European Monitoring Centre for Drugs and Drug Addiction

Prevalence, Consequences and Data Management Unit

Mortality among drug users:
Guidelines for carrying out, analysing
and reporting key figures
2011–12

EMCDDA standard protocol to collect data and report figures for the mortality component
of the Key indicator 'Drug-Related Deaths (DRD) and mortality among drug users'
by the Standard Table 18

EMCDDA CT.99.EP.07/CT.00.EP.13/ CT.10:EPI.003

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Status of these guidelines

These guidelines consist of a protocol to design, carry out and analyse mortality studies among 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 in Europe. The development of the initial guidelines has been carried out by the Agency of Public Health of Lazio Region in close collaboration with the EMCDDA. Revisions took place in 2010 and 2012, following workshops on data analysis. The current revision was part of a contract CT.10:EPI.003.

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' (EU-27);

— 'Implementation, follow-up and analysis of cohort studies on mortality among drug users in the European Union' (EU-27) (CT.97.EP.03);

— 'Coordination of implementation, follow-up and analysis of cohort studies on mortality among drug-users in the European Union' (EU-27) (CT.98.EP.12);

— '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' (CT.99.EP.07);

— *Mortality related to drug use in Europe: Public health implications*, Selected issue, EMCDDA 2011.

Available from: http://www.emcdda.europa.eu/publications/selected-issues/mortality

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Executive summary

The EMCDDA is one of the decentralised agencies of the European Union and has for its mandate the provision of sound, reliable and comparable information on drugs and drug addictions and their consequences.

Drug-related mortality is a complex phenomenon, which accounts for a considerable percentage of deaths among young people in many European countries. The EMCDDA, in collaboration with national experts, has defined an epidemiological indicator with two components at present: deaths directly caused by illegal drugs (drug-induced deaths) and mortality rates among problem drug users. These two components can fulfil several public health and methodological objectives, notably as an indicator of the overall health impact of drug use and the components of this impact, identify particularly risky patterns of use, and potentially identify new risks.

This standard protocol focuses on the second component (mortality), other documents being dedicated to DRD'. It provides national focal points and experts with a guide for carrying out, analysing and reporting to the EMCDDA the key figures on mortality among drug users. It describes the new features of the Fonte web-based interface which, from 2007, allow the Member States to report their mortality data to the EMCDDA, through the Standard table 18. Before constructing mortality figures among drug users, it is essential to ensure the confidentiality of the information and to make sure that the national legislation on data protection is respected.

Mortality figures are measured within a cohort study; a defined group of drug users, followed over a period of time to assess the occurrence of the mortality. For logistical reasons, the EMCDDA recommends conducting cohorts amongst drug users in treatment. However, other populations of drug users may contribute to the knowledge of mortality among drug users as well.

The cohort should consist of current drug users with complete and valid identifiers whose vital status (i.e dead or alive) is likely to be ascertained in the future. To enhance interpretation, the recruitment setting and related inclusion criteria should be described in detail. Moreover, the moment an individual's observation time starts should be defined (e.g. treatment intake).

The best option for ascertaining vital status, and specify the end of observation time is through the Population Registers or Vital Statistics Bureau and the use of unique personal numbers for linking the records of the selected drug users with the population register. Observation time ends at date of death, date of emigration (lost to follow up) or the end of the study period. General Mortality Registers should be used to retrieve the cause of death. The EMCDDA suggests a classification in four major subgroups for reporting the causes of deaths (drug-induced mortality, HIV/AIDS, other and unknown causes).

In addition to the data needed for the linkage (i.e. to identify the drug users in population and mortality register and link both to assess the vital status), additional information can be collected and analysed about demography, drug use and serological status. Most recommended variables are part of the core set of the EMCDDA Treatment demand indicator.

Although crude mortality rates of defined cohorts of drug users give valuable information as such, comparison of mortality rates between different populations may be compromised by different distributions of age and gender. To adjust for these differences in age and gender distributions, the protocol describes how to calculate the direct standardised rates using the Standard European population as a referent population or the Standardised mortality ratio, using the mortality rates observed within the European population. Alternatively, we may adjust for differences in age and gender distribution in a multivariate model.

