European Monitoring Centre
for Drugs and Drug Addiction

EMCDDA Scientific report

Mortality of drug users in the EU: coordination of implementation of new cohort studies, follow-up and analysis of existing cohorts and development of new methods and outputs

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1. Executive summary

Mortality can be considered a valid indicator of health effects of different exposures, including drug abuse, giving its high level of reliability and validity. This is particularly true for overall mortality, while, when cause-specific mortality is considered, temporal and geographical heterogeneity in methods used to classify causes of death must be taken into account.

Drug-related deaths and mortality among drug addicts is one of the five key epidemiological indicators used by the European Monitoring Centre on Drugs and Drug Addiction (EMCDDA) to estimate the prevalence and health consequences of drug addiction.

In most European countries data on drug-related deaths are commonly used for estimating mortality related to substance abuse among the general population and as an indicator to assess the health impact of drug addiction. Many sources of information on drug-related deaths using different criteria for data collection are actually available in the EU countries. Although most European countries have national and/or regional mortality registers, where deaths are coded on the basis of the International Classification of Diseases (ICD), there is a wide heterogeneity of the ICD codes applied to classify “drug-related death”. A specific EMCDDA project has been developed to implement a standard definition and classification of “drug-related deaths” directly linked to the use of drugs (“overdoses” or “poisonings”) in order to improve comparability across countries. However, problem drug users die from a wide spectrum of other causes, in addiction to overdoses (e.g. AIDS, accidents, etc). Moreover, data on drug-related deaths can not be referred to a proper denominator; they depend on drug users prevalence and overdose incidence and lethality.

Longitudinal studies have their strength in estimating the actual mortality rate among drug users, although it must be taken into account that longitudinal studies are carried out on selected groups that may be not representative of the whole drug addicts population. In order to assess vital status and ascertain cause of death, identifiers of the population enrolled are necessary. For this reason, drug addicts recruited through treatment centres represent the most suitable study population. Drug addicts seeking treatment, even though not representative of the overall population of drug users, represent the most problematic part of this population where most of serious health effects actually develop.

Since 1996, the Department of Epidemiology – ASL RM E, Rome, Italy – has been coordinating a project promoted by the EMCDDA, aimed to produce and compare mortality rates estimates across European countries by the implementation of cohorts of problem drug users enrolled and followed-up according to a common methodology.

The overall objective of the EMCDDA project is to promote and co-ordinate the setting up of cohorts of problem drug users recruited through treatment centres in EU Member States, in order to estimate overall and cause-specific mortality rates and analyse and compare temporal trends in mortality across countries for monitoring purposes.

The project has been developed in the following phases, carried out in co-operation with a team of key experts from the 11 European countries involved (see Annex 1):

- Overview of published studies on mortality of problem drug users that have been undertaken in Europe and development of a standardised protocol to assess overall and cause specific mortality rates among PDUs.

The narrative literature review of published studies on mortality among drug addicts showed that comparability of results from longitudinal studies only on the basis of published data is difficult and unreliable. The information necessary to identify the characteristics of the cohort enrolled in each study is often lacking. For those studies with this information available, a wide heterogeneity of the enrolment criteria of drug users in the studies (type of drug used, severity of use) of the follow-up procedures (vital status and cause of death ascertainment and coding) and of the methods of data-analysis is observed, hampering geographical and temporal comparisons (*EMCDDA project "Review of scientific studies of mortality among drug users and feasibility study for a common methodology for monitoring overall and cause-specific mortality among drug users in Member States of European Union", 1996*).

- Evaluation of the feasibility of implementing the standardised methodology in different European countries.

Within the project a standard protocol for conducting mortality cohort studies among drug users was developed aimed to ensure comparability of results across countries. Detailed information on availability of sources for ascertaining vital status and causes of death and on accessibility to health records of drug users were also gathered. In this preliminary phase it was possible to check the feasibility of conducting prospective mortality cohort studies in the involved countries and to assess the availability of data from already enrolled and possibly followed-up cohorts of drug addicts. It was assessed that vital status and cause of death ascertainment and coding of cause of death can be carried out according to the standardised rules in all countries. Most of the information on the study population, as specified in the standard protocol, are available although with some differences across study sites (*EMCDDA project "Co-ordination of implementation, follow-up and analysis of cohort studies on mortality among drug users in European Union Member States", 1998*).

In order to help researchers in implementing mortality cohort studies and to enhance comparability of results from different countries, the EMCDDA drafted specific guidelines based on the standard protocol.

- Promoting and co-ordinating the implementation of cohorts of problem drug users recruited in treatment centres.

The project aims to implement new (prospective) cohorts of drug addicts and to follow them up periodically in order to produce updated mortality rates estimates.

When the project started, in some countries/cities data from cohorts of drug addicts already established were available while in other cases, the cohorts had still to be followed-up (retrospective cohorts). In general, it was considered that retrospective mortality studies are worthwhile conducting only in those countries where mortality rates have never been estimated and if data are easily available.

- Joint analysis of data from the available cohorts.

A comparative analysis of already followed-up cohorts has been performed producing useful information in order to define the criteria needed for comparability of data. The preliminary pooled analysis showed that comparability of results from different cohorts is hampered by the heterogeneity of periods of enrolment and follow-up, setting and study population and classification of causes of death. A Poisson regression analysis of determinants of overall mortality was also carried out on two cohorts (Rome and Barcelona) where additional information such as severity of drug use and socio-demographic characteristics were available (*EMCDDA project "Implementation, follow-up and analysis of cohort studies on mortality among drug users in European Union Member States", 1997*).

In order to improve for each study site the description of the retrospective and/or prospective cohorts as well as to obtain a structured qualitative description of the 'drug problem' at local and national level, a questionnaire was developed by the co-ordinating centre and delivered to each study site. This information is essential for improving comparability of results coming from the analysis of the cohorts enrolled in different sites (*EMCDDA project "Co-ordination of implementation, follow-up and analysis of cohort studies on mortality among drug users in European Union Member States", 1998*).

2. Introduction

The specific objectives of the project 1999/2001 were:

- to monitor the implementation of new cohorts of drug addicts cohort in the participating countries according to the standard methodology developed within previous EMCDDA project phases;
- to carry out an advanced comparative analysis of data from cohorts with a significant follow-up period completed according to the work plan established by the co-ordinating centre and the EMCDDA in collaboration with the experts from Spain and The Netherlands (Annex 2);
- to check the feasibility for studying morbidity as outcome other than mortality;
- to submit for publication a paper describing the objectives and the results of the cohort mortality project
- to draft the guidelines to carry out longitudinal study of mortality among problem drug users (Annex 3).

3. Cohorts enrolment and follow-up: state of the art

In this paragraph the state of the art, updated as of June 2001, of the cohort recruitment and follow-up, in the involved study sites, is summarised (Table 1).

Within the project, an operative definition of "prospective" cohort has been provided. A cohort is defined as "prospective" when the enrolment and the follow-up are periodically updated according to the procedures specified in the standard protocol.

In Vienna a retrospective cohort was enrolled between 1987-1998 and followed-up through 1998. In the future, period of enrolment could be enlarged and other Austrian cities involved, if extra funding was available at national or international level.

The retrospective cohort enrolled in Hamburg between 1990-1996, and followed-up through June 1999, was analysed despite the high percentage of lost to follow-up (18.8%) must be taken into account in interpreting the results. Since January 2000 a prospective cohort, including opiate users attending three outpatient and one inpatient treatment centres, has been enrolled.

The recruitment of the cohort in Rome, starting in 1980, was updated to 1998, but the vital status ascertainment hasn't still performed. Between 1980 and 1991 the recruitment was performed in three large Public Treatment Centres while since 1992 drug addicts have been enrolling through the Local Surveillance System. Within the national study on the evaluation of effectiveness of heroin addiction (VEdeTTE) a cohort of 1735 heroin addicts has been enrolled between 1998-2000 involving 19 Public Treatment Centres (PTCs) in the Lazio region (where Rome is located). The follow-up of the prospective cohort has been completed while a new phase of enrolment will start in September 2002 and will continue for the following two years.

Denmark keeps an ongoing enrolment (started in 1996) and follow-up of drug addicts recorded in the National Treatment Registry run by National Board of Health. The follow-up of the cohort, already performed through March 2000, will be updated through 2001.

Amsterdam keeps an ongoing enrolment but the vital status ascertainment has been performed as of December 1996 on people enrolled between 1985/1996. Since 1997 the enrolment of a prospective cohort started.

In Barcelona a retrospective cohort was enrolled between 1992 and 1996 and followed-up through June 1999. The recruitment of a prospective cohort started in 1998 and the enrolment is still going on.

In Dublin a retrospective cohort was enrolled between 1994 and 1997 and followed-up through 1997. Data from this cohort have been included in the comparative analysis, but as for the cohort enrolled in Hamburg, the high percentage of losses to follow-up (23.9%) could bias the mortality pattern. A prospective cohort has been enrolled between 1999 and 2000 and it will be followed up through 2001.

Sweden keeps an ongoing enrolment and follow-up of inpatient drug addicts at Public Treatment Centres. The follow-up of the cohort, enrolled since 1987 has been updated as of 1998.

The cohort enrolled in Lisbon included subjects enrolled between 1992 and 1998 and followed-up through 1999. Data from this cohort have been already processed. Subjects recruited in Lisbon in 1999 have not been traced yet.

Table 1. Cohort enrolment: state of the art

Study site	*Retrospective cohort*	*Prospective cohort*
Barcelona	1992-1996	1998 - ongoing
Rome	1980-1991 3 outpatients treatment centres	1992-1998 all outpatient centres of Rome 1998-2000 19 outpatient treatment centres
Sweden		1987 - ongoing
Amsterdam	1985-1996	
Vienna	1987-1998	Extra funding to enlarge enrolment period and include new cities
Denmark		1996 - ongoing
Lisbon	1992-1998	1999
Dublin	1994-1997	ongoing
Hamburg	1990-1996	Starting January 2000 3 outpatient, 1 inpatient treatment centres

4. Comparative overall mortality analysis

A comparative analysis was carried out in the framework of the previous phase of the project for Sweden, Denmark, Amsterdam, Vienna, Barcelona, and Rome. Temporal trend of overall mortality has been described, and for the cohorts enrolled in Rome, Barcelona, Vienna and Sweden cause specific mortality analysis has been performed (*EMCDDA project "Co-ordination of implementation, follow-up and analysis of cohort studies on mortality among drug users in European Union Member States", 1998*).

Within the new phase (1999-2001) of the project the comparative analysis has been restricted to opiates users aged 15-49 yrs. The comparative overall mortality analysis has been carried out also including the cohorts recruited in Lisbon, Dublin and Hamburg; moreover, data from the Swedish and Danish cohorts with a longer period of enrolment and follow-up have been reanalysed.

Age-standardised mortality rates were computed to analyse temporal trend using the total population of European Union Community (EUC) (15-49 years) as the standard.

The figures of the resident population in each country of European Union were extracted from the Demographic Yearbook, 1997 (United Nations).

The cumulative risks of death from all causes, at two and four years of follow-up since enrolment, were estimated using Kaplan-Meier product limit method, along with 95% confidence intervals. This analysis included all cohorts except those of Hamburg and Dublin (because of the high proportion of lost to follow-up).

4.1 Characteristics of the analysed cohorts (tables 2, 3, 4)

The Swedish cohort was enrolled between 1987 and 1997 and followed-up through 1997. The cohort consisted of 4023 (71% males) subjects entered at inpatient Public Treatment Centres.

In the Amsterdam cohort 4853 opiates users (77% males) entering outpatient methadone programs were enrolled and followed-up from 1985 to 1996.

The Barcelona cohort was enrolled between 1992 and 1996 and consisted of 4501 opiate addicts (76% males) entering outpatient treatment centres. The follow-up period was from 1992 through December 1998.

The cohort recruited in Rome included all opiate users entering three large Public Treatment Centres between 1980-1991 and, since 1992 till the end of 1995, those treated at all PTCs and non-governmental organisations of the city. All subjects enrolled (N= 10332, 82% males) were followed-up through 1996.

The cohort enrolled in Vienna during the period 1987-1998 and followed-up through 1998 included opiates users (N= 4683) in methadone maintenance treatment only (69% males).

In Denmark, all opiates addicts (N= 7472), entering treatment in 1996 were followed-up through 1998. The Danish cohort was the oldest at enrolment among all cohorts (mean age 30.6).

In Dublin, the cohort was recruited between 1994 and 1997 and followed-up through 1997; the study population included a high proportion of people with unknown vital status (23.9%). In the analysis a conservative criterion was adopted considering addicts lost to follow-up as alive at the end of the study period. The opiate users recruited in Dublin were the youngest entering treatment (mean age 24.9) compared with those of the other countries.

The cohort recruited in Hamburg included 4504 opiate addicts entering methadone treatment between 1990-1996 and followed-up through 1998 (72% males; mean age at enrolment 28.2).

Table 2. Description of the cohorts and setting

Place	*Study population*	*# Subjects*
Barcelona	Opiate addicts entering outpatient centres	4501
Rome	Opiate addicts entering TCs	10332
Sweden	Opiate addicts entering public inpatient TCs	4023
Amsterdam	Opiate addicts in methadone programs	4853
Vienna	Opiate addicts in methadone Maintenance treatment	4683
Denmark	Opiate addicts entering treatment Cohort from National Treatment Database	7472
Lisbon	Opiate addicts entering TCs	2525
Dublin	Opiate addicts entering TCs and treated by GPs	5283
Hamburg	Opiate addicts entering methadone treatment	4504

Table 3. Description of the analysed cohorts (opiate addicts, 15-49 years)

Place	*Period of enrolment*	*# Subjects*	*Follow-up period*
Barcelona	1992-1996	4501	1992 – 1998
Rome	1980-1995	10332	1980 – 1996
Sweden	1987-1997	4023	1987 – 1997
Amsterdam	1985-1996	4853	1985 – 1996
Vienna	1987-1998	4683	1987 – 1998
Denmark	1996-1999	7472	1996 – 1999
Lisbon	1992-1998	2525	1992 – 1999
Dublin	1994-1997	5283	1994 – 1997
Hamburg	1990-1996	4504	1990 – 1998

Table 4. Description of analysed cohorts (opiate addicts, 15-49 years)

Age at enrolment	*Barcelona*		*Rome*		*Sweden*		*Amsterdam*		*Vienna*		*Denmark*		*Lisbon*		*Dublin*		*Hamburg*	
	N	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*
≤ 19	200	4.4	774	7.5	186	4.6	223	4.6	378	8.1	250	3.3	312	12.4	1023	19.4	349	7.7
20-24	974	21.6	3502	33.9	761	18.9	1103	22.7	1248	26.6	1138	15.2	955	37.8	1954	37.0	1066	23.7
25-29	1452	32.3	3225	31.2	1039	25.8	1456	30.0	1424	30.4	1424	19.1	770	30.5	1169	22.1	1349	30.0
30-34	1191	26.5	1736	16.8	977	24.3	1113	22.9	998	21.3	1536	20.6	322	12.8	710	13.4	979	21.7
35-39	470	10.4	798	7.7	620	15.4	615	12.7	449	9.6	1385	18.5	132	5.2	292	5.5	501	11.1
40-44	149	3.3	234	2.3	293	7.3	261	5.4	151	3.2	1183	15.8	29	1.1	104	2.0	198	4.4
45-49	65	1.4	63	0.6	147	3.6	82	1.7	35	0.7	556	7.4	5	0.2	31	0.6	62	1.4
Total	**4501**		**10332**		**4023**		**4853**		**4683**		**7472**		**2525**		**5283**		**4504**	
Mean (SD)	28.6	5.9	26.6	5.8	30.1	7.1	29.0	6.4	27.6	6.2	32.7	7.9	25.3	5.3	24.9	6.1	28.2	6.6

4.2 Overall mortality analysis (tables 5, 6; figure 1)

The number of deaths occurred in each cohort during the observation periods and mean age at death are shown in tables 5 and 6. Figure 1 shows the overall mortality trend of each cohort. The highest mortality rate was observed in Barcelona (75.9/1000 person-years) in 1994 and the lowest in Amsterdam, where mortality rates were consistently below 14.0/1000 person-years over time. In the Rome cohort mortality rates increased from 1987 (9.1/1000 person-years) to 1994 (29.1/1000 person-years), showing a relatively unstable trend afterwards. In the Swedish cohort overall mortality rates decreased constantly between 1988 (43.2/1000 person-years) and 1991 (22.8/1000 person-years) but peaked again in 1994 (37.2/1000 person-year). In the Danish cohort mortality rates lowered during the four years of follow-up (from 33.3/1000 in 1996 to 13.8/1000 in 1999). Mortality in the Vienna cohort peaked in 1993 (27.7/1000 person-years) and decreased afterwards. Mortality rates in Dublin increased from 11.0/1000 in 1994 to 16.1/1000 and lowered in the following year (9.6/1000). In Hamburg, overall mortality rates peaked in 1991 (51.5/1000) decreasing afterwards.

