

**German model project of
heroin-assisted treatment of
opiate dependent patients –
a multicentre, randomised,
controlled treatment study**

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Background

- Coalition agreement (fall of 1998)
- Announcement of Ministry of Health (29.9.1999)
- “Directing Group” (MoH, States, Cities)
- Heroin use according to § 3 (2) German Law on Narcotics
- Multicentre study
 - Randomised clinical trial (GCP)
 - Psychosocial treatment
 - Implementation into addiction services system
- Target group: heroin addicts
 - Not reached by addiction services so far
 - Not successfully treated

Relevance of heroin treatment

- Limitations of present addiction services system
- 10% - 20% of those maintained on methadone do not or insufficiently profit from treatment
- In Hamburg about 1/3 of those not in maintenance treatment are untreated, consumers in drug scene mainly great treatment needs
- Untreated opiate dependency → higher risks
 - Mortality, morbidity
 - Health risks for social surroundings
 - Costs due to criminality, treatment of concurrent disorders
- In Germany about 35,000 - 40,000 methadone patients
- At least 35,000 presently not in treatment

Aim of the study

Aim of the study is to examine if with medical prescription of pharmacologically clean *heroin* in a *structured and controlled treatment setting* for specific groups of heroin addicts those goals can be easier reached, which generally are associated with (long-term) standard addiction treatment – i.e. harm reduction, integration into health care system, reduction of illicit drug consumption and respective parallel problems, physical, mental and social improvement and stabilisation, controlling and overcoming the addiction.

Target groups

- “Methadone-substituted” (MS) patients
 - Opiate addicts presently in methadone-maintenance programs, who have not profited sufficiently from treatment
- Untreated / not reached patients (“Nicht-Erreichte”: NE)
 - Heroin addicts, who have not been effectively reached by present treatment services and are therefore not in treatment, but in need of treatment due to their state of health or present life situation