Preferred design and setting: the main points

- The easiest study design is that of a cohort study with data linkage.
- All members of the cohort should be verified drug users at the beginning of their observation time.
- Preferably, but not necessary, they are enrolled at the start of a new treatment episode.
- Vital status should be periodically ascertained, preferably by the population register or vital statistics office.
- The cohort should only enrol drug users whose death, would appear and be recognised in the register used to ascertain the vital status.
- At least date of birth, gender, date of onset/end of follow-up time and vital status should be available.
- Core Treatment demand indicator (TDI) variables and serologic status of bloodborne viruses are recommended as co-variables.
- Causes of death should be specified in ICD-10 codes.
- European mortality rate and European standard population are used as referent populations to calculate standardised mortality ratios and directly standardised rates.
- Although there are no age limits for the cohort, Standard table 18 only considers the age band 15–49 years.

Abbreviations

DRD	Drug-related death
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
GMR	General Mortality Register
ICD-10	International Classification of Diseases 10th edition
NFP	national focal point
PDU	Problem drug users
SR	Special Register
TDI	Treatment demand indicator
WHO	World Health Organization

Glossary

— **Mortality cohort study in drug users**: a study in which a defined group of drug users are followed over a period of time to assess the occurrence of the mortality.

— **Date start observation time**: at study entrance (t=0) which will often correspond to the date of treatment entrance, police arrest or other specified event.

— **Date end observation time**: at the end of the study period, death, or migration (lost to follow-up).

— **Linkage**: matching dataset of drug users to mortality registers by their identifier (e.g. names, unique national ID, social number ID), to assess their vital status (i.e. dead or alive).

— (Total) **Person-time at risk**: the sum of all follow-up time. Expressed in person-years.

— **Lost to follow up**: observed ends of observation time because the vital status can no longer be ascertained.

— **Periodical follow up**: periodical update of the vital status and cause of death of the study population.

— **Mortality rate:** crude mortality rate is defined as the quotient of the sum of all deaths and the total of all person-time at risk, often expressed as the number of deaths per 1000 person-years

— **Direct standardisation:** Direct standardised rates (standardised by gender and age bands) are calculated for each cohort using the standard European population age and gender distribution as a reference, i.e. by applying the mortality rates observed in the cohort for each gender and age-band, to the reference population: they are used in order to compare results across cohorts, by calculating the overall mortality that would have occurred in the reference population.

— **Standardised mortality ratio (SMRs):** SMR and their 95 % confidence intervals (95 % CI) are used to compare the mortality experience of a particular cohort of drug users with that experienced by the general (national) population for the same age and gender distribution and period. It measures the excess mortality in the study compared to the general population. The expected numbers of deaths are calculated using sex and age specific local mortality rates.

— **Cumulative survival probability**: cumulative proportion of survivors after a certain time-period (generally analysed by Kaplan Meier method; adjusted for differences in follow-up time).

1.   Introduction / objectives

The EMCDDA is one of the decentralised technical agencies of the European Union (EU). Since it was established in 1993, its mandate is to provide sound, reliable and comparable information on drugs and drug addictions and their consequences. The reporting of information covers: the epidemiological situation; responses; and drug strategies and policies. The Centre currently works with 30 European countries, including all 27 Member States, the candidate countries Croatia and Turkey, and Norway who participates in EMCDDA activities under special agreement. The Centre works with national focal points located in all participating countries to develop standard and comparable methods, measures, and reporting tools.

Among the most established of the EMCDDA monitoring systems are the Key epidemiological indicators, although other important core data are collected to monitor the situation. The European Council Recommendation endorsed the key indicators in 2001 ([1]). Subsequently, the Key indicators were endorsed by the EU action plan on drugs (2004–08) and more recently by the new EU action plan (2009–12), which calls for increased compliance of Member States with implementation criteria for key indicators ([2]). Key indicators include: 'General population surveys (GPS)', 'Problem drug use (PDU)', 'Treatment demand indicator (TDI)', 'Drug-related infectious diseases (DRID) and 'Drug-related deaths (DRD) and Mortality among drug users (DRD)'.