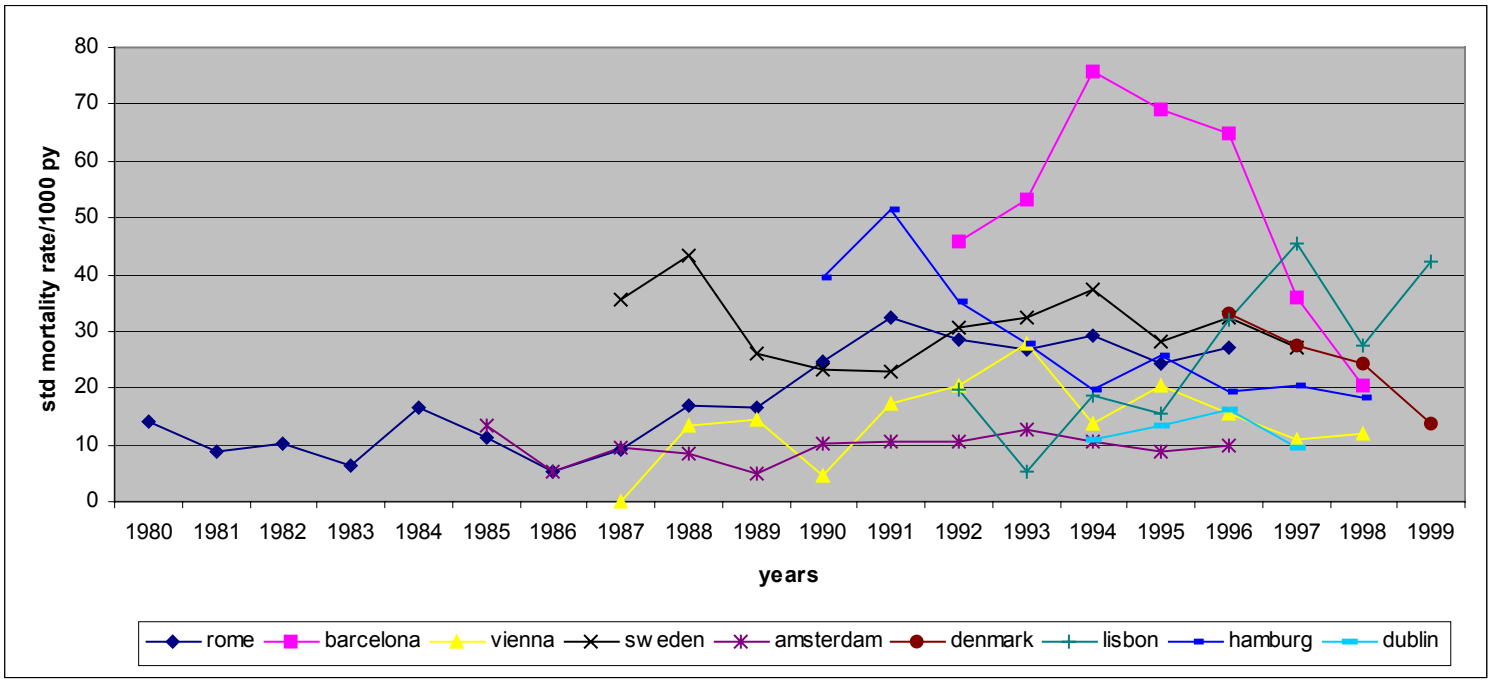
Table 5. Description of analysed cohorts (opiate addicts, 15-49 years)

Study site	*% Male*	*Mean age at enrolment*	*# Deaths*	*%*	*Mean age at death*
Barcelona	76	28.6	918	20.4	31.8
Rome	82	26.6	1445	14.0	33.1
Sweden	71	30.1	592	14.7	33.8
Amsterdam	77	29.0	446	9.2	34.9
Vienna	69	27.5	282	6.0	33.2
Denmark	74	32.7	383	5.1	36.0
Lisbon	80	25.3	307	12.1	29.4
Dublin	71	24.9	113	2.1	29.6
Hamburg	72	28.2	390	8.6	32.1

Table 6. Description of analysed cohorts (opiate addicts, 15-49 years)

Age at death	*Barcelona*		*Rome*		*Sweden*		*Amsterdam*		*Vienna*		*Denmark*		*Lisbon*		*Dublin*		*Hamburg*	
	N	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N %*	
≤ 19	11	1.2	11	0.8	3	0.5	0		1	0.4	6	1.6	8	2.6	5	4.4	7	1.8
20-24	82	8.9	116	8.0	44	7.4	23	5.2	27	9.6	26	6.8	62	20.2	26	23.0	49	12.6
25-29	219	23.8	268	18.6	111	18.8	70	15.7	56	19.9	55	14.4	103	33.6	20	17.7	93	23.8
30-34	334	36.4	459	31.8	166	28.0	130	29.1	77	27.3	69	18.0	65	21.2	40	35.4	104	26.7
35-39	188	20.2	390	27.0	153	25.8	109	24.4	71	25.2	83	21.7	47	15.3	16	14.2	77	19.7
40-44	62	6.7	163	11.3	77	13.0	82	18.4	43	15.2	84	21.9	15	4.9	4	3.5	41	10.5
45-49	22	2.4	38	2.6	38	6.4	32	7.2	7	2.5	60	15.7	7	2.3	2	1.8	19	4.9
Total	**918**		**1445**		**592**		**446**		**282**		**383**		**307**		**113**		**390**	
Mean (SD)	31.8	5.7	33.1	5.9	33.8	6.5	34.9	6.4	33.2	6.2	36.0	7.8	29.4	6.4	29.6	6.3	32.1	7.0

Figure 1. Mortality from all causes: standardised mortality rates (males and females)



4.3 Preliminary Kaplan-Meier analysis

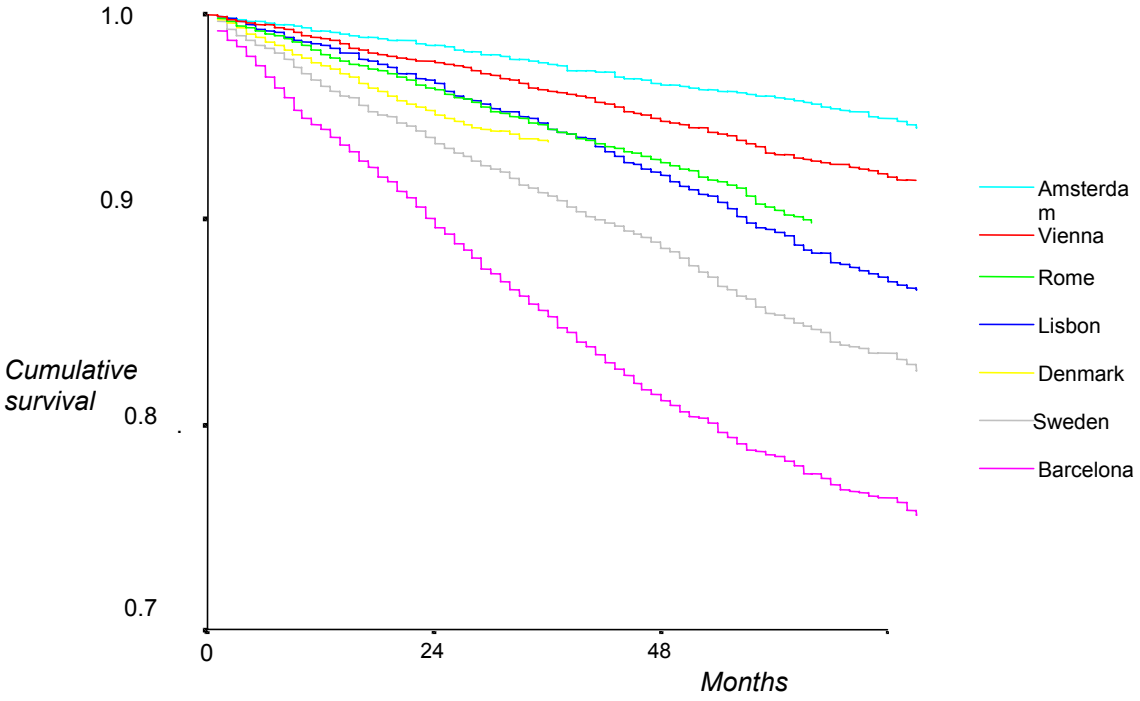
The results of Kaplan-Meier analysis (survival probability in figure 2; risks of death and their 95% C.I. in table 7) refer to the first years of observation period. The survival curves of the analysed cohorts describe the overall mortality trend, showed above (figure 1), in terms of probability to be alive after different points in time since the enrolment.

The cumulative risk of dying within two years since entry into treatment ranges from 11% in Barcelona to 1.6% in Amsterdam. The differences in cumulative risk of death, already strong early after few months, remains in the following period doubling every where except for Denmark where it remains more or less constant. Different factor could be responsible of these differences, age, gender, time of enrolment, route of administration, etc. A Cox regression analysis will be carried out for those cohorts where additional information on potential determinants or confounders are available.

Table 7. Risk of death, Kaplan-Meier analysis

Place	*Risk of death at 24 months of follow-up*	*95% C.I.*	*Risk of death at 48 months of follow-up*	*95% C.I.*
Barcelona	0.110	0.101 - 0.120	0.194	0.182 –0.206
Rome	0.038	0.034 - 0.042	0.074	0.069 – 0.079
Sweden	0.065	0.058 - 0.073	0.116	0.106 – 0.126
Amsterdam	0.016	0.013 - 0.020	0.035	0.030 – 0.040
Vienna	0.026	0.021 - 0.030	0.054	0.048 – 0.061
Denmark	0.051	0.046 - 0.056	0.065	0.059 – 0.070
Lisbon	0.034	0.027 - 0.041	0.079	0.068 – 0.089

Figure 2 - Survival curves of opiate ***addicts***



5. Advanced analysis

5.1 Overall and cause-specific mortality of opiate addicts in different European countries

Further analyses have been carried out on the cohorts (table 8) in order to investigate the impact of drug use on mortality of young adults in different EU countries. For the Rome cohort a shorter period of follow-up (1992-1997) has been considered.

Table 8 - Characteristics of the analysed cohorts

Study site	*Study population (N) and setting*	*Mean age at enrolment*	*Number of deaths*
Sweden	Opiate addicts entering in-patients TCs Recruitment through the National Hospital Discharge Registry *(4023)*	30.1	592
Denmark	Opiate addicts entering any kind of treatment. Recruitment through from the National Treatment Database *(7472)*	32.7	383
Amsterdam	Opiate addicts entering methadone programs at specialised out-patient TCs and General Practitioners Data from Central Methadone Register (CMR) *(4853)*	29.0	446
Vienna	Opiate addicts in methadone maintenance programs at GPs, specialised residential, specialised out-patient, specialised in prison *(4683)*	27.6	282
Barcelona	Opiate addicts entering out-patient specialised out-patient TCs *(4501)*	28.6	918
Lisbon	Heroin addicts entering one specialised residential TC and 9 specialised out-patient TCs *(2525)*	25.3	307
Rome	Opiate addicts entering Public TCs and Non Governmental Organisations. Recruitment through the Local Surveillance System *(5919)*	28.9	367
Dublin	Opiate addicts entering TCs and treated by GPs *(5283)*	24.9	113
Hamburg	Opiate addicts entering methadone treatment *(4504)*	28.2	390

Standardised Mortality Ratios (SMRs), stratified by age (in five-year bands), were calculated separately for male and female, using as standard the mortality rate of the individual country. Since year specific mortality rates were not available, a single reference rate has been chosen in the middle of the follow-up period of each cohort (table 9).

To analyse AIDS and overdose mortality among men and women, according to age group, direct age-standardised mortality rates were computed. For those countries where causes of death were available (Rome, Barcelona, Vienna and Sweden), SMRs have been estimated excluding deaths from AIDS from overall mortality. Moreover, for AIDS, overdose and other causes (other than AIDS and overdose) direct age-standardised mortality rates have been also computed.

Table 9 - Reference rates, in bold, used as standard to compute SMRs

Country	*Mortality rates: available year*		*Follow-up period*
Spain	***1994***	1996	1992-1998
Italy	1991	**1994**	1992-1996
Sweden	***1994***	1996	1987-1996
The Netherlands	***1995***	1996	1985-1996
Austria	***1995***	1997	1987-1998
Denmark	1995	**1997**	1996-1998
Portugal	***1995***	1997	1992-1999
Ireland	***1995***	1996	1994-1997
Germany	***1995***	1996	1990-1998

Table 10 shows the standardised overall mortality rates by gender for each cohort and standardised mortality rates for AIDS, overdose and "other causes" for both sexes.

Table 10 - Direct standardised overall and cause-specific mortality rates (per 1000 py)

Study site	***All causes***			***AIDS***	***Overdose***	***Other causes***
	M+F	***M***	***F***	***M+F***	***M+F***	***M+F***
Vienna	14.8	16.3	11.6	3.8	5.0	6.1
Dublin	13.9	15.8	9.4			
Amsterdam	10.5	12.1	7.1			
Rome	25.5	26.2	25.7	7.8	8.5	9.2
Lisbon	34.8	33.0	47.4			
Denmark	22.3	24.6	17.7			
Hamburg	18.9	17.9	21.4			
Sweden	31.0	32.7	26.8	2.4	12.2	16.3
Barcelona	51.0	52.3	46.0	18.9	17.5	14.6

The highest overall mortality rate has been observed in Barcelona (51.0/1000 person-years) and the lowest in Amsterdam where mortality rate was 10.5/1000 person-years. In Lisbon and in Sweden high mortality rates have been observed (34.8/1000 py and 31.0/1000 py respectively) while in Vienna, Dublin, Rome, Denmark and Hamburg mortality rates were below 26.0/1000 py. Analysis by gender revealed that in all cohorts males had always lower mortality rates than females, except in Lisbon (33.0/1000 in males py vs 47.4/1000 in females) and Hamburg (17.9/1000 py in males vs 21.4/1000 py in females).

The cause-specific mortality analysis highlighted that overdose was responsible of about a third of overall mortality in all the sites for which cause specific mortality was available. Particularly, it was the leading cause of death in the cohorts of Vienna, Rome and Sweden (5.0/1000 py, 8.5/1000 py and 12.2/1000 py respectively).

In Barcelona the major cause of death was AIDS (18.9/1000 py), overdose being the second (17.5/1000 py).

The lowest mortality rate for AIDS was observed in Sweden (2.4/1000 py).

Table 11 shows the Standardised Mortality Ratios (SMRs) comparing mortality of each single cohort with the expected figures derived from (its own) general population of the same age and sex of the same country. SMRs for all causes have been calculated for all cohorts, while SMRs excluding deaths from AIDS have been computed only for the cohorts of Vienna, Rome, Sweden and Barcelona.

In the Barcelona cohort, males and females showed a risk of dying respectively 24 and 64 times higher in comparison with individuals of the same age and gender in the general population in Spain.

Females in the cohorts of Lisbon, Hamburg, Rome, and Sweden showed a risk of dying ranging between thirty to forty-fold higher than females in their own general population.

For the cohorts of Vienna, Rome, Sweden and Barcelona mortality has been analysed excluding deaths from AIDS. A very strong decrease in mortality has been observed both for males and females among drug users in Barcelona, Rome and Vienna. In Swedish cohort the exclusion of deaths from AIDS did not lead to an appreciable reduction in the overall mortality (SMR estimates: from 25.9 to 23.6 for females and from 40.0 to 35.5 for males).

Table 11 - Standardised Mortality Ratios

Study site	Observed		Expected		SMR (95 C.I.)		SMR (95 C.I.) Excluding deaths from AIDS	
	M	F	M	F	M	F	M	F
Vienna	232	50	20.5	3.5	11.3 (9.9-12.9)	14.2 (10.6-18.8)	8.3 (7.2-9.7)	9.3 (6.4-13.0)
Dublin	98	15	9.2	1.3	10.7 (8.7-13.0)	11.4 (6.4-18.7)		
Amsterdam	358	88	39.7	7.3	9.0 (8.1-10.0)	12.0 (9.6-14.8)		
Rome	303	64	22.4	1.8	13.6 (12.0-15.1)	35.9 (27.6-45.8)	9.6 (8.4-11.0)	20.4 (14.4-28.2)
Lisbon	254	53	26.7	1.7	9.5 (8.4-10.7)	30.6 (22.9-40.0)		
Denmark	298	85	24.2	4.9	12.3 (11.0-13.8)	17.4 (13.9-21.4)		
Hamburg	270	120	21.5	3.4	12.6 (11.1-14.2)	35.4 (29.3-42.3)		
Sweden	453	139	17.5	3.5	25.9 (23.6-28.4)	40.0 (33.6-47.2)	23.6 (21.4-26.0)	35.5 (29.6-42.3)
Barcelona	724	194	29.8	3.0	24.3 (22.5-26.1)	64.1 (55.4-73.8)	13.6 (12.3-14.9)	35.4 (29.2-42.5)

Figure 3 shows the temporal trend for overall mortality for the cohorts of Vienna, Rome, Sweden and Barcelona. The highest overall mortality rate has been observed in 1994 in Barcelona (75.9/1000 person-years) and the lowest in 1990 in Vienna. In Sweden mortality rates ranged between and 43.2/1000 py in 1988 22.8/1000 py in 1991. In Rome mortality rate increased in 1993-1994, then decreased in 1995 and it peaked again in 1996 (32.8/1000 py). Since for these cohorts the causes of death were available, direct standardised mortality rates have been computed excluding from overall mortality deaths due to AIDS. The results of the analysis (figure 4) highlighted that the exclusion of deaths from AIDS led to a strong reduction in overall mortality. For the cohort of Barcelona Vienna, Rome deaths from AIDS were responsible of about a third of overall mortality, while in Sweden it has not been highlighted an appreciable reduction.

Figure 3 - Overall mortality: standardised mortality rates (males and females)

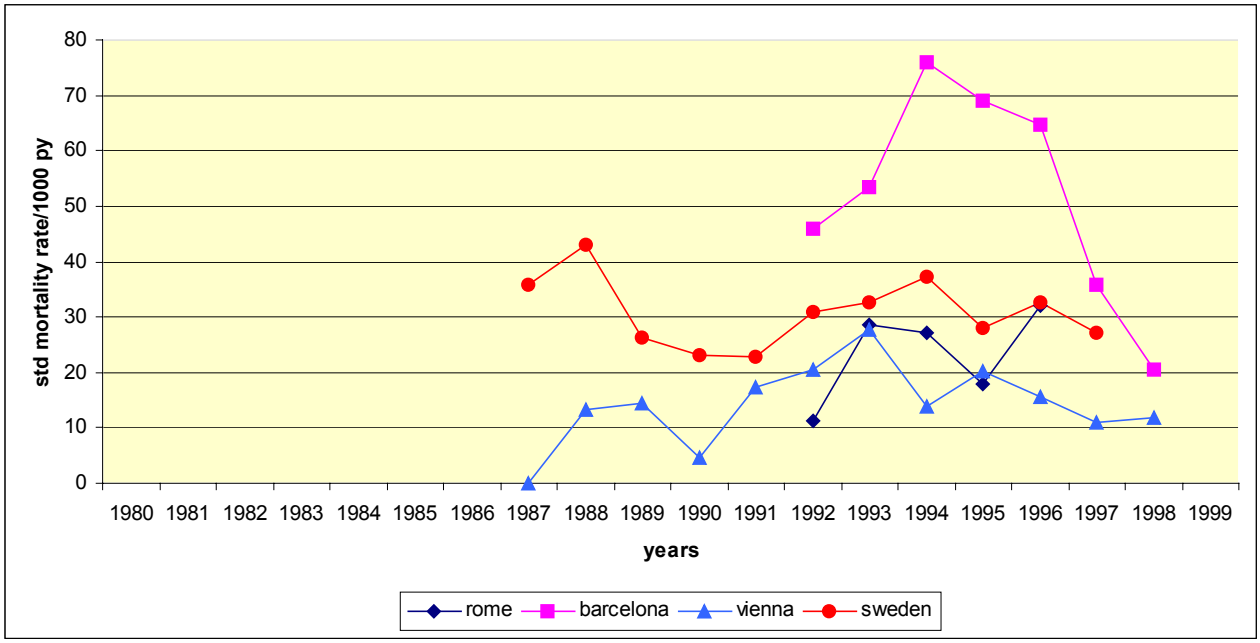
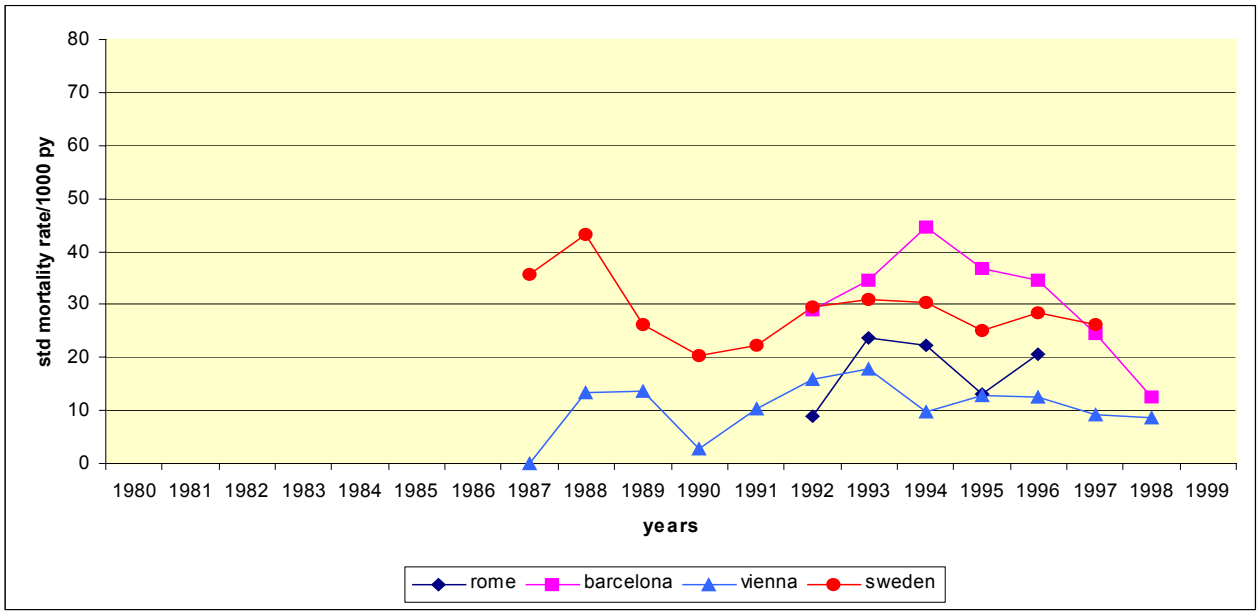


Figure 4 - Overall mortality excluding deaths from AIDS: standardised mortality rates (males and females)



5.2 Survival analysis by gender and age on cohorts of opiate addicts in different European countries

Kaplan-Meier analysis has been performed in order estimate survival probability at different points of time for each cohort. The survival curves of the analysed cohorts describe the overall mortality trend, in terms of probability to be alive after different points in time since the enrolment.