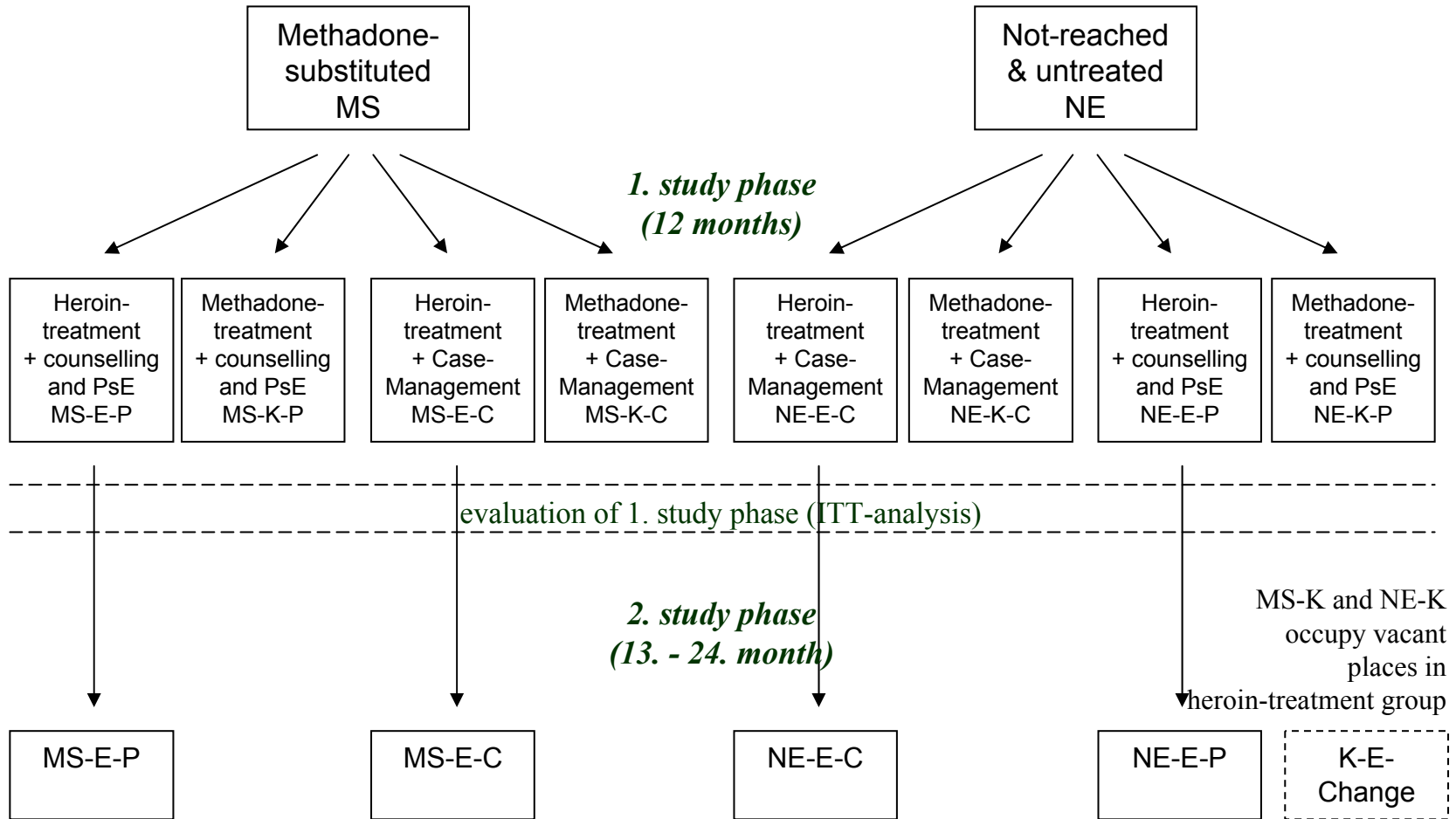
Goals of the study

- **Medication study / Clinical trial acc. to GCP:**
Efficacy of prescribing i.v. heroin compared to oral methadone in similar treatment settings
→ Substance approval (indication / target groups)
- **Comparison of psychosocial concomitant treatment:**
Case management (incl. motivational interviewing) vs. addiction counselling with psychoeducation → importance of medical and psychosocial treatment elements
- **Parallel patient and health care relevant special studies:**
 - Reduction of criminality (quantitative and qualitative interviews, police data analysis)
 - Implementation into health care system, cooperation processes
 - Cost-benefit and cost-effectiveness analyses
 - Neuropsychological and cognitive-motor examinations
 - Effects of psychosocial treatment

Study design [1]

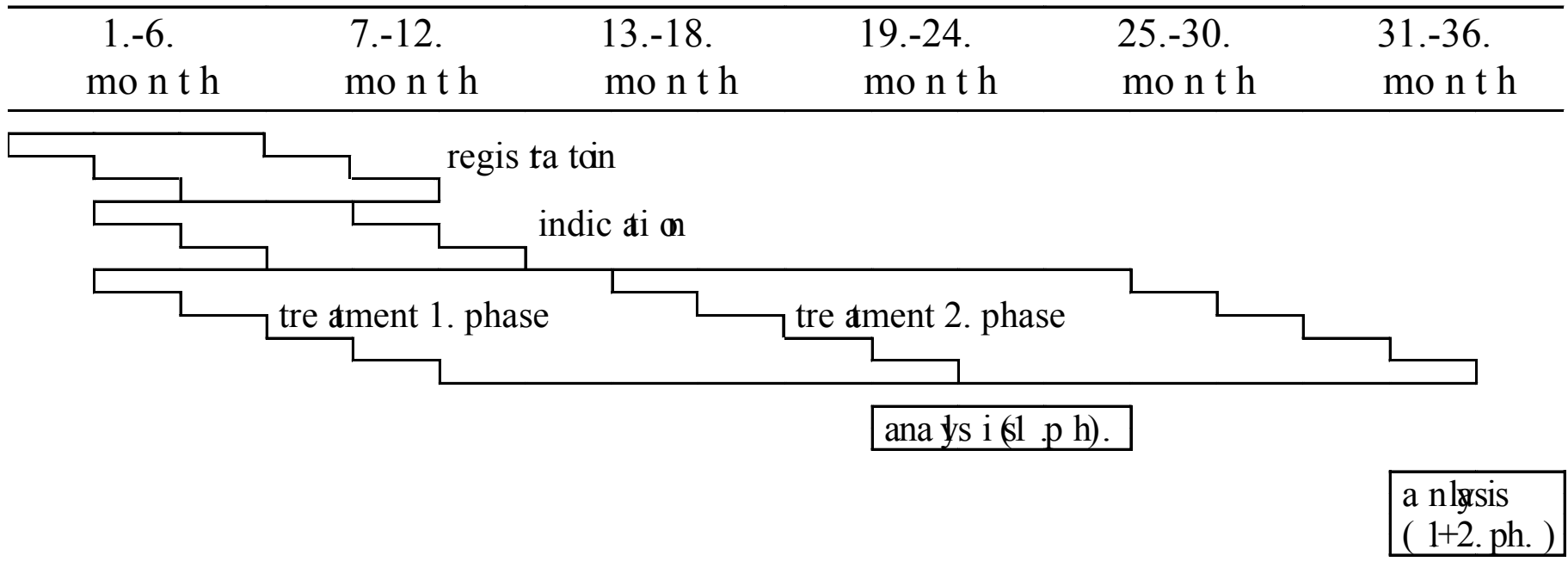
- 4 x 2-stratified randomised control group study according to GCP
- Clinical medication trial (AMG, BtMG)
- 2 study phases: total duration 24 months
- Medication: heroin i.v. *vs.* methadone p.o.
- Psycho-social care: Case-Management (incl. MI) *vs.* drug counselling and psychoeducation
- Multi-centre (Hamburg, Hannover, Frankfurt, Cologne, Bonn, Karlsruhe, Munich)