The rationale to develop the 'DRD and mortality among drug users' indicator is that drug-related mortality is one of the major causes of death among young people in Europe (EMCDDA, 2010). Illicit drug use is a major cause of mortality worldwide and involves substantial excess loss of life and potential productivity, particularly among the young. It is a truly international problem not restricted to one region (Darke, S. et al., 2007). Every year, between 6 500 to 8 500 overdose deaths are recorded in Europe (Vicente et al., 2009), and in some countries, overdoses account for more than 10 % of the mortality of young adults. Drug users (in Europe, particularly opiate users) suffer a very high overall mortality (in general, 10 to 20 times higher) compared to the general population (EMCDDA, 2011; Bargagli et al., 2006b; Bloor, M. et al., 2008; Brugal et al., 2005; Davoli et al., 2007).

'Drug-induced deaths and mortality' is one of the five key epidemiological indicators used by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) to estimate the prevalence and health consequences of drug addiction ([3]) (EMCDDA, 2010). Mortality can be considered a valid indicator of health effects of different exposures to risks, including drug abuse, giving the usually high level of reliability and validity of mortality data. The 'drug-induced death' component of the indicator consists of the occurrence of direct drug-related deaths (overdoses) among the total population of a country and the mortality component consists of all-cause mortality among defined groups of drug users, often Problem drug users (PDU) ([4]). Besides drug-induced deaths the mortality component of the indicator describes all causes of death among drug users. These causes are not restricted to drug users and can not be extracted as such from general mortality statistics. The mortality component of the indicator includes all deaths (e.g. fatalities caused by the long-term somatic consequences of drug use and the social context of drug use, such as diseases (e.g. HIV-AIDS, infections, liver disease) or violent deaths (e.g. suicide and trauma).

([1]) Council Resolution on the implementation of the five key epidemiological indicators on drugs, developed by the European Monitoring Centre for Drugs and Drug Addiction, Brussels, November 2001.
http://www.emcdda.europa.eu/themes/key-indicators
([2]) EU drugs action plan for 2009–12
http://ec.europa.eu/justice_home/fsj/drugs/fsj_drugs_intro_en.htm
([3]) See in the DRD protocol Version 3.2 http://www.emcdda.europa.eu/themes/key-indicators/drd
([4]) EMCDDA defines 'Problem drug use' as 'injecting drug use or long duration/regular use of opioids, cocaine and/or amphetamines'. This definition specifically includes regular or long-term use of prescribed opioids such as methadone, but does not include their rare or irregular use, or the use of ecstasy or cannabis. Note that this definition is in the process of being revised.

Most European countries have already conducted mortality cohort studies such as Italy (Antolini et al., 2006; Bargagli et al., 2006a; Davoli et al., 2007; Ferri et al., 2007), the UK and Ireland (Bloor, M. et al., 2008; Cornish et al., 2010; Farrell and Marsden, 2008; Lyons et al., 2010; McCowan, C. et al., 2009), the north European countries (Clausen et al., 2008; Fugelstad et al., 1997; Ødegård, E. et al., 2007; Ravndal, E. and Amundsen, E.J., 2010), Germany (Soyka et al., 2006) the Czech Republic (Lejckova and Mravcik, 2005) and others, although many studies are not published (EMCDDA, 2011). There are differences and similarities in overall and cause-specific mortality rates across different settings, geographical areas and in time. These differences and similarities provide answers, or at least generate hypothesis about specific determinants of mortality. They give insight into the influence of treatment and policy measures that are taken to reduce drug-related mortality in the EU Member States (Giraudon et al., 2012; Degenhardt et al., 2011).

Combined with the Key indicator on prevalence of drug use and the drug-induced component of the indicator, the figures of mortality among drug users facilitate estimations of the total burden of drug use on mortality. More practically, conducting mortality studies among drug users gives insight into the practise of codification of drug related death in the different Member States.

This standard protocol provides national focal points and experts with a guide. The analytical scripts in SPSS® and Stata® for carrying out and, analysing mortality cohort data and a MS Excel® template to calculate SMR and directly standardised rates are provided separately and are available from the EMCDDA DRD web pages. This protocol explains how to report to the EMCDDA the key figures on mortality among drug users through the data collection tool 'Standard table 18 – ST18'. They are based on the standard protocol that was developed within the EMCDDA project on cohort mortality studies and the experiences of the feasibility study performed in the early phase of the project ([5]).