All the survival curves (figure 5) except those of Sweden and of Barcelona were close to each other and the survival probability ranged from 92% to 97% after 48 months since the enrolment. Sweden after 48 months has a survival probability of 88% after 48 months and opiate users in Barcelona had the lowest probability of being alive after 48 months (1 subject out 5 died after 4 years).

Table 12 summarises the risks of dying at 24 and 48 months since entry into treatment by gender.

The cumulative risk of dying within 2 years since entry into treatment ranged from 11% in Barcelona to 1.6% in Amsterdam for males and from 9% in Barcelona to 1% for Amsterdam, Vienna and Dublin for females. The differences between genders in cumulative risk of death observed early after few months, remained strong also in the following period, doubling every where except for Denmark. Kaplan-Meier analysis has been carried out also taking into account the age at enrolment of the enrolled individuals. Subjects have been divided into 3 groups on the basis of the starting age.

Figures 6,7,8 show the survival curves of subjects entering treatment between 15-24, 25-34, 35-39 years. In the younger group, even if with same differences, all the curves are lined up to each other and survival probability ranges from 97% to 87%.

The survival curves of people entering the study between 25-34 years remain lined up to each other, except those of Sweden and Barcelona where the survival probability decreases sharply; for Barcelona the decrease is stronger reaching about 78% after 48 months of follow-up. For the cohort of Barcelona, in this age group deaths from AIDS started contributing to the strong reduction in survival probability, reduction more evident in the age group 35-49 years.

Different factors could be responsible of these differences, age, gender, time of enrolment, route of administration, etc. A Cox regression analysis has been carried out for those cohorts where additional information on potential determinants or confounders are available.

Figure 5

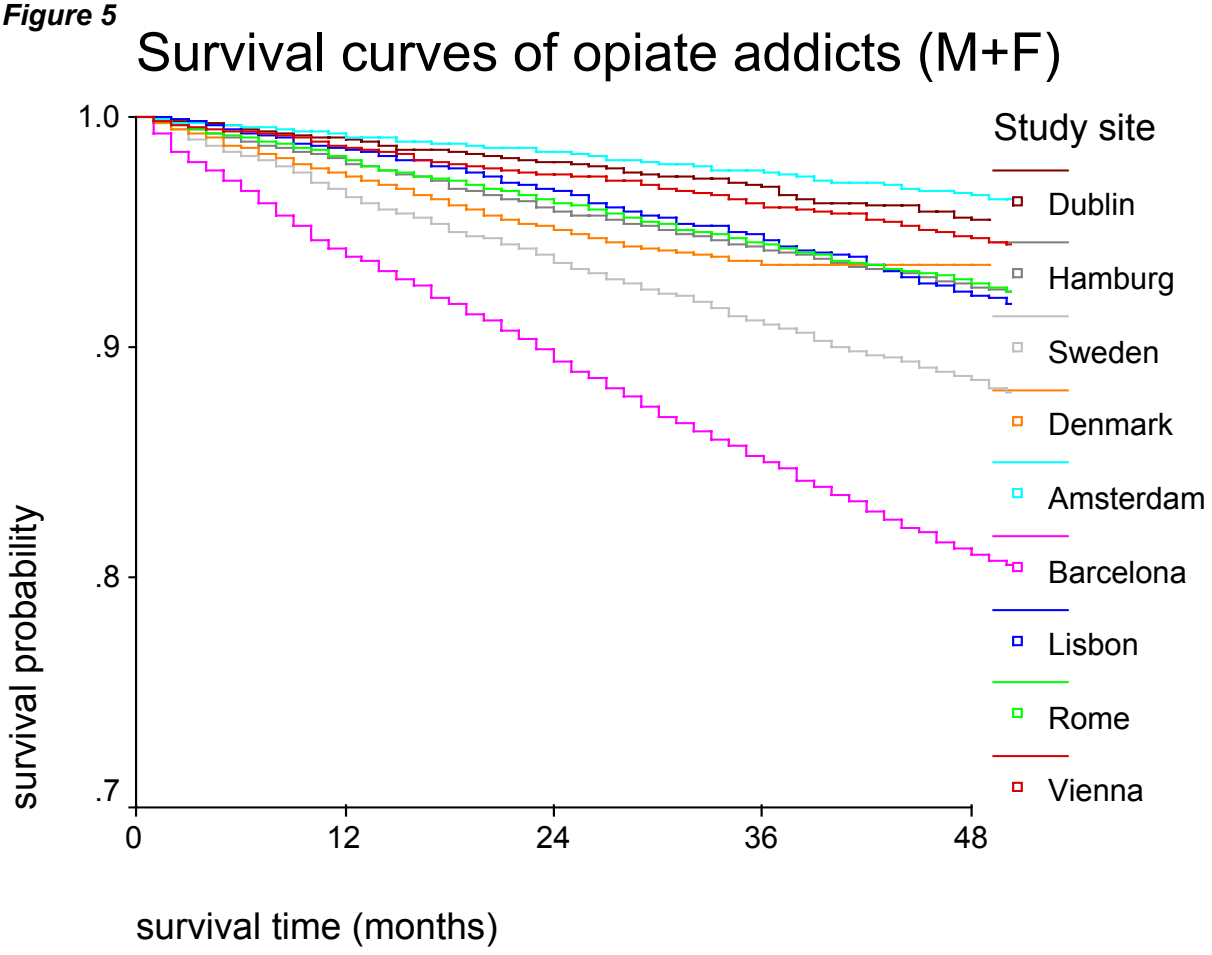


Table 12 - Risk of death by time and gender

Study site	*Risk at 24 months of follow-up and 95% C.I.*				*Risk at 48 months of follow-up and 95% C.I.*			
	Male		Female		Male		Female	
Barcelona	0.112	0.101-0.125	0.087	0.068-0.108	0.198	0.184-0.213	0.166	0.141-0.192
Rome	0.037	0.031-0.043	0.040	0.026-0.057	0.073	0.065-0.081	0.069	0.052-0.090
Sweden	0.068	0.058-0.079	0.052	0.038-0.070	0.123	0.111-0.137	0.092	0.074-0.114
Amsterdam	0.016	0.012-0.022	0.012	0.004-0.023	0.037	0.030-0.044	0.026	0.015-0.041
Vienna	0.030	0.024-0.038	0.012	0.005-0.022	0.065	0.055-0.074	0.028	0.018-0.040
Denmark	0.051	0.045-0.058	0.042	0.032-0.054	0.068	0.061-0.076	0.054	0.043-0.067
Lisbon	0.035	0.026-0.045	0.024	0.007-0.048	0.078	0.065-0.092	0.075	0.048-0.109
Hamburg	0.040	0.032-0.048	0.043	0.031-0.059	0.071	0.061-0.081	0.082	0.065-0.101
Dublin	0.023	0.018-0.029	0.011	0.004-0.019	0.053	0.046-0.062	0.017	0.009-0.027

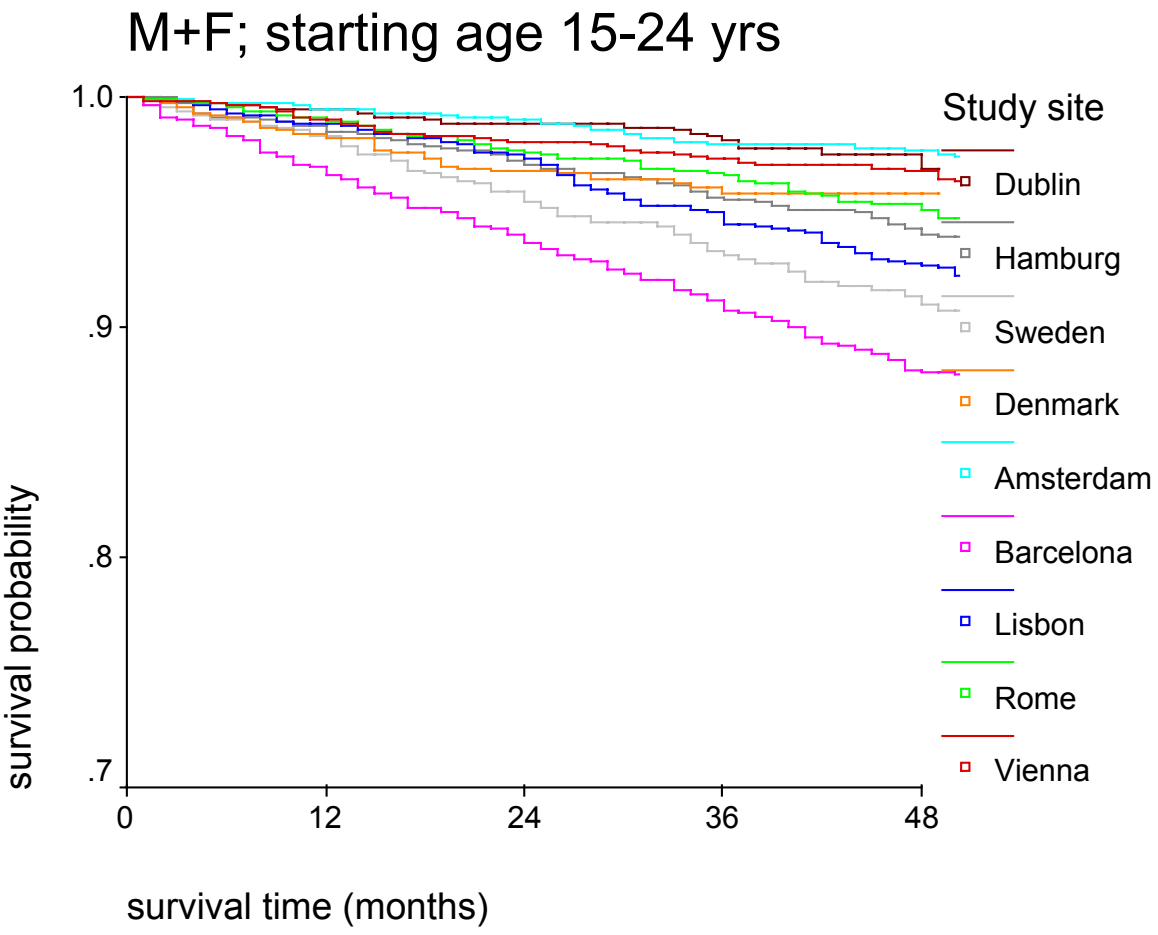


Figure 6

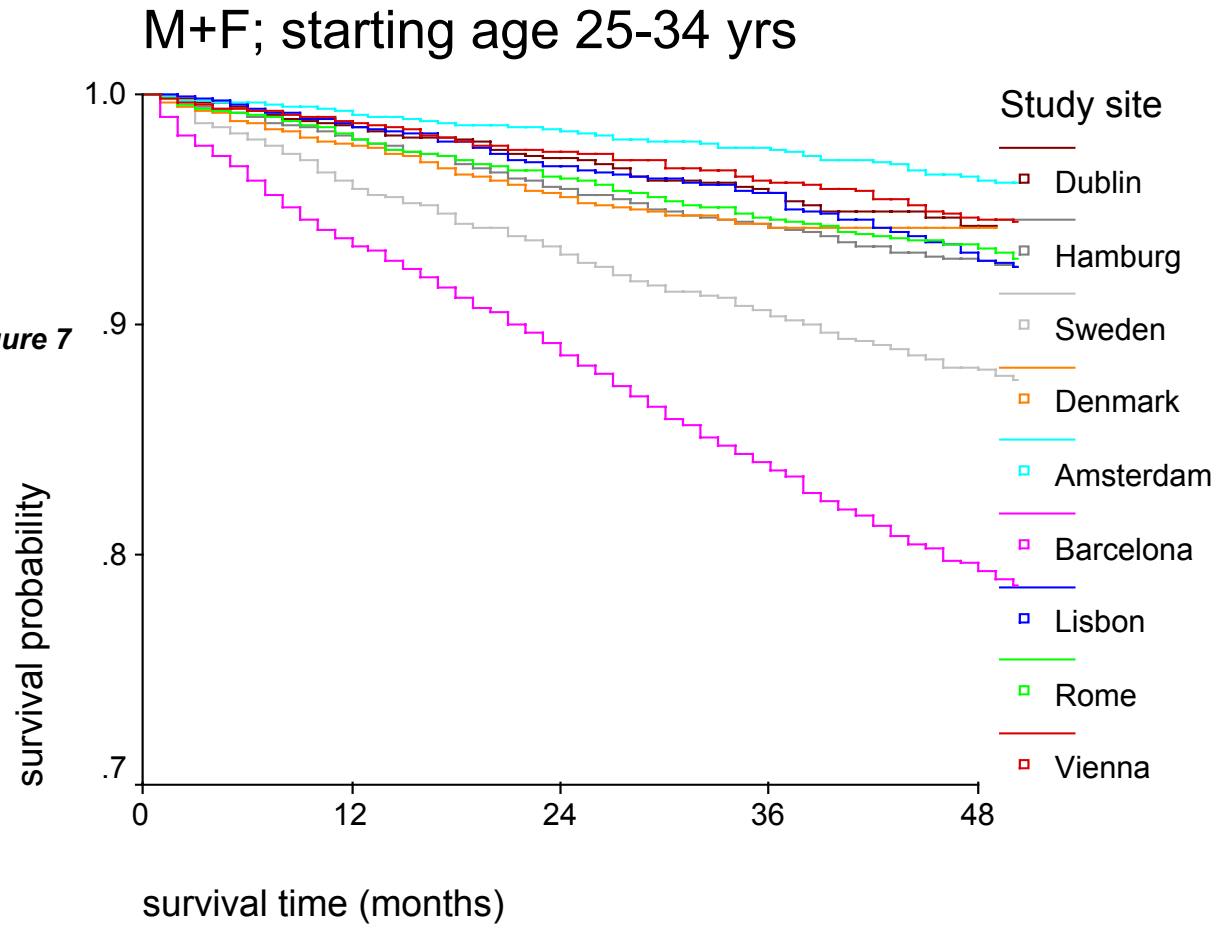
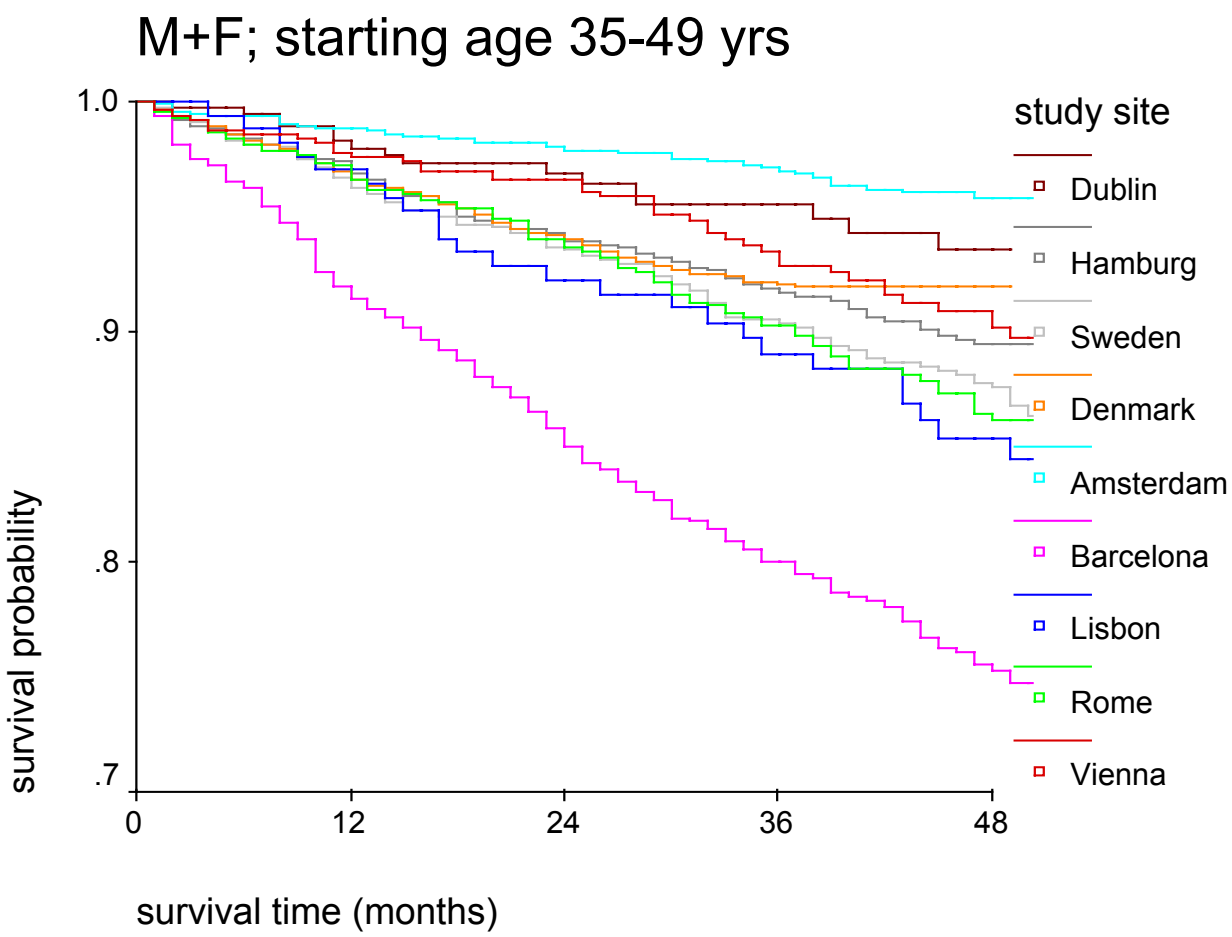


Figure 7


M+F; starting age 35-49 yrs
1.0
.9
.8
.7
survival probability
0
12
24
36
48
survival time (months)
study site
Dublin
Hamburg
Sweden
Denmark
Amsterdam
Barcelona
Lisbon
Rome
Vienna

5.3 Analysis of factors associated to mortality among opiate addicts in different European countries

Table 13 shows all the information available for each cohort. As discussed above, there is a wide heterogeneity among cohorts in age of enrolment, in period of enrolment and in the proportion of males and females enrolled. There were no missing information regarding age at enrolment, gender and calendar year which were the only three variables available for all cohorts. About 50% of drug users enrolled in the cohort of Dublin and Lisbon were younger than 25 years, while subjects recruited in Denmark were the oldest entering treatment (41.9% in the age class 35-49 years) compared with those from the other countries.