Study design [2]



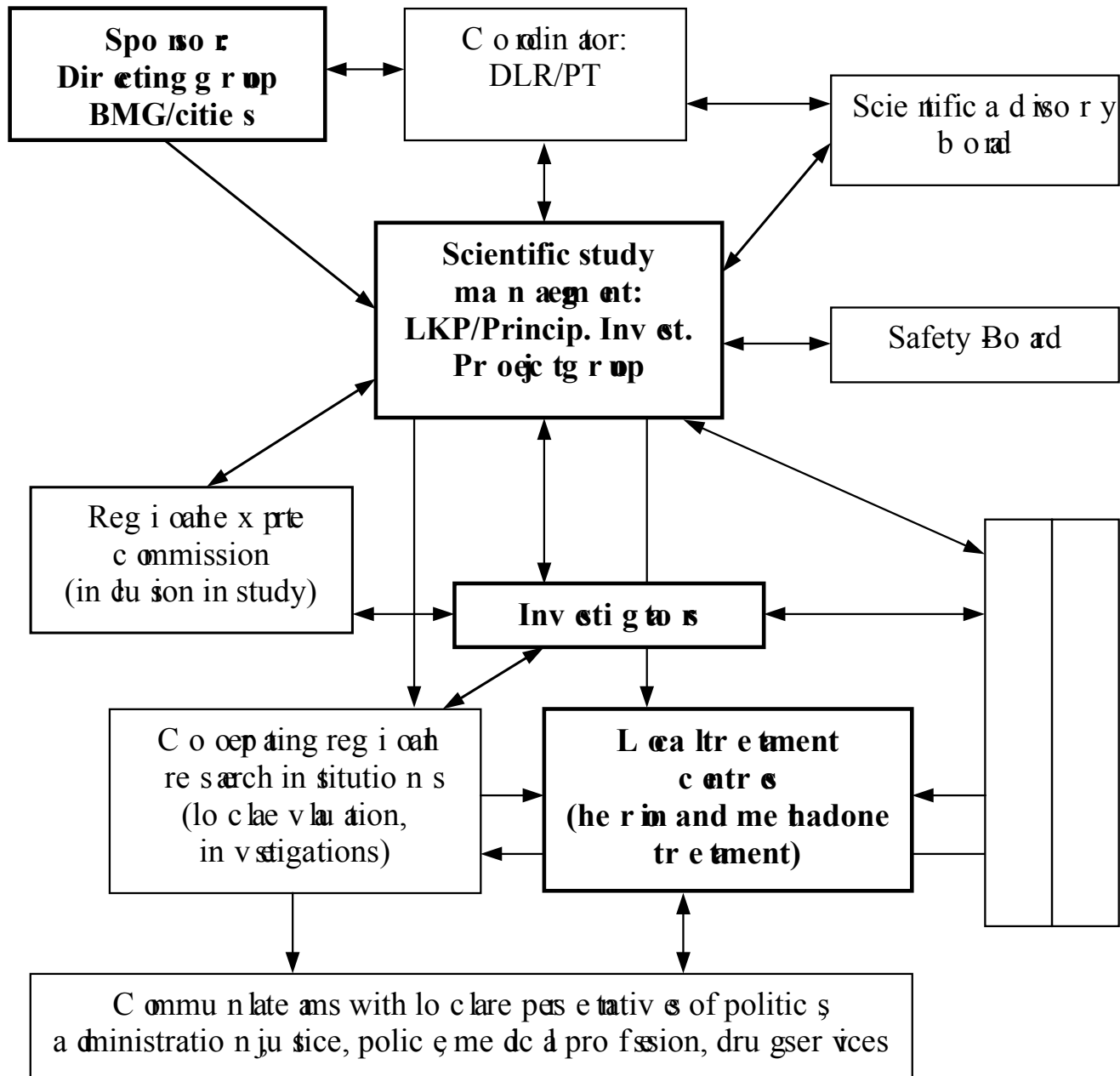
Study groups of the clinical study on heroin-assisted treatment.
1. and 2. study phase