([5]) See current template ST18 and reference documents on Cohort Studies on Mortality in
http://www.emcdda.europa.eu/themes/key-indicators/drd

2. Carrying out mortality studies among drug users

2.1. Confidentiality, ethical approval and consent

When conducting a mortality study, confidential information about drug use, vital status and cause of death will be used. In general, individual identifiers are necessary to ascertain vital status and to assess the cause of death.

Legislation on data protection varies between countries. Each centre must adopt specific and effective procedures to ensure the absolute confidentiality of the information gathered and that the appropriate legislation on data protection, ethical approval and consent are respected.

All data analysis and reporting to the central co-ordinator will be done without identification of any individual's name or other unique identifiers. The EMCDDA will not receive identifying information of drug users, as it is established in its regulation.

2.2. The main principles of a cohort study

When constructing figures on mortality among drug users the main principles of cohort studies are used. In this case, a cohort study is a study in which a defined group of drug users are followed over a period of time to assess the occurrence of the mortality (Figure 1).

Figure 1: Schematic representation of a cohort study
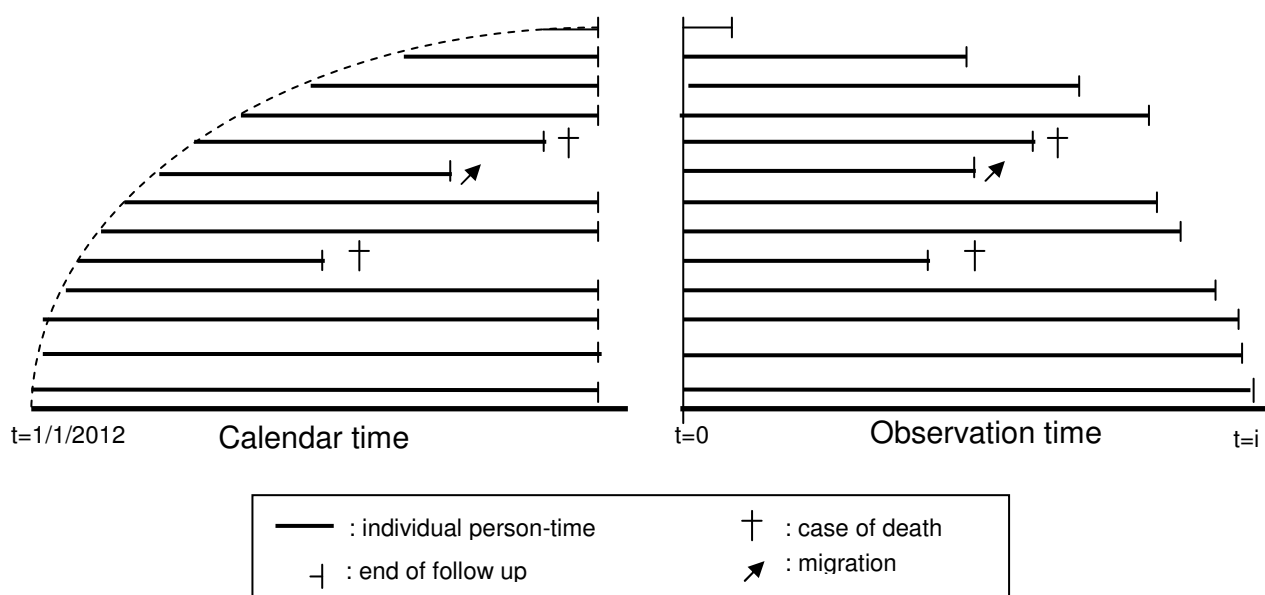
Figure 1 shows a schematic example of the cohort study. Each horizontal line represents an individual period of follow up. The individual observation period starts at study entrance (t=0), which will often correspond to the date of treatment entrance (treatment centres are the preferred study setting by the EMCDDA, to facilitate follow-up and limit the number of persons lost to follow-up). Alternatively, observation time can start, e.g. at police arrest or other specified event. The individual observation time ends (a) at the date of last vital status ascertainment or (b) at the day of death, or (c) date lost to follow up (e.g. emigration).