In all cohorts, most of the study population was represented by males; the proportion of females accounted for less than 20% in the cohorts of Rome and Lisbon; in Vienna and in Sweden about one third of all subjects enrolled in the study were females.

Since period of enrolment was different among study sites, calendar years have been grouped into three classes (1987-1990, 1991-1995 and 1996-1999). Only Vienna, Amsterdam, Sweden and Hamburg enrolled drug addicts over all the three periods. Rome and Denmark enrolled all the subjects only in one period, respectively between 1992-1995 and 1996-1999.

Additional information (age of first use, route of administration, educational level, employment status) was available for some cohorts only. In Rome, Lisbon and Barcelona about 50% of users started using drugs before their twenties. Compared with the other cohorts, in Denmark a lower proportion of opiate addicts started using drugs before 20 years. No information on age of first use was available for about 20% of subjects enrolled in Lisbon and Denmark.

Injection was the main route of administration for subjects enrolled in Rome and in Barcelona (69.5% and 55.4% respectively) while in Denmark and in Lisbon only one out of three addicts injected opiates. The proportion of missing information on route of administration was low in Lisbon, but in Rome, Barcelona and Denmark was higher than 10%.

In Rome, in Lisbon and in Barcelona, more than 65% of opiate addicts had an educational level less than 9 years, while in Denmark, all subjects for whom information was available (83.3%), had an educational level higher than 8 years.

Addicts were employed in 42.5%, 26.6% and 40% of the cases respectively in Rome, Barcelona and Lisbon even though in the latter cohort half of the subjects enrolled in the study had missing information on employment status.

Information on marital status was available only for Rome where 76.6% were single (in this category have been included also divorced, widows/widowers), while for Lisbon a very low proportion of information on marital status has been collected, and missing information accounted for 68.5%. No information was available for the remaining cohorts

5.3.1 Univariate analysis of the association of individual characteristics and mortality

The results of the univariate analysis of the association of individual characteristics and mortality are shown in table 14. A strong association of mortality with age at enrolment has been found for all cohorts. An excess risk of dying has been found in all age classes compared with the age class 15-24: in particular people entered after 34 years had a relative risk of death ranging from 1.31 in Sweden to 2.91 in Rome.

Females had a lower mortality risk than males in all sites, but Hamburg. However, the difference in mortality risk between genders, was not statistically significant in Rome and Lisbon.

No statistically significant association has been found between age of first use and the risk of dying among opiates addicts, but in Lisbon where subjects who started using drugs at the age class 20-24 years and those with missing information had a lower risk of dying compared with addicts who started before their twenties (RR=0.66, p=0.01).

Route of administration seemed to be one of the most important risk factor. Injectors had an higher risk of death than non injectors: the relative risk of death ranged from 1.28 for Denmark to 2.52 for Lisbon. In Rome and in Barcelona a higher risk of dying compared with non injectors has been found among those subjects with no information on route of administration (RR=1.78, p=0.004 and RR=1.56, p=0.001 respectively).

In the cohorts enrolled in Barcelona, Rome and Lisbon (where information on educational level was available), the risk of death of opiate addicts decreased with increasing educational level. In particular, addicts with an educational level higher than 8 years had a lower risk of mortality than those with an education lower than 5 years (RR=0.70, p=0.03; RR=0.56, p=0.001; RR=0.59, p=0.001 respectively in Rome, Lisbon and Barcelona). In Lisbon and in Barcelona, the group with missing information on education showed respectively a lower and an higher risk of dying compared with drug addicts with the lowest educational level. Where information on employment status was available, it has been found that addicts employed had a lower risk of dying than those not having a job (RR=0.65, p=0.001 in Rome and RR=0.66, p=0.001 in Barcelona). In Lisbon subjects with missing information on employment status showed a lower risk of dying (RR=0.56, p=0.001) compared with those without a job.

In Lisbon cohort, drug addicts not single had a mortality risk about 50% higher than those single (RR=1.51, p=0.05) while in Rome no association of marital status with mortality has been found.

5.3.2 Cox regression analysis

To compare mortality between study sites, the potential confounding effect of variables, which univariate analysis showed to be associated with mortality risk, should be taken into account. Unfortunately the only variables available for all cohorts were age at enrolment and gender. The results of the Cox regression analysis are shown in table 15. For the purposes of the multivariate analysis, Rome has been considered as the reference category. Adjusting for age and gender opiate addicts in Vienna, Amsterdam and Dublin showed a lower mortality risk compared with Rome (RR=0.75, 95% C.I0.64-0.88;

RR=0.52, 95% C.I.=0.45-0.60; RR=0.62, 95% C.I.=0.50-0.77 respectively) while Lisbon, Barcelona and Sweden had higher mortality risk (RR=1.35, 95% C.I.=1.16-1.57; RR=2.58, 95% C.I.=2.28-2.91; RR=1.58, 95% C.I.=1.38-1.81 respectively). No difference has been observed in risk of dying for the cohort of Denmark and Hamburg compared with Rome cohort. To investigate the possible differences between genders, Cox regression analysis has been performed separately for males and females. It showed that the higher overall mortality risk observed for the cohort of Lisbon and Sweden compared with Rome was mainly due to mortality among males (RR=1.36, 95%C.I.=1.15-1.61; RR=1.66, 95%C.I.=1.43-1.93) since among females the higher risk of dying was not statistically significant. Females in Vienna, Amsterdam and Dublin had a lower risk of dying than in Rome (RR=0.42, 95%C.I.=0.29-0.61; RR=0.41, 95% C.I.=0.28-0.58; RR=0.31, 95% C.I.=0.18-0.56 respectively).
No strong differences between genders have been observed for the cohorts of Barcelona, Amsterdam, Denmark and Hamburg.

5.3.3 Cox regression analysis for Rome, Lisbon, Barcelona and Denmark

The differences observed in the age and sex adjusted analysis might be due to other characteristics of the selected cohorts. Only four sites (Rome, Lisbon, Barcelona and Denmark) had additional information that could be analysed in multivariate model. In this case, taking into account two additional important variables, such as age at first use and route of administration, which are strongly related to mortality, Lisbon and Barcelona showed (table 16) even higher excess mortality compared to Rome as shown in the previous analysis (table 15), and Denmark showed an excess mortality compared to Rome which was not observed before (table 15).
An inverse relationship has been found between age at first use and risk of dying (20-24 years RR=0.85, 95%C.I.=0.73-0.93; >24 years RR=0.72, 95%C.I.=0.64-0.86).
As already found in the univariate analysis, the risk of dying increased among injectors compared with non injectors (RR=1.64, 95%C.I.=1.47-1.82).

5.3.4 Final remarks

Results of the advanced analysis carried out within the project, confirmed a wide heterogeneity of mortality across countries. Multivariate analysis, in particular, proved that many factors are associated to mortality and can affect comparisons across countries, particularly age and gender distribution, route of administration and social conditions. However, it must be taken into account that other factors not considered here, could be responsible of mortality risk: type of drugs, frequency of use and being in treatment have been found to be associated with the risk of dying. No information were available for these other potential determinants or confounders.
It's worth noting that the category including missing information of some variables showed statistically significant association to mortality. Both the availability of additional information on drug addicts entering treatment centres ant their completeness are important requirements for analysing factors associated to

mortality within each cohort and for improving comparability across different study sites. However, age and gender standardised mortality rates among dug addicts can provide a useful measure of the impact of problem drug use on mortality in different countries, leaving to additional specific study protocols the investigation of potential mortality risk factors.

Table 13 - Characteristics of the analysed cohorts

	Vienna		Rome		Lisbon		Barcelona		Amsterdam		Denmark		Sweden		Hamburg		Dublin	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Age at enrolment																		
15-24	1618	34.6	1644	27.8	1260	49.9	1172	26.0	1324	27.3	1384	18.5	944	23.5	1410	31.3	2969	56.2
25-29	1425	30.4	1987	33.6	775	30.7	1450	32.2	1454	30.0	1420	19.0	1041	25.9	1346	29.9	1174	22.2
30-34	1003	21.4	1344	22.7	322	12.8	1190	26.4	1115	23.0	1536	20.6	977	24.3	984	21.8	711	13.5
35-49	637	13.6	944	15.9	168	6.7	689	15.3	960	19.8	3132	41.9	1061	26.4	764	17.0	429	8.1
Mean age at enrolment		27.6		26.6		25.3		28.6		29.0		32.7		30.1		28.2		24.9
Gender																		
male	3243	69.3	4872	82.3	2024	80.2	3427	76.1	3726	76.8	5496	73.6	2858	71.0	3262	72.4	3766	71.3
female	1440	30.7	1047	17.7	501	19.8	1074	23.9	1127	23.2	1976	26.4	1165	29.0	1242	27.6	1517	28.7
Calendar year																		
87-90	758	16.2							*85-90*	3823	78.8		*87-90*	1305	32.4	*90*	63	1.4
91-95	2081	44.4	*92-95*	5919	100.0	*92-95*	2159	85.5	*92-95*	3912	86.9	*91-95*	895	18.4			*91-95*	1677	41.7	*91-95*	3613	80.2	*94-95*	2478	46.9
96-98	1844	39.4			*96-98*	366	14.5	*96*	589	13.1	*96*	135	2.8	*96-99*	7472	100.0	*96-97*	1041	25.9	*96*	828	18.4	*96-97*	2805	53.1
Age of first use																		
<20			3067	51.8	1155	45.7	2347	52.1			2380	31.9						
20-24			1796	30.3	487	19.3	1299	28.9			1471	19.7						
>24			717	12.1	386	15.3	737	16.4			1937	25.9						
missing			*339*	*5.7*	*497*	*19.7*	*118*	*2.6*			*1684*	*22.5*						
Route of administration																		
non-injection			1214	20.5	1673	66.3	1214	27.0			4279	57.3						
injection			4107	69.5	764	30.3	2495	55.4			2190	29.3						
missing			*598*	*10.1*	*88*	*3.5*	*792*	*17.6*			*1003*	*13.4*						
Education (yrs)																		
<5			925	15.6	1111	44.0	518	11.5										
5-8			2998	50.7	575	22.8	2813	62.5										
>8			1337	22.6	444	17.6	1048	23.3			6221	83.3						
missing			*659*	*11.1*	*395*	*15.6*	*122*	*2.7*			*1251*	*16.7*						
Employment status																		
no			2837	47.9	246	9.7	2941	65.3										
yes			2513	42.5	1015	40.2	1197	26.6										
missing			*569*	*9.6*	*1264*	*50.1*	*363*	*8.1*										
Marital status																		
single			4531	76.6	615	24.4												
not single			1119	18.9	181	7.2												
missing			*269*	*4.5*	*1729*	*68.5*												
Vital status																		
alive	4401	94.0	5525	93.3	2214	87.7	3583	79.6	4407	90.8	7009	93.8	3431	85.3	3269	72.6	3909	74.0
died	282	6.0	367	6.2	311	12.3	918	20.4	446	9.2	383	5.1	592	14.7	390	8.7	113	2.1
lost to follow-up			27	0.5							80	1.1			845	18.7	1261	23.9

Table 14 - Univariate analysis of association of individual characteristics and mortality

	Vienna		Rome		Lisbon		Barcelona		Amsterdam		Denmark		Sweden		Hamburg		Dublin	
	RR	p-value	RR	p-value	RR	p-value	RR	p-value	RR	p-value	RR	p-value	RR	p-value	RR	p-value	RR	p-value
age at enrolment																		
15-24	1,00		1,00		1,00		1,00		1,00		1,00		1,00		1,00		1,00	
25-29	1,49	0,02	1,29	0,10	0,96	0,74	1,61	0,001	1,25	0,08	1,17	0,44	1,23	0,09	1,28	0,01	1,95	0,006
30-34	2,04	0,001	1,92	0,001	1,33	0,09	2,15	0,001	1,20	0,17	1,59	0,01	1,30	0,03	1,39	0,02	2,76	0,001
35-49	2,86	0,001	2,91	0,001	2,44	0,001	2,21	0,001	1,62	0,001	1,95	0,001	1,31	0,03	1,94	0,05	2,54	0,002
gender																		
male	1,00		1,00		1,00		1,00		1,00		1,00		1,00		1,00		1,00	
female	0,44	0,001	0,96	0,75	0,88	0,39	0,83	0,02	0,76	0,02	0,78	0,04	0,72	0,001	1,16	0,18	0,41	0,001
age of first use																		
<20			1,00		1,00		1,00				1,00							
20-24			1,09	0,44	0,66	0,01	0,92	0,32			0,99	0,96						
>24			1,22	0,20	1,00	0,99	0,91	0,34			1,04	0,75						
missing			1,06	0,77	0,66	0,01	1,06	0,75			1,24	0,11						
route of administration																		
non-injection			1,00		1,00		1,00				1,00							
injection			1,63	0,001	2,52	0,001	1,60	0,001			1,28	0,03						
missing			1,78	0,004	0,40	0,11	1,56	0,001			1,24	0,14						
education (yrs)																		
<5			1,00		1,00		1,00											
5-8			0,63	0,001	0,76	0,07	0,82	0,05										
>8			0,70	0,03	0,56	0,001	0,59	0,001										
missing			1,00	0,98	0,53	0,002	1,75	0,001										
employment status																		
no			1,00		1,00		1,00											
yes			0,65	0,001	0,82	0,27	0,66	0,001										
missing			1,13	0,470	0,56	0,001	1,69	0,001										
marital status																		
single			1,00		1,00													
not single			0,94	0,64	1,51	0,05												
missing			1,17	0,54	1,0	0,71												

Table 15 - Cox regression analysis

	Males and females			Males			Females		
	RR	95% CI	p-value	RR	95% CI	p-value	RR	95% CI	p-value
Study site									
Rome	1,00			1,00			1,00		
Vienna	0,75	0.64-0.88	0,001	0,87	0.73-1.04	0,12	0,42	0.29-0.61	0,001
Lisbon	1,35	1.16-1.57	0,001	1,36	1.15-1.61	0,001	1,26	0.87-1.83	0,20
Barcelona	2,58	2.28-2.91	0,001	2,62	2.29-2.99	0,001	2,35	1.77-3.12	0,001
Amsterdam	0,52	0.45-0.60	0,001	0,54	0.46-0.64	0,001	0,41	0.28-0.58	0,001
Denmark	1,00	0.87-1.16	0,95	1,05	0.89-1.24	0,51	0,79	0.57-1.11	0,18
Sweden	1,58	1.38-1.81	0,001	1,66	1.43-1.93	0,001	1,26	0.93-1.71	0,13
Hamburg	1,06	0.91-1.22	0,42	0,98	0.83-1.15	0,82	1,22	0.90-1.66	0,18
Dublin	0,62	0.50-0.77	0,001	0,71	0.57-0.90	0,001	0,31	0.18-0.56	0,001
Age at enrolment									
15-24	1,00			1,00			1,00		
25-29	1,32	1.20-1.44	0,001	1,31	1.18-1.46	0,001	1,31	1.09-1.58	0,004
30-34	1,63	1.49-1.80	0,001	1,71	1.54-1.91	0,001	1,30	1.05-1.59	0,01
35-49	1,96	1.77-2.16	0,001	1,90	1.69-2.12	0,001	2,18	1.77-2.68	0,001
Gender									
male	1,00								
female	0,82	0.75-0.88	0,001						

Table 16 - Cox regression analysis for Rome, Denmark, Lisbon and Barcelona

	RR	95% C.I.	p-value
Study site			
Rome	1,00		
Denmark	1,38	1.16-1.65	0,001
Lisbon	1,73	1.46-2.06	0,001
Barcelona	2,86	2.52-3.24	0,001
Age at enrolment			
15-24	1,00		
25-29	1,38	1.21-1.57	0,001
30-34	2,02	1.76-2.31	0,001
35-49	2,61	2.25-3.04	0,001
Gender			
male	1,00		
female	0,89	0.80-1.00	0,05
Age at first use			
<20	1,00		
20-24	0,85	0.73-0.93	0,005
>24	0,72	0.64-0.86	0,001
missing	0,83	0.70-0.98	0,03
Route of administration			
non injection	1,00		
injection	1,64	1.47-1.82	0,001
missing	1,44	1.24-1.67	0,001

6. Morbidity data

Additional aim of the project, was to test the feasibility of implementing a standardised methodology to assess general and cause-specific morbidity rates among drug addicts and among different subgroups of drug addicts within each cohort (e.g. males and females, injectors and non injectors etc.).

A brief questionnaire was developed in order to gather information on characteristics and availability/accessibility of morbidity data sources (Hospital Discharge Registers – HDRs - or others) and to verify the possibility to link such data with the cohorts enrolled in each study site.

The questionnaire consisted of two sections: in the first section of the questionnaire general information on the characteristics of existing national and/or local HDRs was required while the second one dealt with the description of any other sources of morbidity data (Infectious Diseases Register, TBC register, AIDS register).

More exhaustive information on morbidity data sources can be found in the questionnaires provided by each study site and included in this report (see Annex 4). The results concerning the availability and accessibility of Hospital Discharge Registries are summarised in Annex 5.

Information from the Netherlands were not provided through the questionnaire developed by the co-ordinating centre. Therefore, the characteristics of morbidity data sources are not summarised in table 8 but they are presented below.