Study timecourse



Organisational structure of clinical study within the timecourse of 36 months

Coordination and Cooperations



Primary outcome measures

- (A) Improvement of physical **or** mental state of health

AND

- (B) Reduction of consumption of illicit heroin **and** no increase of cocaine consumption

Secondary outcome measures

- Retention rate
- Reduction of consumption of benzodiazepines, amphetamines, alcohol and other drugs
- Reduction of contacts to the drug scene / contacts to drug consumers
- Decrease of delinquent behaviour
- Stabilisation of living conditions
- Establishment of new social contacts/relationships
- Improvement of quality of life
- Mortality rate

Operationalisation of primary outcome measure A

- (A1) Physical state of health

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

$$(0 \leq A1_n \leq 50)$$

- (A2) Mental state of health

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

$$(0 \leq A2_n \leq 4)$$

The **treatment-response** with respect to improvement of **state of health** is present, if one of the two criteria (A1 or A2) shows an improvement of at least 20% **and** the respective other shows no deterioration.

Operationalisation of primary outcome measure B

- (B1) Consumption of illicit heroin

Number of urine controls (UCs) positive for illicit heroin in 12th treatment month, e.g. of the last 5 UCs prior to T_{12} .

$$(0 \leq B1_n \leq 5)$$

- (B2) Consumption of cocaine

Cocaine concentration in hair analyses (HAs) at T_{-1} and T_{12} within the following range:

$$(B2_n \geq 1 \text{ mg/g})$$

The **treatment response** with respect to the reduction of **illicit drug consumption** results from a reduction of consumption of illicit heroin (B1) *and* no increase of cocaine consumption (B2) between study initiation (indication examination at T_{-1}) and end of 1st study phase after 12 months (final examination at T_{12}).

Recruitment

- N=1,120 with opiate dependency (560 MS, 560 NE)
- Recruitment starts about 3 months before treatment
- Registration outside of individual duration of study
- Over-recruitment by at least 20%
- Screening of inclusion criteria at registration
- Indication/baseline examination 1 month before initiating treatment (T_{-1}), information and first written consent
- Block randomisation per strata (MS/NE)
- Second informed consent before treatment initiation (T_0) and notice of randomisation result

Inclusion criteria

- At least 23 years old
- Opiate dependency for at least 5 years
- Present main diagnosis of opioid dependency according to ICD-10
- Present daily mainly intravenous heroin consumption or continuous consumption under methadone maintenance therapy
- Physical symptoms indicating a poor condition of health (OTI \geq 13) *or* present mental symptoms or impairments (GSI T-Score \geq 60)
- No participation in an addiction treatment *or* negative course of methadone maintenance treatment
- Residency in the respective city/region for at least 12 months
- Voluntary participation and capability to follow the conditions of the clinical study
- Written consent

Exclusion criteria (study initiation)

- Persons presently incarcerated or where an incarceration is probable within the next 3 months
- Persons showing a voluntary abstinence phase of at least 2 months in the last 12 months
- Known epilepsy or generalised seizures within the last 12 months
- Other medical exclusion criteria such as severe bronchial asthma, severe cardiac arrhythmias, life-threatening hepatic disorders, severe renal disorders
- Pregnant women or breast-feeding mothers
- Patients who according to the evaluation of an investigator are unable to follow the conditions of the model project and are unable to participate in the therapeutic and scientific program due to severe physical or mental disorders
- Patients presently participating in another clinical study which also evaluates an element of addiction treatment

Exclusion from treatment

- Patients with severe somatic complications due to the heroin or methadone treatment
- Patients who develop laboratory test abnormalities (blood count)
- Patients who discontinue treatment for a period of 14 days (or longer) due to their own conditions or without stating reasons
- Patients who are incarcerated for one month or longer
- Heroin patients necessitating interruption for longer than 3 months due to in-patient treatment or other special treatment regimes
- Patients who according to evaluation of investigator are unable or unwilling to follow the conditions of the model project and are unable or unwilling to participate in the therapeutic or scientific programme
- Aggression or threat of aggression against project members or other patient □ □ s
- Drug dealing within the rooms of the model project
- Theft, dealing or selling of prescribing/received substances

Randomisation process

- Registration/Screening → first classification for NE or MS
- Indication/baseline examination T_{-1} , information and first written consent
- Examination of inclusion and exclusion criteria by investigator and regional expert commission → final classification for NE or MS
- Information and second written consent
- Opening of the randomisation envelope and announcement of the result of randomisation
→ heroin or methadone, CM or Counselling/PE
- Treatment initiation (T_0)

