosis. According to the documentation, the patient became paranoid psychotic, probably due to a combination of heroin and cocaine use. The patient was confused, and was wandering between traffic on the street.

In the six months co-prescribed heroin treatment group (C), three of the 12 documented SAEs occurred during the first six months of the experimental treatment phase of the trial (i.e. the methadone alone treatment condition), and nine SAEs during the second six months (i.e. the co-prescribed heroin treatment condition). In treatment group C, one fatal event occurred. The patient was admitted to a hospital for continual emesis. The patient developed asystolia, went into coma, and died 14 days after hospital admission. Since the patient had not yet started the co-prescribed heroin treatment in this group (the event occurred 39 days following randomization), the SAE was considered to be not related to the heroin medication. The one documented life-threatening adverse event in group C was considered to be not related to the co-prescribed heroin treatment as well.

Table 23 provides an overview of the relationship between each of the 40 SAEs and the co-prescribed heroin medication. Eight SAEs were considered to be – possibly (six cases), probably (one case), or definitely (one case) – related to the intake of co-prescribed heroin. Besides the two life-threatening SAEs in group B discussed above, these SAEs concerned hospital admissions for a large infiltration in the lung, exacerbation of COPD, pneumonia, mechanic ileus, a drug overdose, and a car accident. The drug overdose, judged as probably related to the heroin medication, concerned a patient who was exhausted after use of cocaine, in combination with heroin. The patient was admitted to a hospital.

Table 23. Relationship of SAEs with heroin medication during the experimental treatment phase of the trial

<i>Relationship with heroin medication</i>	<i># SAEs</i>
Not related	31
Possibly related - lung infiltration (hospital admission; group B) - exacerbation of COPD (hospital admission; group C) - pneumonia (hospital admission; group B) - psychosis, due to combined heroin and cocaine use (life-threatening; group B) - mechanic ileus (hospital admission; group B) - drug intoxication (life-threatening; group B)	1 1 1 1 1 1
Probably related - drug overdose (hospital admission; group B)	1
Definitely related - car accident, involving opiate and benzodiazepine use (hospital admission; group B)	1
Not known	1
Total	40

The only SAE, which was considered to be definitely related to the heroin medication, occurred in treatment group B, several hours after the evening distribution of co-prescribed heroin in the treatment site. According to the documentation, the patient had used opiates and benzodiazepines, and had a car accident. The patient was subsequently hospitalized for one day, and restarted the co-prescribed heroin treatment on the day of discharge from the hospital. The SAE occurred 131 days following the actual start date of the co-prescribed heroin treatment.

The relationship with the heroin medication could not be established for one SAE.

#### *Context of the observed SAEs*

Fourteen SAEs occurred in treatment group B, and nine SAEs during the co-prescribed heroin phase in group C. These SAEs occurred among the 117 patients in group B and 119 patients in group C of the intention-to-treat population. From these, 111 patients started the treatment in group B, and 98 patients in group C (see chapter 5<sup>A</sup>). Thus, the 14 SAEs in group B correspond with an average of 0.13 SAE per patient per treatment-year, compared to an average of 0.10 SAE per patient per year in the methadone alone treatment group. Standardized for one treatment-year, the average number of SAEs in group C would amount to 0.18 per patient. In addition, the observed SAEs in group B and C occurred in a context in which a total of approximately 95,000 heroin prescriptions were dispensed.

### 8<sup>B</sup>.3 Drug overdoses, psychoses and seizures during the experimental phase

Drug overdoses, psychoses and (epileptic) seizures were registered separately throughout the trial. In total, 25 such events occurred during the 12 months experimental treatment phase of the study.

*Drug overdoses*

A drug overdose was defined as an intentional or unintentional intake of a drug dose in a much larger quantity than normal for the individual, or than normal in the context of treating a disease, which is likely to result in a severe toxic reaction or death. A severe toxic reaction was evident in case of a considerably diminished level of consciousness, ranging from clouded consciousness to coma, and in case of respiratory depression, which are life-threatening and/or require treatment with an antagonist.