The Netherlands: morbidity data

In the Netherlands, there is a National Register of hospital admissions that is called Prismant collecting some information on patients (date of birth, gender) and hospital (date of admission, length of admission, name of the hospital, department). In the Register, ICD-10 codes of admission diagnosis are recorded; data are delivered to the Central Office of Statistics. However, since a persons name is not available, personal linkage is impossible. The Municipal Health Service is co-ordinating a project called the “Hospital Project”. If a drug addict enters in a hospital, the hospital informs this project about this admission. The employees of the project advise the hospital regarding methadone dosage, tries to improve the treatment compliance, advises what to do in case of behavioural problems and co-ordinates in case of complicated treatment schedules. In the register of the Hospital Project, detailed information on patients is available and it will be possible to link this register to the mortality cohort. However, in this register, available up from 1989, the registration of diagnoses is poor. Although many letters of discharge are available within medical files, many are missing and diagnoses are not coded. These two registers are complementary and (theoretically, a combination of the two could give us the total picture) the register of the Hospital Project could be used to match hospital admission data to the methadone treatment data. Therefore, based on the

admission data and date of birth etc., data of Prismant could be added to those of the Hospital Register.

Other registers that are available are indeed a TBC register, AIDS register and HIV+ register. The TBC department and the drug department are co-operating, on the one hand methadone clients get an X-thorax at the TBC department, on the other hand the tuberculosis department registers the use of drugs and will advise people to join a methadone treatment. Since 1989, drug users with TBC (date of TBC diagnosis) are registered. There is sufficient patient information to link these data to the treatment data. A special AIDS register is available at the MHS, patient information is available and linkage could be possible. Date of AIDS diagnoses, assumed cause of HIV-infection (IVDU, Homosexual or heterosexual contacts) and mortality (date of death) is available. Finally there is a register of drug users who are found to be HIV+, this register is part of the Hospital Project register. As with the hospital project register, data for personal linkage is available. Some of them are tested within the cohort study, others during a hospital admission. Therefore it these data may be difficult to apply within a cohort study. Information of morbidity of the opiate users could be linked to the treatment data. However, privacy legislation may not allow this linkage and ethical committees should give their approval.

Annex 1

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Annex 2

Advanced analysis: proposals

Introduction

Every year the EMCDDA holds briefing meetings with the co-ordinators to discuss and plan activities to be performed within the projects. This year the Centre suggested, as done for other indicators, to invite one or two national experts (steering group) to broaden the discussion, get extra insight, and assist the co-ordinator in carrying out some tasks. On 19th January 2001 a small meeting has been held with the co-ordinator, the EMCDDA and members of the steering group in order to finalise the work plan to carry out the tasks scheduled by the project and to discuss further analysis to be done using the available data. On the basis of the available data, it was established to perform different analysis described in the following proposals.

The Agency for Public Health and the experts of the steering group will carry out the analysis using the data already collected from all partners participating in the EMCDDA project.

Study population

The study population will be represented by opiate addicts with the following inclusion criteria:

a. aged 15-49 years

b. enrolled between 1988-1998

c. followed-up 1988-1999

The information that will be included in the analysis are gender, date of birth, date of enrolment, vital status, date of death, cause of death, nationality, educational level, age of first use, route of administration, ecological data such as HIV prevalence, % of patients on methadone maintenance.

1st PROPOSAL

Objective

To investigate the impact of opiate use on mortality of young adults in different EU countries.

Methods

Data will be analysed by performing a descriptive analysis and comparing mortality of the cohort with that of the general population specifically for each site. This comparison will be performed through estimation of Standardised Mortality Ratios (SMRs), that involves the following steps:

- an expected number of cases (E), is calculated;
- the number of cases observed in each cohort (O) is compared with this expected number.

(E) is calculated by applying stratum-specific incidence rates obtained from a large reference population (in this contest the general population aged 15-49 of each study site) to the stratum-specific person-time of the study group. If (T) is the total person-time in the cohort, then O/T is the observed crude rate in the study group. E/T is the rate that would be expected in a population with the specific rates of the reference population and the person-time distribution of the cohort. The ratios of

these rates is (O/T)/(E/T)=O/E (*Standardised Mortality Ratio*).

The mortality rates of the general population, to be used as a standard to compute SMRs, will be provided by each study site. A preliminary analysis will be performed by extracting data on general population mortality from "The Demographic Yearbook" (1996 and 1998) where the available year mortality rates specific for gender and age are reported for each country. SMRs stratified by age (in five-year bands), will be calculated separately for males and females. Two sided 95% Confidence Intervals for standardised mortality ratios will be based on the Poisson distribution. For each study site, follow-up periods and the years for which mortality rates are available are shown in table 2.

Table 2

Study site	**Mortality rates: available year**		**Follow-up period**
Barcelona	*1994	1996	1992-1998
Rome	1991	1994*	1992-1996
Sweden	*1994	1996	1987-1996
Amsterdam	*1995	1996	1985-1996
Vienna	*1995	1997	1987-1998
Denmark	1995	1997*	1996-1998
Lisbon	*1995	1997	1992-1999
Dublin	*1995	1996	1994-1997
Hamburg	*1995	1996	1990-1998

*** year from which the mortality rate will be extracted**

The SMR produces an estimate of the excess mortality of opiate addicts compared to the general population of the same gender and age, but it is an appropriate measure for making any comparison across study sites.

Table that will be presented

Country / City	**Observed**		**Expected**		**SMR (95% C.I.)**	
	M	**F**	**M**	**F**	**M**	**F**
Barcelona						
Rome						
Sweden						
Amsterdam						
Vienna						
Denmark						
Lisbon						
Dublin						
Hamburg						

2nd PROPOSAL

Objective

To perform a survival analysis of opiate users of different cohorts.

Methods

Survival will be analysed by gender and age using Kaplan-Meier method. This analysis will provide the cumulative survival probability, that is an estimate of the proportion of all cases still alive at particular point of time. Besides the estimate of cumulative survival probability for each cohort, Kaplan-Meier method will be used to compare survival functions across different study populations. The existence of any difference in mortality between the groups compared will be evaluated through non parametric statistical tests (log Rank test, Wilcoxon test). Survival time will be measured from the start of the observation period (entering treatment) until death or the end of follow-up period, for a maximum length of 48 months.

In order to study the relationship between the risk of death and the population characteristics (individual and ecological) a Cox proportional hazards model will be used. The hazard function provides the estimate of risk of dying at different points of time. The hazard function is not a probability, but a death rate per unit of time.

The general form of the model is: $h(t)=[h_o(t)e^{(B_1X_1+B_2X_2+\ldots+B_pX_p)}]$

$h(t)$ = risk of dying at time t

h_o = risk of dying at baseline

x_1 to x_p = covariates (age, gender, country, HIV prevalence, % of patients on methadone maintenance, presence of harm reduction programs).

3rd PROPOSAL

Objective

1. To analyse aids and overdose mortality trends in the cities of, Barcelona, Vienna and Sweden, in men and women, according to age group.
2. To compare mortality trends in these groups in the increasing mortality period (1992-1995) and in the decreasing one (1996-1998) and analyse the tendency in our cohort versus the tendency in general population.
3. To analyse the effect of the follow-up period on AIDS mortality in the cohorts of Barcelona, Vienna and Sweden.

Methods

A Poisson regression analysis will be carried out in order to investigate whether any difference in mortality for two follow-up periods (Table 3) exists among the cohorts of Barcelona, Sweden and

Vienna. The cut off point of the follow-up periods has been chosen in order to better understand if the introduction of the new antiretroviral therapies since 1995 lead to a decrease in mortality from AIDS.

For AIDS: trends comparison will be carried out through Poisson regression models, testing the interactions between the variable year and other study variables (city, sex and age group). Separate models will be obtained for the two periods of study (1992-1995 and 1996-1998) and for men and women.
For overdose we will do the same analysis changing the periods of study in function of the trends

Table 3

Study site	**Selected Period(s)**	**Cause of death (ICD IX code)**
Barcelona	1992 – 1995, 1996 – 1998	**X**
Sweden	1987 – 1995, 1996 – 1997	**ICD X since 1997**
Vienna	1987 – 1995, 1996 – 1998	**X**

This analysis allows to compare the tendencies in the different cohorts (AIDS and overdose death) and to fix the possible selection bias in the case of the slopes will be different between the cohort curves and the general curves.

4th PROPOSAL

Objective

To perform a survival analysis for overall mortality of opiate users in the cohorts of Barcelona, Rome, Denmark, Lisbon.

Methods

Survival will be analysed by gender and age, age of first use, route of administration, educational level using Kaplan-Meier method. The multivariate analysis will be carried out using a Cox proportional hazard regression model. Survival time will be measured from the start of the observation period (entering treatment) until death or the end of follow-up period for a maximum length of 48 months. Survival will be analysed taking into account the individual data (measured at entering in treatment) such as age of first use (5 yrs age category), route of administration (injection vs other), educational level (low vs high).

Table that will be presented synthesising the results of Cox regression model.

Variable	Exp (B) *	95% CI
Age of first use		
Gender		
Country		
Route of administration		
Educational level		

* hazard ratio estimate

5th PROPOSAL

Objective

To estimate the effect of age, gender and different outcome measures on mortality rates across cohorts of opiate users; the three outcome parameters will be compared are crude mortality rates, standardised mortality ratios (comparison with general population) and adjusted rate ratios (comparison with an index population of drug users).

Introduction

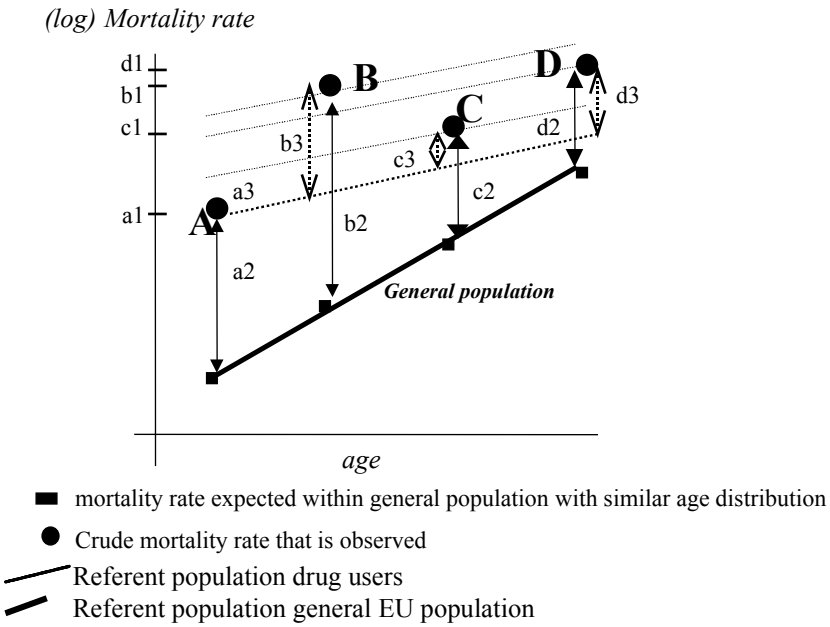
Crude mortality rates lack adjustment for differences in the distribution of age and sex between different populations, Standardised Mortality Ratios use the general population as reference in order to adjust for age and sex differences and the population of drug users is used as a reference when adjusted rate ratios are described. As differences in the distribution of age and sex will explain part of the variation between the different mortality rates that are found, proper adjustment procedures are of major importance in our quest to make mortality figures more comparable.

Some studies among drug users indicate that Standardised Mortality Ratios among the younger populations and populations with a high percentage of females tend to be higher than SMR of older populations or populations with a high percentage of males. Among the general population relative differences in mortality rates between different age categories and between males and females are generally higher than similar relative differences among populations of drug users.

The interaction of age and sex in relation to mortality is expected to limit the comparability of mortality figures among different study populations. In figure 3 an example of four cohorts is given. Cohort A consists of very young drug users. Because the expected mortality is very low, the Standardised Mortality Ratio (a2 / expected at general population) is highest among A. However, the absolute mortality rate of cohort A (a1) is lowest. The highest absolute mortality rate is observed among the oldest cohort (D; d1), however, the lowest SMR (d2/expected at general population) is observed in this cohort as well. Mortality rates and SMR values of cohorts B and C are in between A

and D. However, if we compare the data of the drug users cohorts (a3,b3,c3 and d3 / expected at referent population drug users) in order to adjust for age and sex another ranking order will appear.

Figure 3 Different outcome parameters in mortality studies



Ranking

	Crude MR (1)	SMR(2)	model , RR (3)
A	4	1	4
B	2	2	1
C	3	3	2
D	1	4	3

In this study we will focus on the relationship between age, sex and mortality rates among drug users in order to enhance the comparability between different studies. It is hypothesised that different outcome measures will result in different ranking of cohorts in terms of severity of the mortality problem. Moreover, it is hypothesised that the relation between age and mortality and gender and mortality does not differ between different cohorts of drug users. If this is true, we would be able to adjust for different distributions of age and sex in a proper way and enhance the comparability of mortality figures derived from different cohorts of drug users.

Methods

Data of nine cohorts that were collected by the EMCDDA Working Group of cohort studies among drug users will be used to conduct this analysis. To enhance comparability and limit the effect of trends over (calendar) time the first five years of each cohort are selected. As calendar time increases, the age of the population increases as well and therefore long term trends during (calendar) time may interfere with the relation of mortality and age. Second, as the study period

increases an increasing percentage of the population may have stopped using drugs or misclassification biases may cumulate.

The cohorts of Amsterdam and Barcelona are divided in two periods. Because all contact dates of the individual cohort members are known it is possible to start a new cohort after five years. Most cohort studies run during the 1990s, only the Vienna and Sweden cohorts include observation time of the late 1980s as well.

Analysis

Mortality rates will be presented as number of deaths per 1,000 person-years. Standardised mortality ratios will be calculated with the EU population during the 1990s as a standard population. To analyse the mortality rates of the different cohorts Poisson regression analysis will be conducted. The following regression model will be implemented:

To compare mortality rates of drug users with mortality rates of the EU population and to compare mortality rates of different cohorts of drug users taking into account the interaction parameters.

Mortality Rate = $e^{+ 1\,(age) + 2\,(sex) + 3\,(drug\ use) + 4\,(drug\ use * age) + 5\,(drug\ use * sex) + 6\,;\,15\,(cohort\ 1:\ 9)}$

: represents the baseline mortality incidence rate: youngest age category (15-19yrs) female, general population.

1 represents the rate ratios of age among the population of the European community during the 1990s.
(per five years categories; 15-19 yrs = 0) as a continuous variable. 1 will be higher than 1.

2 represents the rate ratio of males (1) compared to females (0) among the population of the European community during the 1990s. 2 is expected to be higher than 1.

3 represents the estimated rate ratio of drug users compared to the general population of the 'zero' category: youngest 15-19 years and female. 3 is expected to be higher than 1.

4 represents the (relative) interaction of age, drug use and mortality.
4 is expected to be lower than 1: the rate ratio is expected to decrease with increasing age.

5 represents the lower rate ratio of females to males among drug users population, compared to the general population, the (relative) interaction of sex, drug use and mortality. 5 is expected to be lower than 1.

(6:15) represent the nine rate ratios of the distinguishable drug users cohorts.

Tables that will be presented:

Method section:

Size, period and location of the selected cohorts

Country / City	**Selected Period(s)**	**No. of person-years**	**No. of deaths**
Amsterdam	1990 – 1994, 1995 - 1999		
Barcelona	1992 – 1996, 1997 - 1999		
Denmark	1996 – 1999		
Dublin	1994 - 1997		
Hamburg	1990 - 1994		
Lisbon	1992 - 1996		
Rome	1992 - 1996		
Sweden	1987 - 1991		
Vienna	1988 - 1992		

Results section:

Age and gender distribution of different cohorts

Country / City	**Age distribution**							**Sex**	
	15-19	**20-24**	**25-29**	**30-34**	**35-39**	**40-44**	**45-49**	**male**	**female**
European Union	%	%	%	%	%	%	%	%	%
Amsterdam (I: '90 - '94)	%	%	%	%	%	%	%	%	%
(II: '95 - '99)	%	%	%	%	%	%	%	%	%
Barcelona (I: '92 - '96)	%	%	%	%	%	%	%	%	%
(II: '97 - '99)	%	%	%	%	%	%	%	%	%
Denmark	%	%	%	%	%	%	%	%	%
Dublin	%	%	%	%	%	%	%	%	%
Hamburg	%	%	%	%	%	%	%	%	%
Lisbon	%	%	%	%	%	%	%	%	%
Rome	%	%	%	%	%	%	%	%	%
Sweden	%	%	%	%	%	%	%	%	%
Vienna	%	%	%	%	%	%	%	%	%

Results of the multivariate Poisson-regression analysis

Variable	**Beta (SE)**	**Rate Ratio (95% CI)**
Basic Incidence		
Age per 5 yrs age category		
Sex		
Drug users (index)		
Age * Drug users		
Sex * Drug users		

Table 4: Mortality among cohorts of drug users (15 to 49 years)

Country / City	**No. Deaths**	**Mortality rate (95% CI)**	**Rank No.**	**Standardised Mortality Rate (95% CI)**	**Rank No.**	**Age gender adj. Rate ratio**	**Rank No.**
Standard		***None***		***EU population***		***Drug users***	
Amsterdam (I: '90 - '94)							
(II: '95 - '99)							
Barcelona (I: '92 - '96)							
(II: '97 - '99)							
Denmark							
Dublin							
Hamburg							
Lisbon							
Rome							
Sweden							
Vienna							

Annex 3

Guidelines for carrying out mortality cohort studies among drug addicts

The following have contributed to the development of these guidelines on Cohort Mortality Studies:

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Status of these Guidelines

These guidelines consist of a protocol to design, carry out and analyse mortality studies among selected groups of problem drug users. The guidelines have been extensively discussed by a group of experts from several European countries, and they have been applied in different cities or countries is Europe.
The development of the guidelines has been carried out by the Agency of Public Health of Lazio Region in close collaboration with the EMCDDA.

Supporting documents

Review of scientific studies of mortality among drug users and feasibility study for a common methodology for monitoring overall and cause-specific mortality among drug users in Member States of the European Union

Implementation, follow-up and analysis of cohort studies on mortality among drug users in European Union Member States (CT.97.EP.03)

Co-ordination of implementation, follow-up and analysis of cohort studies on mortality among drug-users in European Union Member States (CT.98.EP.12)

Mortality of drug users in the EU: co-ordination of implementation of new cohort studies, follow-up and analysis of existing cohorts and development of new methods and outputs (CT.99.EP.07) Draft

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1. Preface

Drug-related deaths and mortality among drug users is one of the five key epidemiological indicators used by the European Monitoring centre on Drugs and Drug Addiction (EMCDDA) to estimate the prevalence and health consequences of drug addiction. This indicator has two complementary components; a) the general and cause specific mortality among problem drug users and b) the statistics on direct drug-related deaths among the general population.