Treatment

- Separate clinics
- **Heroin:** daily dispensing (up to 3x), possibility for methadone intake at night (max. 60 mg), daily maximum dose 1,000 mg, single maximum dose 400 mg
- **Methadone:** daily dispensing, take-home regulation according to BtMVV, no dose limit
- Individual dosage according to intensity of consumption (target group) → stable steady state dose
- Medical treatment: at least weekly contacts
- Case-Management: oriented along federal model project (structured, person-centred, intervening concept; integrated element: MI)
- Drug counselling and PsE: counselling upon demand and psychoeducation according to manualised group setting

Documentation of treatment

	T ₋₁	T ₀	T ₁	T ₃	T ₆	T ₁₂	T ₁₈	T ₂₄
Patienten information ,consent	X	X						
Inclusion and exclusion criteria	X					X		(X)
Medical examination	X	X	X	X	X	X	X	X
OTI- health scale	X	X	X	X	X	X	X	X
S CL- 90- R	X		X	X	X	X	X	X
CIDI			X					
Blood count	X	X	X	X	X	X	X	X
Urin controls	X	week ly						
Hair ana lysis	X				(X)	X		
Quality of life	X				X	X	X	X
Docu men tation/evaluation of P S B		X	conc urren t to P S B					
<i>Exte rnal eva luation:</i>								
Eur opA SI (expa nde d)	X				X	X	X	X
Delinquen cy (i nter view)	X					X		X
Crim inality, qua litat ive exa m ina tion						X		
Crim inality, police da ta ana lysis	toward en d of s tudy, retr ospect ive over 3 years							
Eco nom ic situa tion	X				X	X	X	X

Examination and assessment timepoints within the frame of the 2-year treatment study.

T₋₁ = timepoint for indication, T₀ = timepoint for treatment initiation, T_{1,3,6,12,18} = 1, 3, 6, 12 and 18 months after treatment initiation, T₂₄ = end of study.

Analysis after 12 months

- Safety:
 - AEs, SAEs (emergency and death cases) → prevalence, severity
- Efficacy:
 - ITT-analysis
 - If missing information LOCF
 - Four-factorial logistic regression
 - Primary effect: heroin vs. methadone considering the factors *target group, concurrent treatment, study site* (likelihood-ratio-test)
 - Test for interactions between treatment effect and pertaining to a target group (MS vs. NE)

The experimental treatment (heroin treatment) is considered **successful**, if the results of logistical regression analysis show the following:

- compared to control group treatment (methadone maintenance) a significantly higher response rate for the primary outcome measure “improvement of state of health” (A)

and

- compared to control group treatment (methadone maintenance) a significantly higher response rate for the primary outcome measure “reduction of illicit drug consumption” (B).

Sample size determination

- Efficacy expectations in control groups (methadone) with respect to both primary outcome measures:
 - $\leq 30\%$ portion of responders
- Efficacy expectations in experimental groups (heroin) with respect to both primary outcome measures:
 - $> 50\%$ portion of responders
- Multiple total power = 80%
(power per primary outcome measure = 90% , for stochastic independence of both measures)
- Drop-outs (not reached at follow-up) as “worst case”
 - Experimental group 5% , control group 10%
 - Effect size reduction: from 30% vs. 50% to $37,0\%$ vs. $47,5\%$
- At least 482 patients per treatment group (4×121)
 - Rounded up to 140 (per strata) $\times 4 = 560$ for heroin and methadone group \rightarrow total number of study patients: $N=1,120$

Analysis after 24 months

- Stabilisation or change of those effects found after 12 months
- Long-term effects of different settings of psychosocial therapy within the frame of heroin treatment

Strata M S(target group methadone-substituted)		Strata NE (target group “not-reached”)					
Long-term analysis of effects of <u>psychosocial</u> concurrent treatment for <i>heroin treatment</i>		Analysis of long-term effects (stabilisation) for <i>heroin treatment</i>		Long-term analysis of effects of <u>psychosocial</u> concurrent treatment bei <i>heroin treatment</i>		Analysis of long-term effects (stabilisation) for <i>heroin treatment</i>	
M SE-C	M SE-P	<i>intra-individual:</i> M SE-C M SE-P		NE-E-C	NE-E-P	<i>intra-individual:</i> NE-E-C NE-E-P	

- Evaluation as “On-Treatment”-analysis (“per protocol”) of those patients remaining in treatment

Further Information

Flyer:



Internet:

www.heroinstudie.de

www.bmgesundheit.de