Drug users enter the study at different points during the study period and can exit the cohort at different points in time by mortality or emigration. Therefore individual follow up time varies

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between subjects ([6]). As a result, to indicate the size of the cohort it is better to refer to the sum of all follow-up times than to the number of individuals. The sum of all follow-up time is also referred to as '(total) person-time at risk' ([7]). Person-time is expressed in person-years.

The main outcome parameter of the cohort study is the incidence rate or, in case of mortality studies, crude mortality rate. The crude mortality rate is defined as the quotient of the number of deaths and the total 'person-time at risk' often expressed as the number of deaths per 1 000 person-years.

Mortality rate = number of deaths/number person-time at risk

To make a valid estimation of the mortality rate it is necessary that:

- _only_ those deaths that occur to persons who are selected in the study population and occur during their 'follow up' should be counted in the numerator;
- _each_ individual contributing 'person-time at risk' that dies should be counted in the numerator and contribute person-time until the date of death.

This implies that the researcher should be able to identify each case of death. When this is no longer possible (e.g. when a subject emigrates to another country) the person contributes person-time until the latest date when the notification of the occurrence of his/her death was possible but not afterwards.

2.3.   Study population and inclusion criteria

The study population generally is a selection of the current population of drug users. The selection should be based on clear and unambiguous inclusion criteria. Only those drug users who satisfy all criteria can be included in the study. Some inclusion criteria are necessary to ascertain the vital status and calculate person-time afterwards (see Chapter 2.4). Other criteria will be related to the location where drug users are encountered, and to the characteristic of their use (e.g. opiates users, injectors). Drug users in Europe are mainly represented by heroin users, amphetamine users in the Czech Republic and in Scandinavian countries and more recently, cocaine users in south European countries such as Spain and Italy.

There is strong evidence that study characteristics predict mortality levels (Degenhardt et al., 2011). Therefore, additional inclusion criteria may limit the generalisability of the mortality figures. However, they will increase the validity of the mortality figures among various subsamples of drug users and will facilitate the interpretation of mortality figures. Moreover, within a European framework and EMCDDA monitoring perspective, this improves the comparability with other studies.

Although there are many possible settings, the feasibility study revealed that in most countries, a study amongst drug users entering treatment centres seemed the most feasible and valid option. Treatment centres have an ongoing influx of new treatment episodes and they register identifiers. In the framework of a longitudinal study, these will be necessary for a future assessment of vital status and cause of death. However, it is possible to enrol a study population recruited in other settings (e.g. police or judicial services, outreach services, hospital, needle exchange facility, etc.) (Lopez et al., 2004; Marzo et al., 2009), provided that the complete identifiers are available.
The inclusion criteria define the cohort being studied and the drug-using population to which the results apply. The criteria relate to the status (demographic, geographic) at the time of entry into the cohort.

([6]) This type of cohort is called an 'open' cohort as new members are gained over time and members who are still alive can be lost, by migration. A 'closed' cohort adds on new members over time and loses members only due to death (Rothman and Greenland, 1998).
([7]) The total amount of person-time at risk divided by the study period equals the average size of the population.

Recommended inclusion criteria:

- to be a current drug user (recent history of drug use at the date when the observation starts);
- have complete identifiers, or sufficient/relevant identifiers to link with no doubt with population or mortality registers (personal number or name, date of birth, place of birth, gender);
- being traceable for vital status ascertainment. In general, this would mean: be officially registered in the local or national population register;
- have a well defined date of onset of observation time (e.g. date of treatment intake)
- enrolled during the study period (e.g. from 1/1/20xx–31/12/20xx);
- in case of treatment cohort, preferably include those people starting a new (but not necessarily the first) treatment episode.

Besides these general inclusion criteria, additional criteria are related to the country-specific recruitment setting of the cohort (e.g. outpatient methadone treatment) including additional inclusion or exclusion criteria of the treatment centre itself (e.g. age limits, exclusion of drug users with serious additional psychiatric disorders).

Select only those drug users whose vital status is likely to be ascertained in the future.
Describe recruitment setting and related inclusion criteria in detail, in order to enhance the interpretation of differences and similarities with other mortality figures among drug users.