There is strong evidence that problem drug users have a higher risk of death in comparison with general population of the same gender and age. The increased risk is only partly due to acute intoxication (overdoses) but other causes of death have a strong impact on mortality of this population. Therefore, data on drug related-deaths and mortality figures estimated in defined groups of drug addicts followed-up over time constitute useful complementary indicators of health effects of drug abuse.

Longitudinal studies have their strength in estimating the actual mortality rate among drug users, although it must be taken into account that longitudinal studies are carried out on selected groups that may be not representative of the whole drug addicts population.

The EMCDDA is co-ordinating a project aimed to promote and co-ordinate the setting up of cohorts of problem drug users recruited through treatment centres in EU Member States, in order to produce comparable and reliable estimates of overall and cause-specific mortality rates and analyse temporal trends in mortality for monitoring purposes.

The project has been developed in the following phases:

- overview of published studies on mortality of problem drug users that have been undertaken in Europe;
- development of a standardised protocol to assess overall and cause specific mortality rates among problem drug users (PDUs);
- evaluation of the feasibility of implementing the standardised methodology in different European countries;
- promoting and co-ordinating the implementation of cohorts of problem drug users recruited in treatment centres;
- joint analysis of available cohorts.

The literature review of studies on mortality among drug users in Europe (published between 1980-1996) aimed to outline the knowledge available on PDUs mortality and to assess the

comparability of data from different countries.
The literature revision pointed out that comparability of results on the basis of published data is difficult, because of heterogeneity of enrolment criteria of drug users, follow-up procedures and methods of data analysis. Most studies have been conducted in eight European countries only, and no data were available for the other countries.

In order to promote the recruitment and follow-up of cohorts of drug addicts in the UE countries according to a common methodology, a standard protocol has been drafted by a group of experts from eleven European Countries (Austria, Denmark, Finland, Germany, Greece, The Netherlands, Ireland, Italy, Portugal, Spain and Sweden) collaborating in the EMCDDA project co-ordinated by the Agency of Public Health of Lazio Region, Italy.

The protocol has been used to develop these guidelines that are intended to help researchers in implementing cohort studies on drug addicts mortality and to enhance the comparability of results from different countries.
More specifically, the guidelines focus on the most important issues to be taken into account in enrolling and following-up cohorts of drug addicts.

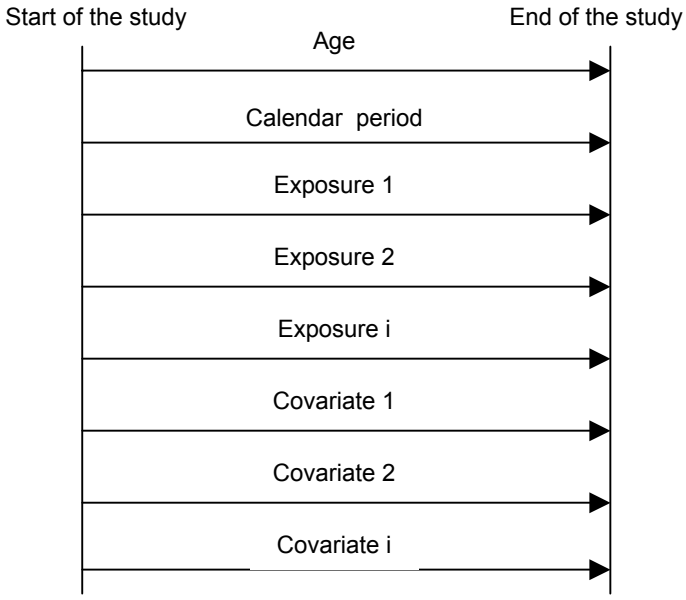
Improving comparability of overall and cause-specific mortality rates estimates in European countries, is not the only aim of the guidelines. Actually, although many evidences have been produced on mortality of drug addicts, there are a number of remaining questions and types of analysis which need to be addressed such as analysing specific mortality patterns related to different substances of abuse and evaluating the protective effect of different types of treatments on drug addicts mortality. A specific section has been included introducing a possible case-control approach to address these issues.

2. Epidemiological background

The cohort or follow-up study is an observational analytic study in which a group or groups of individuals are defined on the basis of presence or absence of exposure to a suspected risk factor for a disease or another specific condition (such as drug addiction). Subjects enrolled are followed over a period of time to assess the occurrence of the event of interest which must be absent at the recruitment (death, incidence of disease, change in a biologic measure, or health status). The follow-up should be long enough to allow the development of the outcome.

The cohort design explicitly includes the passage of time. During the follow-up experience of members of a cohort, some determinants of health may continually change as the participants age, calendar period, cumulative exposure, exposure rate, latency, time to the end of exposure, exposure to potential confounders (figure 1). The dynamic nature of many risk factors and their relations in time to disease can only be considered in the cohort design while it is absent from cross-sectional investigation and may be investigated with difficulty through the case-control study design.

Figure 1: Multiple dimension of time in a cohort study



From Epidemiologic Reviews 1998, vol 20

Cohort studies may be classified as either prospective or retrospective, depending on the temporal relationship between the initiation of the study and the occurrence of the event. In retrospective cohort studies both the exposure and outcome have already occurred when the study is initiated.

Obtaining complete and accurate information on all participants is the primary requirement for the validity of a cohort study. Since retrospective cohort studies evaluate exposures occurred in the past, the validity of the study depends on the ability to collect information from pre-existing data recorded for other purposes. Nevertheless difficulties can arise from the inability to collect information on potential confounding factors, often missing from such records. On the contrary in the prospective studies, information can be collected according to the research questions being evaluated and taking into account possible confounding variables.

The cohort members must be classified according to factors and period of exposure. Retrieving information on exposure at individual level could be useful in making relationship between exposure and risk of developing the outcome.
Follow-up procedures and criteria for selecting exposed and non-exposed (reference population) individuals must be well defined.

2.1 Study population and inclusion criteria

The choice of a particular group to serve as the study population for any given cohort study is related both to the hypotheses under investigation and specific features of the study design.

The objectives can vary widely among different cohort studies, and much attention must be paid in planning a retrospective or prospective study. An important phase in designing a cohort study is represented by the selection of subjects to be included in the study. The inclusion criteria must be clear and not ambiguous. For each individual, the date on which observation begins must be well defined; after that date the individual contributes person-years of observation and is at risk to develop events of interest. It's possible to distinguish between a close and an open study population. In the former there are not new people entering the cohort after the beginning of the study and in the latter members can be gained over time.

An individual does not enter the cohort, until all entry criteria have been satisfied. The date of exit from the study is the last date on which an individual can contribute person-years at risk. For each subject, the beginning and the end of the observation period have to be specified. For each subject enrolled in the study at the end of the follow-up period the occurrence of the outcome is ascertained. It's important to note that for each subject, date of entry into the study and date of first exposure are not necessarily the same, and will often be different. It's possible to distinguish between prevalent and incident cases. Subjects entering a prevalent cohort (prevalent cases) are those who are present at the beginning of the study. In incident cohort, people can be enrolled over time as soon as they satisfy the inclusion criteria.

Another important consideration in designing cohort study is the selection of an appropriate comparison population that is presumed to be non-exposed to the factor(s) of concern. Actually the first research question addressed in a cohort study is whether the occurrence of the outcome observed is different between exposed and non-exposed individuals.

The choice of the reference population depends on the possibility of making comparisons among subgroups, with different levels of exposure, within the same cohort. Since often it's very difficult to identify a subgroup of the cohort that can safely be assumed to be non-exposed for comparison, the general population can be used as reference group.

2.2 Data collection

The information on individuals selected to be enrolled in the study can be collected from a variety of sources (e.g. hospital register, clinical records). It's necessary to obtain complete and accurate data on all study participants. Some data such as demographic characteristics are essential to be collected to allow the vital status ascertainment. Completeness of identifier has to be considered as inclusion criteria to be enrolled in the study. When this information is missing subjects must be considered not eligible for the inclusion into the study.

Information concerning the exposure may be obtained from medical records; these may contain sufficient data to classify individuals according to exposure status as well as provide demographic and other necessary information. The advantage is that information is available for a high proportion of the cohort and is relatively inexpensive to obtain, but the level of detail may be insufficient. Information on exposure can be recorded in qualitative or in quantitative terms and supplied by the study subjects themselves, through interviews or questionnaires. This is the best way to get information on potential confounding variables, even if the individuals could not be able to provide details on their level of exposure; moreover this approach is rather expensive, time consuming and arises problems of reliability of the information, particularly relevant for multisite studies. It is important that the information obtained on confounding variables are reasonably accurate.

The information on the outcome of interest may be ascertained from existing registries (population based, hospital based, cancer registries, mortality registries), including death certificates or medical records, from questionnaires, or from physical examinations.

2.3 Follow-up procedure

Follow-up over time of the individuals enrolled in a cohort study is the essential feature of this study design. The validity of the study depends on the accuracy both in assessing the exposure and ascertaining outcome data.

The purpose of the follow-up process are threefold:

- to determine which cohort members are currently under observation, by recording deaths and losses due to migration, i.e. to determine the denominator information
- to determine the events that are defined endpoints of the study (disease, death, etc.) i.e. to determine the numerator information
- to obtain further information on the cohort members

Follow-up procedures are different according to the outcome of interest. In longitudinal studies on morbidity, outcome data can be retrieved form physicians' records, hospital discharge registries, population based disease registers and directly from participants as well.

In a cohort mortality study, the vital status is ascertained for all subjects enrolled; for those who die during the follow-up period, date of death must be retrieved. Moreover, if any cause-specific mortality analysis is to be done, it's necessary to obtain information on cause of death. Subjects not traced at the end of the study, are considered lost to follow-up. If the proportion of lost to follow-up is large (higher than 5%) the validity of the study can be compromised.

2.4 Coding of disease

International Classification of Diseases (ICD) code should be retrieved for people dying during the study period; most countries have mortality registers with ICD codes recorded even though some times there are legal restrictions in the access to these data.

The follow-up may cover a period of many years; several disease categories are subdivided differently in different revisions, confusing the comparisons between time periods. Only one revision of ICD should be used to codify the causes of death using the available conversion procedures from older revisions to the newest ones. Moreover, although most European countries have national and/or regional mortality registers, where deaths are coded on the basis of the ICD, there is a wide heterogeneity of the ICD codes applied to classify deaths (especially "drug-related deaths").

2.5 Data analysis: standardised mortality rates and Standardised Mortality Ratios (SMRs)

Analysis of cohort data typically involves the calculation of rates of a specified outcome among the cohorts under investigation and a comparison between those exposed and non-exposed. The occurrence of the event of interest (disease, death, survival) is most appropriately measured in terms of incidence rates and since it can vary widely according to sex, age, calendar time and a number of other demographic characteristics, rates standardised for these variables should be calculated. It's possible to standardise the rates using as standard the specific rates or the age distribution of the general population. Indirect standardised rates can be calculated by applying specific rates of the general population to the age distribution of the cohort. Specific rates of the general population are not always available and it can be more easily to compute indirect standardised rates. This last procedure allows to estimate the Standardised Mortality Ratio (SMR).

In analysing cohort data the correct procedure to deal with subjects lost to follow-up is to consider as date of end of follow-up the date of the last date their vital/health status is known. Individuals lost to follow-up can be considered alive/healthy or dead/ill at the end of the study; in the first case the outcome will be underestimated, in the second case it will be overestimated.

The mechanisms to be used for mortality follow-up vary from country to country, depending on the national systems of population registration and on local rules to access these data. Record-linkage with local or national population registries can be used for ascertaining vital status in those countries where they are available. This is the best procedure to retrieve information on vital status for each subject enrolled into the cohort, but record-linkage with alternative sources as local or national mortality registries, can also be done. In some countries it's possible to get information on vital status also for emigrants, while in other countries it's not possible to follow-up the subjects once they change residence and they are to be considered lost at the end of the study. Occasionally, follow-up may be active in the sense that the investigators attempt to see each cohort member on a regular basis. Such an approach has tended to be used mainly when the cohort is under some form of clinical care. Using mortality registries or making an active follow-up have some limitations due to the assumptions to be done: 1) each subject who did not find a link in mortality register is assumed to be alive and this may be not always right because it depends on the coverage of the mortality register; 2) if a subject can't be seen by the investigator it doesn't necessarily mean he's died, but there can be other explanations to his absence instead of his death.

Therefore when for vital status ascertainment a mortality registry has been used or an active follow-up has been carried out, possible bias can be yielded.

2.6 Strengths and limitations

As a consequence of the design, cohort studies offer a number of advantages for evaluating the relationship between exposure and outcome.

Because of the participants are free from the disease at the time of their exposure status is defined, this kind of study can elucidate temporal relationship between exposure and disease. Cohort studies allow direct measurements of incidence of disease in the exposed and non-exposed groups. Moreover, cohort studies are particularly suited for assessing the effects of rare exposures and provide information about a range of outcomes related to a single exposure.

It is however worthwhile to highlight some limitations of the study design. Since cohort studies often involve following large numbers of individuals for many years, they are generally very time-consuming and expensive especially the prospective design. Consequently, cohort studies are often conducted after a hypothesised relationship has been explored and evaluated in a case-control design. Moreover, the validity of the results can be seriously affected by losses to follow-up.

3. Complementary methods to estimate and analyse mortality among different groups of drug users: the case-control approach

Longitudinal cohort studies of mortality among drug users can be easily carried out among populations of treated drug users which differ between countries in the European Union and are mainly represented by heroin users, amphetamine users in the Scandinavian countries and more recently cocaine users in the southern European countries such as Spain and Italy. The expected excess mortality among treated drug users is very high for the overall mortality and the cohort approach is the most suitable one.

While longitudinal cohort studies are very powerful for measuring and comparing overall mortality among treated drug users, different approaches should be adopted to:

a) better investigate determinants of cause-specific mortality among treated drug users
b) measure excess mortality attributable to the use of other drugs such as synthetic drugs.

3.1 Nested case-control studies to investigate risk factors for cause-specific mortality among drug users

Nested case-control studies within a cohort can be carried out to investigate whether specific patterns of drug use, treatment for drug abuse or specific behaviours, are associated with cause

specific mortality. Only essential information is collected within the protocol of the cohort studies. This information is usually not enough to investigate possible determinants of specific causes of death. The nested case-control approach allows to select a limited number of cases and controls and collect more detailed information regarding specific risk factors previously hypothesised. An added value of nested case control studies is that they can make good use of multisite studies in order to increase the statistical power, particularly when rare causes of deaths are considered.

Population

The case-control approach will be part of the retrospective-prospective cohort study. The population will therefore comprise all drug-exposed subjects included in the historical-prospective cohort study.

Case definition

Cases would be defined as deaths for specific causes (i.e. overdose) occurring among the cohort of drug users during the follow up period.

Control definition

Controls will be defined as cohort subjects alive at the time of death of each corresponding case matching to each corresponding case for variables a priori known to be associated with risk factors and death (age and sex).

Sample size

Number of case-control sets and different case-control ratios in a matched case-control study will be selected in order to achieve a given power at a given level of statistical significance for different values of the relative risk. For example if 80% power is selected to detect an odds ratio of 3.0 with 95% Confidence Interval, 1% significance level and selection of 4 controls per case, a total sample size of 380 would be required (76 cases and 304 controls). Different calculations can be performed for specific situations.

Sampling procedure

All deaths for the specific cause identified will be included in the nested case-control study. The appropriate number of controls would be matched to each cohort subject dying by sex and year of birth. The selection of controls will be randomly carried out among all subjects alive at time of death of each corresponding case, and meeting the inclusion criteria stated above.

Data collection

Data for cases and controls will be collected from clinical records according to the hypothesis to be tested.

Data analysis

The dummy tables below present an illustration of type of analysis expected in this study design. Several such comparisons will be made using cause-specific deaths and risk factors variables, for example:

Treatment	Cases (i.e. Overdose deaths)	Controls i.v. drug users alive
Yes		
No		

Duration of treatment	Cases (i.e. Overdose deaths)	Controls i.v. drug users alive
< x yrs		
> x yrs		

The above dummy tables illustrate the general type of crude analyses that will be applied to data collected in this study. Appropriate statistical methods will be used to control for confounding and to investigate interactions.

3.2 Case-control study involving the general population to study risk factors of rare causes of deaths or deaths for causes with long latency (such as cancer or other selected causes) and to measure excess mortality attributable to the use of other drugs such as synthetic drugs

Some causes of deaths among drug users are too rare to be studied in longitudinal cohort studies and specific populations of drug users are too difficult to be defined in order to be enrolled in cohort studies. When the events we expect are rare, we should follow tremendously large numbers of individuals in order to accumulate a sufficient number who develop a particular outcome.

The case-control approach is especially useful in the early stages of the development of knowledge about a particular outcome of interest which is exactly the case of adverse events associated to the use of synthetic drugs. This approach is likely to be more suitable to analyse risk factors of incidence of specific disease.

Population

Case-control studies can be carried out to investigate whether exposure to drugs is associated with the occurrence of selected health conditions.

Case definition

Subjects dying or with a diagnosis of selected health conditions a priori known to be associated to drug use (i.e. road accident, cancer, etc.)can be selected from exiting registers available at different study sites.

Control definition

Controls should be selected from the same sources as cases among those without disease or health conditions of interest. They should be comparable to the source population of the cases for all variables except those of interest for our investigation.

Sample size

Sample size is calculated as mentioned previously.

Sampling procedure

Detailed description of sampling procedure should be provided for each specific study protocol.

Data collection

Data will be collected in the same way from cases and controls (i.e. biological data, or data from standardised interviews)

Data analysis

Data will be analysed as in the following dummy table:

		Road accident	
		Yes	No
Drug exposure			
	Yes		
	No		

Crude estimates of the association between selected diseases and drug exposure will be calculated. Appropriate statistical methods will be used to control for confounding and to investigate interactions.

4. Guidelines for carrying out a cohort study on mortality among drug addicts

4.1 Introduction

These guidelines attempt to analyse the most important elements for consideration when planning a cohort study on mortality among drug addicts. They are mainly based on the standard

protocol that was developed within the EMCDDA project on cohort mortality studies taking into account the results of the feasibility study performed in the early phase of the project.
In brief, the guidelines were developed in four stages:

- first, published studies on mortality of drug addicts carried out in Europe were reviewed;
- second, a standard protocol was drafted in collaboration with the group of experts from eleven EU countries;
- third, the feasibility of implementing the standardised methodology in different countries in terms of accessibility to health records of drug addicts and availability of sources for ascertaining vital status and causes of death was assessed;
- fourth, the guidelines were developed based on the results of the literature review and the feasibility study.