Six drug overdoses were registered, three of which occurred in one of the two co-prescribed heroin treatment groups. The severity of the six overdoses was judged as moderate for three overdoses, and severe for three overdoses. Four drug overdoses were considered to be SAEs; one of these was probably related to the heroin medication. None of the drug overdoses were considered to be definitely related to the heroin medication.

Table 24. Relationship of drug overdoses, psychoses and seizures with heroin medication during the experimental treatment phase of the trial

<i>Type of event / treatment group</i>	<i># Events</i>	<i># SAEs</i>	<i># Definitely related events</i>
Drug overdose			
- treatment group A	3	3	0
- treatment group B	1	1	0
- treatment group C	2	0	0
Psychosis			
- treatment group A	2	1	0
- treatment group B	7	1	0
- treatment group C	1	0	0
(Epileptic) seizure			
- treatment group A	4	1	0
- treatment group B	2	0	0
- treatment group C	4	0	0
Total	25	7	0

*Psychoses*

A psychosis was defined in terms of the diagnosis psychosis/hallucinosi, involving signs and symptoms which are observed during an acute schizophrenic episode, like hallucinations and delusions.

Ten psychoses were reported during the 12 months treatment period. Two of these were registered as SAE, one of which was considered to be possibly related to the heroin medication. The latter psychosis – registered as life-threatening, because the patient was wandering between traffic in a confused state – was discussed earlier in this paragraph.

*Seizures*

An (epileptic) seizure was present (1) in case of a grand mal attack, or epileptic state which met the criteria usually applied in the treatment of epilepsy, and (2) in case of an epileptiform seizure, including all other types of seizures with contractions and diminished level of consciousness, which did not meet the criteria mentioned under (1).

Eight patients reported a total of ten (epileptic) seizures. The four seizures in treatment group A involved three patients; one patient reported two seizures. The two seizures in treatment group

B involved the same patient. Lastly, the four seizures in group C involved four patients. None of the (epileptic) seizures was assessed as severe. In addition, none were considered to be related to the heroin medication.

#### 8<sup>B</sup>.4 SAEs, drug overdoses, psychoses and seizures following the discontinuation of co-prescribed heroin treatment

As described earlier in chapter 5<sup>B</sup>, a total of 80 patients completed the 12 months treatment with co-prescribed inhalable heroin, and 82 patients completed the treatment in the six months co-prescribed heroin group. In this group of 162 treatment completers, six SAEs were documented during the two months following the discontinuation of this treatment. From these, one SAE occurred in group B, and five SAEs in group C. The six SAEs involved five subjects; one patient had two SAEs.

The six SAEs were classified as hospital admission in five cases, and as a life-threatening event in one case. The patient with the life-threatening event was pushed from the platform in a subway station, and fell on the train track. The patient had a commotio cerebri, with loss of consciousness for one minute. Prior to this event, the patient had used heroin, cocaine, and alcohol. None of the SAEs in this study phase were related to the (discontinuation of the) heroin medication.

Among the 162 treatment completers in treatment groups B and C combined, no drug overdoses or psychoses were documented during the two months following the discontinuation of the co-prescribed heroin treatment. One seizure occurred during this period. The seizure, which involved a patient in treatment group C, was assessed as mild, and was considered to be not related to the (discontinuation of the) heroin medication.

- The incidence of serious adverse events during the twelve months treatment period was comparable between the co-prescribed heroin treatment group and the methadone alone group.
- The observed total of 23 serious adverse events in the co-prescribed heroin groups, of which eight events were considered to be at least possibly related to the study medication, occurred in the context of approximately 95,000 heroin dispensations.
- No serious adverse events were observed that were related to the discontinuation of the co-prescribed heroin treatment at the end of the experimental treatment period.