Some specific issues:

— *Inclusion of drug users already participating in treatment*

The study population may include patients already participating in treatment at the beginning of the study period. However, it is likely that they constitute a 'selected' group of people that are likely to have different characteristics than subjects who also started treatment but (instead of continuing treatment) died or left for other reasons. Moreover, information on the drug users' characteristics is collected at treatment intake. If we use this information for those already participating in treatment, the information (e.g. injection status) may be outdated when the patient enters into the study. The better way to proceed is to select only those subjects starting a new treatment episode.

— *Period of enrolment / follow up*

The traditional cohort approach (option I in Figure 2) allows us to observe the natural history of a cohort of people defined as drug users at study-entrance. The EMCDDA, however, has a priority of monitoring the state of the current drug users across EU countries.

As time proceeds, the selected population of drug users will show an increasing proportion of people not using drugs anymore. Since the data linkage procedure does not imply standard follow-up data collection after the date of enrolment (other than vital status assessment), it is impossible to adjust for the proportion of people who actually reached and maintained abstinence. Moreover, especially if only mortality registers are used and 'being alive' can not be confirmed, drug users lost to follow up (because of migration) may not always be identified and possible mistakes in identifiers may lead to misclassification of the vital status. Over time, these errors will accumulate and lead to a risk to underestimate the mortality figure.

Therefore, the figure of a certain year of a certain Member State derived from a (for example) three-year old cohort of drug users selected at addiction treatment centres will differ from the figure derived from a cohort with a period of enrolment and maximum follow up of 13 years.

Thus, it is advised to limit the follow up to a maximum period of ten years. This could be done simply by starting a new cohort after 10 years and end the observation time for all drug users who are still alive at the end of the period (option II in Figure 2). Another possibility (option III in Figure 2) is to start a new cohort but to continue the observation time of the drug users of the old cohort until a maximum of 10 years after enrolment. That way, the average observation period at any moment (average period from collecting data concerning drug use to vital status assessment) will stabilise, which ensures a constant proportion of mis-classification due to the effects mentioned above.

Figure 2: Three variations on follow up time of cohort studies
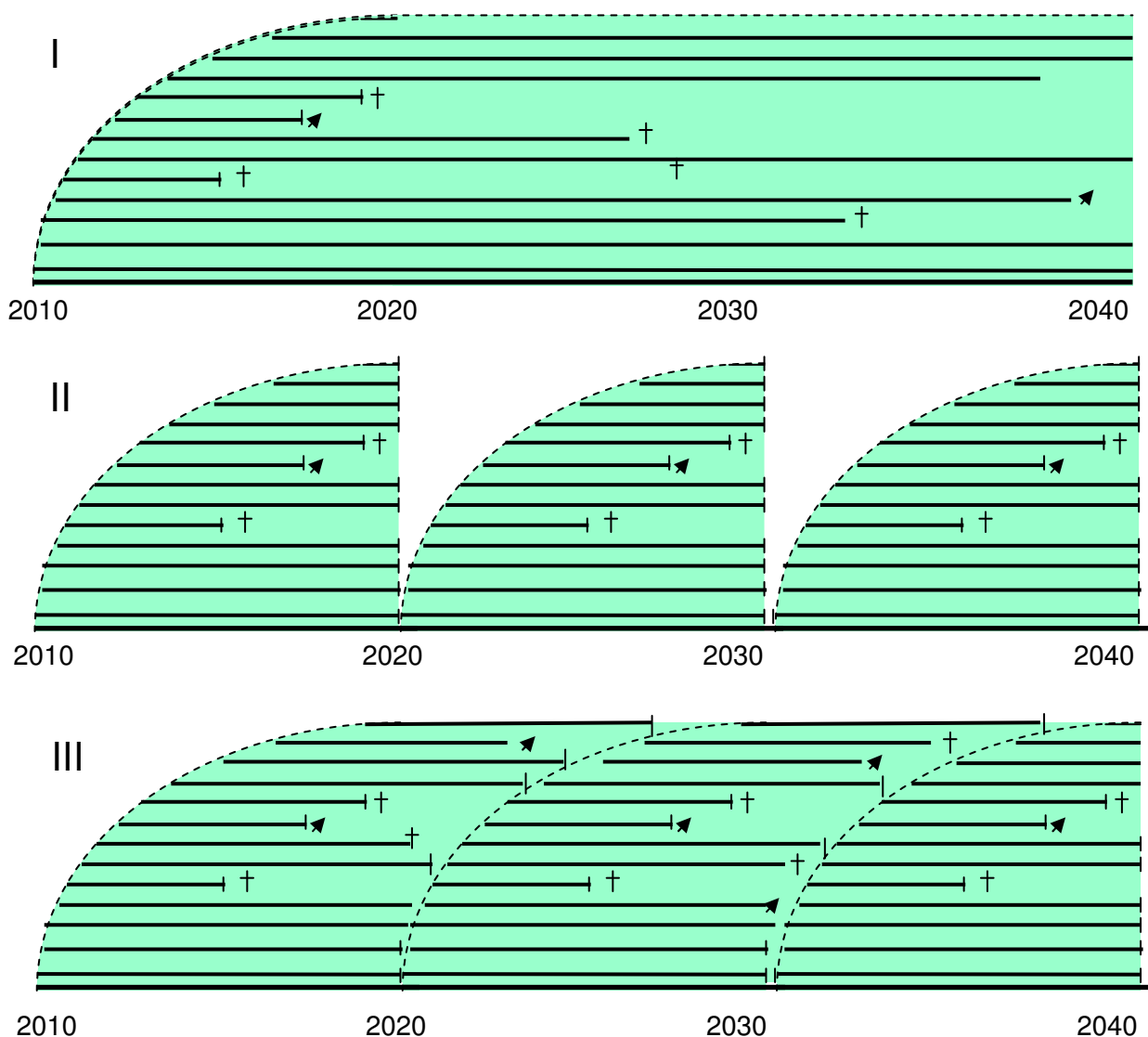
A proper baseline measurement still allows studies with a longer time frame of observation, and aim at describing, for example the natural history of persons identified as drug users 30 years ago.