4.2 Feasibility study: main results

The feasibility study results showed that the available study population in most countries was mainly constituted by addicts entering treatment centres, with some differences regarding both type of substance abused and treatment. Using treatment centres as sources of study population seemed the most feasible and valid option, since identifiers of people enrolled are necessary to assess vital status and cause of death. Moreover, drug addicts seeking treatment represent the most problematic portion of all abusers, even though not representative of the overall drug users population. Additionally, it was considered that at present most PDUs entering treatment in European countries are opiates users. Non opiates users (cocaine, amphetamines, cannabis etc.) entering treatment constitute a very selected group, and mortality figures derived from this sub-population may be highly biased and non representative of the source population. Local and comparative analysis for both opiates and non-opiates users has to be carried out where they do not represent a selected group.

The feasibility study showed that retrospective analysis of mortality data is advisable and useful in those countries where mortality rates have never been estimated, but only when access to the necessary information is easily available. The implementation of “new” cohorts (prospective cohorts) according to the standard methodology enhances the comparability of results; moreover, the improvements in both the number and the quality of information on people enrolled, allows to perform more specific analysis finalised to assess possible mortality determinants.

4.3 The guidelines

The most important issues to be considered for carrying out a cohort mortality study are:

1. definition of the objective;
2. definition of cohort;

3. definition of the study population;
4. data collection;
5. follow-up procedures;
6. cause of death determination and coding;
7. methods of data analysis.

4.3.1 Objective

The first step is to focus on the what the researcher wants to investigate in a defined study population of drug addicts using a cohort mortality study design. Here are some examples:

- to estimate overall and/or cause-specific mortality rates;
- to estimate the excess risk of death compared to the general population or across specific subgroups within the cohort;
- to describe temporal trends in mortality;
- to test hypothesis about determinants of mortality;
- to build up a database of "incident" cases (deaths from …..) for a further case-control study nested in the cohort.

Different objectives imply different procedures of data collection and different strategy of data analysis.

Defining the objective/s is an important step of the study since not specified objectives can lead to an inappropriate data collection. In some cases, specific analysis could be impossible because few or useless information have been collected. The opposite situation occurs when a large amount of time and money has been spent in collecting data eventually not interesting for the study. This is particularly relevant to prospective cohort study designs where information is gathered through specific instruments without using existing records.

4.3.2 Definition of cohort

Taking into account the monitoring purposes of the EMCDDA on mortality among drug addicts, an operative definition of "prospective cohort" has been used: a cohort is defined as "prospective" when the enrolment and the follow-up are periodically updated according to the standard methodology. The cohort is *dynamic* since members can enter the study at different points in time which correspond to moment of their entry into treatment. Therefore the population at risk is open to new members who become eligible with passing time. Similarly, individuals can exit from the person-time of observation by dying and emigrating, if only mortality follow-up is performed, or becoming diseased and developing other outcomes when active follow-up is performed.

The study population may include both "incident" and "prevalent" individuals with respect to treatment. Incident subjects are those starting treatment for the first time or starting a new treatment during the study period; prevalent individuals are those already in treatment at the beginning of the study period. The inclusion of prevalent cases into the study population requires some considerations to be done. Drug addicts already in treatment at the beginning of the study constitute a “selected” group of people including survivors that are likely to have different characteristics in respect to subjects who died and therefore did not have the possibility of being enrolled in the study. Moreover, if information on treatments undergone before entering the cohort are relevant for the analysis, it will be difficult to collect them retrospectively. The better way to proceed is to recruit subjects entering a treatment centre for the first time gathering information about possible previous contacts with treatment centres in order to distinguish people who have never been treated before.

4.3.3 Study population and inclusion criteria

Another important step is “the identification of the population of drug users” out of the overall population. The use of psychotropic drugs in Europe is an illicit behaviour, even though with different levels of tolerance, therefore drug users can be considered a hidden population. The available observation systems only allow to identify drug users referring to health services for either treatment for drug abuse or health problems related to their drug use. Therefore, different variables affect the likelihood of identifying drug users:

a) the potential for harm of the drug used, itself depending on biological, social, environmental and behavioural factors;
b) the availability of health services;
c) the accessibility and acceptance of health services.

Cohort studies on mortality of drug addicts are generally carried out by enrolling people entering treatment centres since identifier information are necessary to ascertain their vital status. This kind of studies actually describes the mortality trend among a selected group of drug addicts. Therefore, in making inference on the basis of the subset of people recruited, it must be considered that the study population is by definition a “selected group”. It can not be excluded that selection factors for including subjects in the study population could be themselves determinants of mortality. Maximum effort must be made to check whether the study population can be considered representative of the actual population of drug users. On this issue, a first consideration is that an extended period of recruitment increases the likelihood of enrolling drug addicts seeking care at least once during their lifetime history of drug addiction. Secondly, information should be retrieved on the proportion of people currently not in treatment who had entered treatment centres at least once. For example, data supporting the generalizability of results of a longitudinal study on mortality of drug addicts in Rome (follow-up period 1980-1999),

came from surveys carried out in the city in 1990 and 1992 showing that "*80% of subjects contacted in the street had entered treatment centres at least once"* (Addiction 2001 in press).

The cohort to be enrolled in the study is represented by all subjects who, among a target group, satisfy the criteria of inclusion in the cohort. The criteria must be necessarily specified before starting the study, i.e. "*all male and female drug users, 15-49 years old, who started using opiates during the last three years and who lived in the city of Rome"*.
Only those with the above mentioned criteria will enter the cohort, all the other will be excluded from the study.
The study population includes drug addicts (by injection or other routes of administration) entering (or starting or demanding treatment) a treatment centre at least once during the study period. Type of substance that predominantly maintains the addiction (primary drug) must to be specified. Subjects using tobacco and alcohol as primary substances are excluded from the study population.
Inclusion criteria to enrol subjects into the cohort are the following:

a) entering treatment centre during the defined recruitment period;
b) availability of data for ascertaining vital status;
- name and surname (or other identifiers such as social security number)
- date and place of birth;

c) availability of information on:
- place of residence
- date of entry into treatment centres.

For each individual the date on which observation begins is the date of entry into treatment centre: if a subject applies to different centres or refers to a centre more than once during the recruitment period, the date of entry into the study corresponds to the less recent one (when he/she refers to the treatment centre for the first time during the study period).

The date of entry into treatment centres has also to be obtained to distinguish "incident" and "prevalent" cases at the beginning of the study (at the moment of enrolment).

Data describing characteristics of the original study population together with the reasons for exclusion must be described in detail in order to check if any differences between people enrolled and those not included exist.

4.3.4 Confidentiality

The study does not involve data collection from drug addicts themselves. Only information

already available on clinical records will be used.

The local studies will respect the appropriate legislation on data protection. Identifiers are only necessary at local level to ascertain vital status and will not be transmitted to third parties. All data analysis and reporting to the central co-ordinator will be done without identification of any individual's name and drug use status. The EMCDDA will not receive identifying information of drug users, as it is established in its regulation.

Each centre must adopt specific and effective procedures to ensure the absolute confidentiality of the information gathered. The data on drug users enrolled will have to be managed by a limited number of people, all of whom will be bound by official secrecy.

4.3.5 Data collection

Once the cohort has been defined, for each member enrolled in the study a minimum data set must be retrievable. The basic information to collect include: *socio-demographic variables* such as gender, age, educational level, employment status, residence; *information on pattern of drug use* such as age of first use, type of drug, route of administration, severity of dependence (duration and frequency). Different sources of data can be used, e.g. clinical records, special registers such as Hospital Discharge Register, surveillance systems, methadone registers.
These sources largely differ for number and type of information available. In general, in retrospective cohort studies it is only possible to collect variables from existing sources where data have been recorded for other purposes. Using a standardised form or a questionnaire for collecting data is advisable in prospective cohort studies since it allows to finalise the data collection to those variables relevant to the study. For example it should be possible to have more detailed information on the "exposure", i.e. type of drugs used, route and frequency of administration and variables necessary to better describe the study population. These variables should then be taken into account as potential confounders in multivariate analysis.
In order to enhance comparability of data from cohorts enrolled in different study sites, the variables collected from each case should be consistent, as far as possible, with the EMCDDA guidelines for the Treatment Demand Indicator. These guidelines are contained in the joint EMCDDA/Pompidou Group Protocol on the Treatment Demand Indicator. Some variables included in the "Estimating and comparing mortality Guidelines" are not present in the Treatment Demand Indicator Protocol.

The expert group who drafted the standard protocol within the EMCDDA project considered the following information necessary for describing the study population. These information have to be gathered for each drug addict at the enrolment and refers to the time of enrolment into the study.

A. Data necessary to assess vital status:

- name and surname or other identifiers such as social security number
- date (dd, mm, yy) and place of birth

B. Place of residence

C. Gender

- 1. Male
- 2. Female
- 0. Not known

D. Legal nationality

- 1. National of this country
- 2. EU national
- 3. National of another country
- 0. Not known

E. Date of entry into treatment centre (dd, mm,yy)

F. Primary drug

- 1. Opiates (total)
  - 11. heroin
  - 12. methadone
  - 13. other opiates
- 2. Cocaine (total)
  - 21. cocaine
  - 22. crack
- 3. Stimulants (total)
  - 31. amphetamines
  - 32. MDMA and other derivatives
  - 33. other stimulants
- 4. Hypnotics and sedatives (total)
  - 41. barbiturates
  - 42. benzodiazepines
  - 43. others
- 5. Hallucinogens (total)
  - 51. LSD
  - 52. others
- 6. Volatile inhalants
- 7. Cannabis (total)
- 8. Other substances (total)

G. Route of administration of primary drug

- 1. Inject
- 2. Smoke
- 3. Eat/drink
- 4. Sniff
- 5. Other
- 0. Not known

H. Frequency of use of primary drug

- 1. Used once per week or less
- 2. Used 2-6 days per week
- 3. Used daily
- 4. Not used in past month
- 0. Not known

I. Other drugs used (the data set structure will allow to codify up to three substances)

- 1. Opiates (total)
  - 11. heroin
  - 12. methadone
  - 13. other opiates
- 2. Cocaine (total)
  - 21. cocaine
  - 22. crack
- 3. Stimulants (total)
  - 31. amphetamines
  - 32. MDMA and other derivatives
  - 33. other stimulants
- 4. Hypnotics and sedatives (total)
  - 41. barbiturates
  - 42. benzodiazepines
  - 43. others
- 5. Hallucinogens (total)
  - 51. LSD
  - 52. others
- 6. Volatile inhalants
- 7. Cannabis (total)
- 8. Alcohol (only as secondary drug)
- 9. Other substances (total)

J. Marital status

- 1. Married
- 2. Unmarried
- 0. Not known

K. Educational level

- 1. Never went to school/never completed primary school
- 2. Primary level of education
- 3. Secondary level of education
- 4. Higher of education
- 0. Not known

L. Employment status

- 1. Regular employment
- 2. Pupil/student
- 3. Economically inactive (pensioners, housewives/-men, invalids)
- 4. Unemployed
- 5. Other
- 0. Not known

M. Injection status

- 1. Ever but not currently
- 2. Currently
- 3. Never
- 0. Not known

N. First treatment ever

- *1. Yes*
- 2. No
- 0. Not known

O. Type of initial treatment assigned

- Methadone detoxification
- Methadone maintenance
- Naltrexone
- Other pharmacological treatments
- Drug-free long term/psychological
- Counselling/support

P. Data on specific laboratory test performed (specify for HIV, HBV and HCV)

- 1. Positive
- 2. Negative
- 3. Never tested

- 0. Information not available

Q. Date of last contact with treatment centre (dd, mm, yy)

R. Vital status

- 1. Alive
- 2. Dead
- 0. Not known

S. Date of death (dd, mm, yy)

T. Cause of death (ICD code)

4.3.6 Follow-up

Feasibility of follow-up is a key consideration, since completeness of follow-up is essential for the internal validity of the study results. Actually, retention begins during the enrolment and the recruitment's strategy should be defined in order to increase the rate of subsequent follow-up. This is particularly true for drug addicts that constitutes a "hard-to-reach" population. The study population should not include those people who are known a priori to be not traceable, such as not resident people or subjects with incomplete identifiers. This assumes that bias due to losses at the baseline is lower than that due to failure in tracing people at the end of follow-up: the former are less likely to be influenced jointly by exposure (drug addiction) and outcome (mortality) than the latter.

Failure in retrieving information on vital status for a large proportion of the study population is a major source of potential bias in a mortality cohort study. It's advisable for the validity of the study that the proportion of losses to follow-up does not exceed 5% of whole study population. There are different options to treat losses to follow-up in the analysis implying different consequences on study results. The more conservative approach assumes losses to follow-up alive at the end of the study period. It is also possible to consider that all those who were lost to follow-up died. The results of these different approaches provide a range of mortality rate estimates within which the true estimate will lie. However, if losses to follow-up are large, the observed range will be so wide to provide little useful information.

Each subject enrolled contributes to person-year of observation from the time of entry into the cohort (the date of entry into treatment centre) to the end of the study period or the date of death. Subject not traced at the end of follow-up can contribute to person-year of observation till the date of last contact with treatment centre if it is available.

Data of entry into the study, date of end of follow-up or date of death (if they die during the study period) are essential variables and they must be retrievable for each member in the cohort.

The best option for ascertaining vital status is through the Population Registers or Vital Statistics Bureau. The vital status has to be checked at the Register of the last municipality of residence at the end of the follow up, following-up individuals who change place of residence.
Local or National Population Registers are not available or easily accessible in some EU countries and different types of sources can be used:

- National and Local Mortality Registers (in this latter case all subjects not found are supposed to be alive);
- Health Care Services
- Active follow-up

Where possible, the use of population registers instead of the mortality ones is preferable; when only the latter is available we have to assume that people are alive if not found in mortality registry. This assumption is not always met.
The validity of a cohort study depends on complete ascertainment of the events of interest and correct computation of the population at risk. Major accuracy should be put in tracing subjects especially as regards migrant drug users and in limiting the proportion of losses to follow up to a maximum of 5% of the subjects enrolled.

Causes of death are ascertained through record linkage with General Population Mortality files, if available, or through death certificate revision. Causes of death should be classified by a nosologist trained in the rules specified by the ICD volumes.
Additional sources of data on cause of death can be used to complement information from the previous sources:

- Forensic Institutes
- Registers on post-mortem toxicology
- Registers of Drug Related deaths
- Coroners' Registers
- Hospital Records
- Hospital Discharge Registers
- Police data

A 90%-95% cause of death determination rate in the study population is a desirable target.

Death certificates are completely acceptable when overall mortality is the outcome of interest. Differently for cause-specific, death certificate information is less reliable, since the cause of death registered may be subject to interpretation. Mainly in multicentric studies difficulties in analysing cause-specific mortality can arise from the different criteria used to codified causes of death. The comparative analysis carried out on retrospective cohorts within the EMCDDA project emphasised this issue: *in the cohorts recruited in Rome and Sweden overdose was codified as "mental*

disorders" (ICD IX - 304, subheading "drug dependence"). In the cohorts of Barcelona this cause of death was exclusively codified as "injuries and poisoning" using codes ICD IX - E850-E858 and E959.2. In Vienna overdose was mainly codified as "injuries and poisoning" (ICD IX - 965) and in part as "mental disorder" (ICD IX - 304).

In order to enhance comparability across countries, coding of the cause of death has to be made, on the basis of the causes registered in death certificates, by a nosologist according to the last revision of the International Classification of Diseases (ICD). This option is more feasible in prospective studies where the vital status and cause of death ascertainment can be carried out systematically for example every two or three years.

Taking into account that some countries are changing from ICD IX to ICD X, conversion tables can be used to avoid heterogeneity in coding causes of death across countries.

The availability of coding of cause of death is essential for making comparisons across countries. Some specific causes such as AIDS may be so different distributed across countries limiting the usefulness of comparing overall mortality.

4.3.7 Data Analysis

The quality and completeness of each form have to be checked before the data are entered in a database for the purpose of correcting errors where possible and of verifying any data not supplied.

Data analysis includes a number of analytic strategies. One aspect of analysis involves calculation of person-years at risk of dying; each subject is to be considered from the date of first enrolment through the end of the study period, or to the date of death or loss to follow up.

Both overall and cause-specific mortality analysis can be carried out. As far as drug-related deaths (DRD) as concerned, in the analysis it will be taken into account the output of the specific EMCDDA project aimed to implement a standard definition and classification of DRD.

- <u>Local analysis</u>

  Direct standardised rates are calculated for each cohort using as a standard the local population truncated at 15-49 years.

  Although the standard age group for the other indicators is 15-64 years, the mortality analysis on the cohorts enrolled within the EMCDDA project, was performed using the age range 15-49. Since drug addicts contribute very few person-years at risk to age over 49, the mortality estimates above this age do not reach acceptable precision.

  Standardised Mortality Ratios (SMRs) and their 95% confidence intervals are used to compare the mortality experience of drug users with that of the national population for the same age, sex and period. The expected numbers of deaths are calculated using sex and age specific local mortality rates.

- Pooled analysis
    - Direct standardised rates are calculated for each cohort using as a standard the European population truncated at 15-49 years (or the person-years at risk of the pooled cohort) for making temporal and geographical comparisons.
    - The analysis of the heterogeneity of mortality could be conducted by using Poisson Regression and including as covariates both individual data and geographical indicators.
    - Survival analysis using Kaplan Meier product limit method along with 95% Confidence Intervals is used to estimate cumulative risk of death at different follow-up time.

Cox regression models are applied to analyse mortality at different study site according to age, sex, calendar year of enrolment, and other potential risk factors available.

Annex 4

Questionnaires on the availability of morbidity data

STUDY SITE: DENMARK

Part 1: Hospital Discharge Registers

1. Are there in your country national Hospital Discharge Registers?

yes [x] no [ ]

2. Are there in your Region/County local Hospital Discharge Registers?

yes [x] no [ ]

3. What is the Institution who manages the Register?

3.1. National **National Board of Health**

3.2. Local **National Board of Health**

4. Could you have access to national or local Hospital Registers?

4.1. National

yes [x] no [ ]

4.2. Local

yes [x] no [ ]

5. Please, specify if the following information refer to:

[ ] National Register

[ ] Local Register

[x] Both Registers

6. When the Register was set up?

1977

What kind of Hospitals are covered by the Register?

All kinds of public hospitals (somatic and psychiatric)
There are very few private hospitals in Denmark

7. What is the proportion of hospitals covered by the Register?

near 100

8. What type of information are registered?

8.1. Data on patients (socio-demographic information: identifiers, sex, age, place of residence ..), please specify

unique identifier with information on sex and age, community,

8.2. Data on the hospital (county/region, hospital, department ….), please specify

unique hospital and department number

8.3. Administrative data (date of admission, date of discharge, length of stay, acute/planned/day hosp admission…), please specify

data of admission, data of discharge, type of patient (day, night, out-patient causality department) referred from, mode of admission (acute/not acute) referred to, discharged to (if another hospital) contact reason (accident, suicide attempt etc. , length of each stay (treatment days), accident (if contact reason is accident, a special code describing the accident.

8.4. Medical data (main diagnosis, secondary diagnoses, surgical procedures ….), please specify

diagnoses, (action and bi-diagnoses) procedure (kind of operation) date of operation, department where the patient was operated

9. What ICD revision is used?

ICD-10 since 1994

10. For how many years are data available?

Since 1977

11. What is the delay in getting data?

2 months

12. Is it possible to link the Register with your mortality cohort?

yes ☒ no ☐

13. If yes, what are the linkage-keys?

- **unique person identifier number**
-
-
-

14. Could you get information on subjects hospitalised in a county/region where he/she is not resident?

yes ☒ no ☐ don't know ☐

15. If yes, how:

15.1. Access or inquiry to National Register

yes ☒ no ☐

15.2. Access or inquiry to other Local Registers

yes ☐ no ☐

15.3. Access or inquiry to other sources of data, specify:

But not for patients on hospitals outside Denmark

P*art 2: Other sources of morbidity data (e. g. : AIDS Register, TBC Register)*

1. Please, specify type of Register:

Causes of Death Register

2. Does the Register gather information at:

2.1. National level

yes ☒ no ☐

2.2. Local level

yes ☐ no ☐

3. Could you have access to national or/and local Registers?

3.1. National

yes ☒ no ☐

3.2. Local

yes ☒ no ☐

4. Please, specify if the following information refer to:

☐ National Register

☐ Local Register

☒ Both Registers

5. When the Register was set up?

1970

6. What type of information are registered?

- **unique person identifier number, residence municipality, data of death, age at death, place of death (hospital, institution, home etc)**
-
- **type and place of accident (if accident), (if natural death, accident, suicide, homicide)**
-
- **cause of death(underlying cause ICD-no) Secondary cause, tertiary cause, fourth cause**
-
- **autopsy performed**
- **code for coroner certificate**
-
-
-

7. What is the delay in getting data?

3½ year

8. Is it possible to link the Register with your mortality cohort?

yes ☒ no ☐

9. If yes, what are the linkage-keys?

- **unique person identifier number**
-
-
-

10. Could you get information on subjects notified in a county/region where he/she is not resident?

yes ☒ no ☐ don't know ☐

But not if the person died outside Denmark

11. If yes, how:

11.1. Access or inquiry to National Register

yes ☒ no ☐

11.2. Access or inquiry to other Local Registers

yes ❑ no ❑

11.3. Access or inquiry to other sources of data, specify:

---

12. If it is not possible to follow-up the cohort, please specify main reasons:

It is possible

STUDY SITE: HAMBURG

Part 1: Hospital Discharge Registers

1. Are there in your country national Hospital Discharge Registers?

yes ☐ no ☒

2. Are there in your Region/County local Hospital Discharge Registers?

yes ☒ no ☐

3. What is the Institution who manages the Register?

3.1. National

3.2. Local

In general, each hospital manages its own register. 70% of all hospitals in the Hamburg region are affiliated to the «LBK» which is a central management of all public (state) hospitals. The University Hospital, private hospitals and hospitals for the public welfare in charge of the church are not included. The public (state) hospitals have just established a central data base which enables access to discharge data.

4. Could you have access to national or local Hospital Registers?

4.1. National

yes ☐ no ☐

4.2. Local

yes ☒ no ☐

5. Please, specify if the following information refer to:

☐ National Register

☒ Local Register

☐ Both Registers

6. When the Register was set up?

Each hospital of the «LBK» set up registers at different points of time starting from 1996. But with the beginning of the year 2000, data can be processed by a central management.

7. What kind of Hospitals are covered by the Register?

All public hospitals

8. What is the proportion of hospitals covered by the Register?

About 70%. (The treatment of drug addicts is covered by them in more than 70% of all treatments, for example, all drug addict outpatient departments are affiliated to the «LBK».

9. What type of information are registered?

9.1. Data on patients (socio-demographic information: identifiers, sex, age, place of residence ..), please specify

Identifiers: Name, Birthday, Place of residence, sex.

9.2. Data on the hospital (county/region, hospital, department ….), please specify

Hospital department

9.3. Administrative data (date of admission, date of discharge, length of stay, acute/planned/day hosp admission…), please specify

Admission and discharge

9.4. Medical data (main diagnosis, secondary diagnoses, surgical procedures ….), please specify

Main and secondary diagnoses at the time of discharge, procedures coded by ICD-M

10. What ICD revision is used?

ICD 10 starting 1.1.2000 for morbidity data

11. For how many years are data available?

See above

12. What is the delay in getting data?

Some weeks

13. Is it possible to link the Register with your mortality cohort?

yes ☒ no ☐

14. If yes, what are the linkage-keys?

0. **Name**

1. **Birthday**
2. **Residence**

15. Could you get information on subjects hospitalised in a county/region where he/she is not resident?

yes ☐ no ☒ don't know ☐

16. If yes, how:

16.1. Access or inquiry to National Register

yes ☐ no ☐

16.2. Access or inquiry to other Local Registers

yes ☐ no ☐

16.3. Access or inquiry to other sources of data, specify:

17. If it is not possible to follow-up the cohort, please specify main reasons:

18. Comments:

Confidentiality of data which are desired. Personal consent of the participants of the cohort is absolutely important.
It wouldn't be not easy to get data from all hospitals in the Hamburg region because this means applying for data at each hospital which is not affiliated to the «LBK»-State Hospital community. This would make such a project more expensive.
We could also include data of the University Hospital which we are affiliated to with our institute.

Study site: Sweden

Part 1: Hospital Discharge Registers

1. Are there in your country national Hospital Discharge Registers?

yes [x] no [ ]

2. Are there in your Region/County local Hospital Discharge Registers?

yes [x] no [ ]

3. What is the Institution who manages the Register?

3.1. National **National Board of Health and Welfare**

3.2. Local

County council administrations, but that would be on regional level. The national data can be split into regional or local levels

4. Could you have access to national or local Hospital Registers?

4.1. National

yes [x] no [ ]

4.2. Local

yes [x] no [ ]

5. Please, specify if the following information refer to:

[x] National Register

[ ] Local Register

[x] Both Registers

6. When the Register was set up?

1987

7. What kind of Hospitals are covered by the Register?

All inpatient clinics

8. What is the proportion of hospitals covered by the Register?

100%

9. What type of information are registered?

9.1. Data on patients (socio-demographic information: identifiers, sex, age, place of residence ..), please specify

Personal Identity number, sex, age, county-municipality-parish, responsible authority, hospital, clinic, primary diagnose, secondary diagnose, e-code, operations

9.2. Data on the hospital (county/region, hospital, department ….), please specify

County, type of clinic, specific hospital

9.3. Administrative data (date of admission, date of discharge, length of stay, acute/planned/day hosp admission…), please specify

Entry-date, duration, planned treatment, entering from? Exiting to? Payment, "mortality-flag" (dead or alive when exiting)

9.4. Medical data (main diagnosis, secondary diagnoses, surgical procedures ….), please specify

Primary diagnose, secondary diagnose, e-code, operations (up to 6) classified according to type of operation

10. What ICD revision is used?

ICD 10 from 1997

11. For how many years are data available?

1987-1998

12. What is the delay in getting data?

Approx 1 year

13. Is it possible to link the Register with your mortality cohort?

yes ☒ no ☐

14. If yes, what are the linkage-keys?

- **Personal identity number**
-
-
-

15. Could you get information on subjects hospitalised in a county/region where he/she is not resident?

yes ☒ no ☐ don't know ☐

16. If yes, how:

16.1. Access or inquiry to National Register

yes ☒ no ☐

16.2. Access or inquiry to other Local Registers

yes ☐ no ☐

16.3. Access or inquiry to other sources of data, specify:

17. If it is not possible to follow-up the cohort, please specify main reasons:

18. Comments:

Part 2: Other sources of morbidity data (e. g. : AIDS Register, TBC Register)

1. Please, specify type of Register:

The examples referred to are listed as transmittable diseases. For such diseases there are a notification system.

2. Does the Register gather information at:

2.1. National level

yes ☒ no ☐

2.2. Local level

yes ☐ no ☒

3. Could you have access to national or/and local Registers?

3.1. National

yes ☒ no ☐

3.2. Local

yes ☐ no ☐

4. Please, specify if the following information refer to:

☒ National Register

☐ Local Register

☐ Both Registers

5. When the Register was set up?

To be checked

6. What type of information are registered?

- **Age, Sex, Route of administration, Date of diagnose, County, County of origin, Place of infection – county and continent**
-

7. What is the delay in getting data?

To be checked

8. Is it possible to link the Register with your mortality cohort?

yes ☐ no ☐

Don't know.

9. If yes, what are the linkage-keys?

- **Personal identity number**
-
-
-

10. Could you get information on subjects notified in a county/region where he/she is not resident?

yes ☒ no ☐ don't know ☐

11. If yes, how:

11.1. Access or inquiry to National Register

yes ☒ no ☐

11.2. Access or inquiry to other Local Registers

yes ☐ no ☐

11.3. Access or inquiry to other sources of data, specify:

12. If it is not possible to follow-up the cohort, please specify main reasons:

13. Comments:

Study site: Spain

Part 1: Hospital Discharge Registers

1. Are there in your country national Hospital Discharge Registers?

yes [x] no [ ]

2. Are there in your Region/County local Hospital Discharge Registers?

yes [x] no [ ]

3. What is the Institution who manages the Register?

3.1. National **Health Ministry**

3.2. Local **Autonomous Health department**

4. Could you have access to national or local Hospital Registers?

4.1. National

yes [ ] no [x]

4.2. Local

yes [ ] no [x]

Part 2: Other sources of morbidity data (e. g. : AIDS Register, TBC Register)

1. Please, specify type of Register:

AIDS Register
TBC register
Hepatitis B register
Hepatitis C register

2. Does the Register gather information at:

2.1. National level

yes ☒ no ☐

2.2. Local level

yes ☒ no ☐

3. Could you have access to national or/and local Registers?

3.1. National

yes ☐ no ☐

3.2. Local

yes ☒ no ☐

4. Please, specify if the following information refer to:

☐ National Register

☒ Local Register

☐ Both Registers

5. When the Register was set up?

All registers start in 1987. AIDS register gathered information since 1981

6. What type of information are registered?

- **Demographic data**
- **Main diagnosis**
- **Date of death and cause**
- **Laboratory test**
- **Some risk factors**
- **Some habits**
- **Type of treatment**
-
-
-
-

7. What is the delay in getting data?

The average is 6 month

8. Is it possible to link the Register with your mortality cohort?

yes [x] no [ ]

9. If yes, what are the linkage-keys?

- **Name**
- **Surname**
- **Date of birth**
- **National identification code**

10. Could you get information on subjects notified in a county/region where he/she is not resident?

yes [x] no [ ] don't know [ ]

11. If yes, how:

11.1. Access or inquiry to National Register

yes [x] no [ ]

11.2. Access or inquiry to other Local Registers

yes [ ] no [ ]

11.3. Access or inquiry to other sources of data, specify:

12. If it is not possible to follow-up the cohort, please specify main reasons:

13. Comments:

Study site: Portugal

Part 1: Hospital Discharge Registers

1. Are there in your country national Hospital Discharge Registers?

yes [x] no [ ]

2. Are there in your Region/County local Hospital Discharge Registers?

yes [x] no [ ]

3. What is the Institution who manages the Register?

3.1. National **Ministry of Health – Institute for the Financial Management**

3.2. Local **Ministry of Health – Institute for the Financial Management**

4. Could you have access to national or local Hospital Registers?

4.1. National

[x] yes [ ] no

4.2. Local

[x] yes [ ] no

5. Please, specify if the following information refer to:

[ ] National Register

[ ] Local Register

[x] Both Registers

6. When the Register was set up?

1991

7. What kind of Hospitals are covered by the Register?

Public Hospitals

8. What is the proportion of hospitals covered by the Register?

+/- 98%

9. What type of information are registered?

9.1. Data on patients (socio-demographic information: identifiers, sex, age, place of residence ..), please specify

Gender, age, date of birth, place of birth

9.2. Data on the hospital (county/region, hospital, department ….), please specify

Name of hospital, typology, unit in the hospital

9.3. Administrative data (date of admission, date of discharge, length of stay, acute/planned/day hospital admission…), please specify

Date of admission, date of discharge, length of stay typology of the admission

9.4. Medical data (main diagnosis, secondary diagnoses, surgical procedures ….), please specify

Main diagnosis, secondary diagnoses (max 7), main surgical procedure, secondary surgical procedures (max 7), mental health diagnosis

10. What ICD revision is used?

ICD IX

11. For how many years are data available?

7 years; 1993 → 1999

12. What is the delay in getting data?

1 year

13. Is it possible to link the Register with your mortality cohort?

yes ☐ ☒ no

14. If yes, what are the linkage-keys?

- .....
- .....
- .....
- .....

15. Could you get information on subjects hospitalised in a county/region where he/she is not resident?

yes ☐ no ☐ don't ☐ know

16. If yes, how:

16.1. Access or inquiry to National Register

yes ☐ no ☐

16.2. Access or inquiry to other Local Registers

yes ☐ no ☐

16.3. Access or inquiry to other sources of data, specify:

17. If it is not possible to follow-up the cohort, please specify main reasons:

Main reason is: We don't have identified data, so the database is about episodes in hospital and not about people in hospital.

18. Comments:

Part 2: Other sources of morbidity data (e. g. : AIDS Register, TBC Register)

1. Please, specify type of Register:

Infectious diseases register

2. Does the Register gather information at:

2.1. National level

yes ☒ no ☐

2.2. Local level

yes ☐ no ☐

3. Could you have access to national or/and local Registers?

3.1. National

yes ☒ no ☐

3.2. Local

yes ☐ no ☐

4. Please, specify if the following information refer to:

☒ National Register

☐ Local Register

☐ Both Registers

5. When the Register was set up?

6. **What type of information are registered?**

- **AIDS**
- **Hep B and Hep C**
- **…**
-

7. **What is the delay in getting data?**

+/- 3 months

8. **Is it possible to link the Register with your mortality cohort?**

yes ☐ no ☒

9. **If yes, what are the linkage-keys?**

-
-
-
-

10. **Could you get information on subjects notified in a county/region where he/she is not resident?**

yes ☐ no ☐ don't know ☐

11. **If yes, how:**

11.1. Access or inquiry to National Register

yes ☐ no ☐

11.2. Access or inquiry to other Local Registers

yes ☐ no ☐

11.3. Access or inquiry to other sources of data, specify:

12. **If it is not possible to follow-up the cohort, please specify main reasons:**

13. Comments:

Study site: Italy

Part 1: Hospital Discharge Registers

1. Are there in your country national Hospital Discharge Registers?

yes [x] no [ ]

2. Are there in your Region/County local Hospital Discharge Registers?

yes [x] [ ] no

3. What is the Institution who manages the Register?

3.1. National **Ministry of Health**

3.2. Local **Agency for Public Health, Lazio region**

4. Could you have access to national or local Hospital Registers?

4.1. National

[x] yes [ ] no

4.2. Local

[x] yes [ ] no

5. Please, specify if the following information refer to:

[ ] National Register

[x] Local Register

[ ] Both Registers

6. When the Register was set up?

1994

7. What kind of Hospitals are covered by the Register?

All Public and Private Hospitals

7. What is the proportion of hospitals covered by the Register?

100%

8. What type of information are registered?

8.1. Data on patients (socio-demographic information: identifiers, sex, age, place of residence ..), please specify

Name, surname, gender, place of birth, date of birth, place of residence,

civil status, major occupation, educational level, general practitioner, referred by

Other information on patients can be retrieved by record linkage with the municipal registry

8.2. Data on the hospital (county/region, hospital, department ….), please specify

Identifier, location, typology. Other information on the hospital characteristics are obtained through linkage with different Registries managed by the Agency for Public Health of the Lazio Region

8.3. Administrative data (date of admission, date of discharge, length of stay, acute/planned/day hospital admission…), please specify

Date of admission, date of discharge, typology of the admission (planned or acute, day hospital), cause of the admission (surgery, medical therapy, delivery, poisoning or trauma), diagnosis at admission

8.4. Medical data (main diagnosis, secondary diagnoses, surgical procedures ….), please specify

Main diagnosis (the main condition treated or investigated during the stay at the hospital), secondary diagnosis (max 3), main surgical procedure, secondary surgical procedures (max 3), department of discharge, typology of discharge (moved to other hospital or department, home, death, voluntary)

9. What ICD revision is used?

ICD IX till 1999 and ICD IX CM from 2000

10. For how many years are data available?

4 years; 1996 → 1999 (incomplete data for 1995 are available

11. What is the delay in getting data?

4 months

12. Is it possible to link the Register with your mortality cohort?

yes [x] no [ ]

13. If yes, what are the linkage-keys?

- **Name**
- **Surname**
- **Gender**
- **Date and place of birth**

14. Could you get information on subjects hospitalised in a county/region where he/she is not resident?

yes [x] no [ ] don't know [ ]

15. If yes, how:

15.1. Access or inquiry to National Register

yes [ ] no [ ]

15.2. Access or inquiry to other Local Registers

yes [x] no [ ]

15.3. Access or inquiry to other sources of data, specify:

16. If it is not possible to follow-up the cohort, please specify main reasons:

17. Comments:

Data are delivered to the Agency for Public Health every three months through Local Health Authorities (8 in the Lazio Region). From 1st January 2000 it is possible to register 5 secondary diagnosis and 5 secondary surgical procedures

Part 2: Other sources of morbidity data (e. g. : AIDS Register, TBC Register)

1. Please, specify type of Register:

AIDS register

2. Does the Register gather information at:

2.1. National level

yes [x] no [ ]

2.2. Local level

yes [x] no [ ]

3. Could you have access to national or/and local Registers?

3.1. National

yes [x] no [ ]

3.2. Local

yes [x] no [ ]

4. Please, specify if the following information refer to:

[ ] National Register

[x] Local Register

[ ] Both Registers

5. When the Register was set up?

1985

6. What type of information are registered?

- **Name, surname, age, date and place of birth**
- **educational level, vital status at diagnosis (for those dead: date of death)**
- **AIDS defining illnesses, modality of exposure, last HIV negative test**
- **first HIV positive test, first CD4 count , CD4 count at AIDS diagnosis,**
- **Viral load*, information on anti-retroviral therapies***
- ***** since 1999**

7. What is the delay in getting data?

3-6 months

8. Is it possible to link the Register with your mortality cohort?

yes [x] no [ ]

9. If yes, what are the linkage-keys?

- **Name, surname, date and place of birth, gender**
-
-
-

10. Could you get information on subjects notified in a county/region where he/she is not resident?

yes [x] no [ ] don't know [ ]

See comments

11. If yes, how:

11.1. Access or inquiry to National Register

yes [x] no [ ]

11.2. Access or inquiry to other Local Registers

yes [ ] no [ ]

11.3. Access or inquiry to other sources of data, specify:

12. If it is not possible to follow-up the cohort, please specify main reasons:

13. Comments:

It is possible to get information on people notified but not resident in the Lazio region through the Local registry and on people resident in the Lazio region but notified elsewhere through the National registry