— *Retrospective cohort versus prospective cohort study to derive mortality figures*

Based on the inclusion criteria mentioned above, the mortality figures can be derived from a retrospective study. In retrospective cohort studies, data to define and describe the study population and to ascertain vital status and cause of death are already available at the onset of the study. If similar criteria are used, as would have been the case when conducting a prospective

study (in which the data still have to be collected) and if identifiers of the drug users are complete and correct, then the results of a retrospective study will be similar to those derived from a prospective study. However, in general in retrospective cohort studies, the possibilities to collect additional data (Chapter 2.4.3) for further analysis may be limited and therefore the possibilities to adjust for potential confounding (e.g. because of differences in the proportion of injectors between countries) will be compromised.

2.4.   Data collection

2.4.1.   Ascertainment of vital status

The purpose of the follow-up process are:

— to determine the amount of 'person-time at risk', the <u>denominator</u> of the mortality figure. Determination of the vital status (by recording deaths) and losses due to migration, are necessary to specify the end of the observation period.
— to determine the number of deaths, i.e. the <u>numerator</u> of the mortality figures.

Feasibility of follow up is a key consideration, since completeness of follow up is essential for the validity of the mortality figure. Failure in retrieving information on vital status should be prevented by excluding people who are a priori known to be not traceable, such as, depending on the countries, non- resident people or subjects with incomplete identifiers.

The methods 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.
The best option for ascertaining vital status is through the Population Registers (i.e. a list of all residents, where information on death would be systematically updated) or Vital Statistics Bureau.

— In case a person is still registered as an inhabitant of the country at the end of the study period, the end of the study period is considered as the end of the observation period.
— In case a person has died before the end of the study period, the date of death is considered as the end of the individual observation period.
— In case people are no longer traceable in the registers (e.g. due to emigration) cases are considered as 'lost to follow up' as their vital status is unknown after a certain date. This date is considered as the end of their observation period ([8]).

Using national registers, only those emigrating abroad will be considered 'lost to follow up'. If local population registers are used (e.g. as is done in the Netherlands, in Amsterdam), drug users who change residence within a country could be followed by registers of other municipalities. Alternatively, subjects can be considered lost to follow up at the date of changing place of residence within a country. This however, may lead to a bias in case of selective migration (e.g. migration to a residential nursing home for people suffering from AIDS or migration of those abstaining from drugs). Homeless drug users may disappear from a local population register without being registered in another one, and periods of detention, common in drug users, may result in a temporary change of the place of residence.
If population registers are not available or accessible, general mortality registers can be used to assess the vital status. However, we have to assume that people are alive if not found in a mortality registry and this assumption may not always be justified, especially when local mortality registers are used.

([8]) In some countries, vital status of emigrants can be assessed as well. If this is the case, the observation period may continue. One of the goals of the indicator is to study mortality figures within different settings (various treatment possibilities, policy) and therefore, the observation period may end at the date of migration.

Practice of record linkage (Clark, 2004)

Linkage with population registers may be conducted manually when the study population is limited to a few hundred subjects but will soon be too time consuming if the study population consists of thousands, especially if the study dataset is periodically updated by linkage with the mortality data.

If personal numbers that are also used in population or mortality registers are available, it is preferable to use these unique numbers. Otherwise, identifiers have to include date of birth, the first three letters of the surname and gender, and, in some countries, other information (e.g. the place of birth for the INSERM register in France). The use of the full name may lead to mismatches due to spelling errors. When tracing married females, one must be sure the maiden name is used for data linkage instead of the husband's surname. When identifier information is missing, subjects must be considered as not eligible for the inclusion into the study.

We may distinguish deterministic (there is either a match or not) or probabilistic linking (indicating the probability of a match). In the latter case, more variables can be taken into account (e.g. date of birth, initials, full name) and a certain likelihood of matching can be chosen. With probabilistic linking, records with small registration errors in the identifiers may be included.
The best way to proceed is a deterministic linkage with an identifier that is checked at enrolment and found to be correct. If other methods have been used, they should be explained and reported on the ST18 table.

2.4.2.   Overall and cause-specific mortality

Beyond quantifying the number of deaths, cohort studies aim to provide information on the causes of deaths, and allow the computation of cause-specific mortality rates.

National mortality registers are the best option to ascertain the causes of death for those known to be deceased. In these registers, causes of death are coded by trained nosologists according to the International Classification of Diseases (ICD) ([9]). Most countries have mortality registers with ICD codes recorded, even though sometimes there are legal restrictions in the access to these data ([10]).

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-induced deaths') (EMCDDA, 2010) ([11]). The current version of the table to be filled in ST18 is as follows:

2.2.4 Cause-specific mortality
(distribution of deaths by cause) ([12])

	Number
HIV-AIDS	
Overdoses	
All other causes	
of which, ill-defined conditions	
All codified cases	
Unknown causes	
Total number of deaths during follow-up	

([9]) Available from: http://www.who.int/classifications/icd/en/
([10]) Some statistical offices do not deliver individually linked data on cause of death but nonetheless give an opportunity to link the data and report the frequency tables by calendar year, gender and age groups.
([11]) In some countries, overdose was codified as 'mental disorders' (subheading 'drug dependence'); in others, it was exclusively codified as 'injuries and poisoning'.
([12]) For specific ICD codes, see Appendix 1.

The category of unknown or ill-defined causes may be used in case a drug user is found dead with surrounding paraphernalia and there are no witnesses who are able to give more information about the cause of death. Coroners and nosologists can either choose between fatal intoxication or an unknown/ill-defined cause of death and this practice could differ between countries. This may result in some over- or under-estimation of the drug-related causes of death. The rate of unknown or ill-defined causes among drug users as opposed to the rate of overdoses may give clues on this issue.

Other sources of data on causes of death can be used, depending on national regulations, to complement information from the previous sources e.g. Forensic Institutes, Registers on post-mortem toxicology, Registers of drug-related deaths, Coroners' Registers, hospital records, Hospital Discharge Registers, police data.

On their own, however, these following sources collate selected causes of deaths, and are not suitable to collect data of the causes of general mortality among drug users. Specific causes will be over-represented: either 'non-natural' causes (such as accidents, suicides or homicides) through forensic sources, or 'natural' causes through hospital admission sources.

Furthermore, the use of the same source (e.g. general mortality register) to inform mortality among drug users and the prevalence of drug-induced deaths enhances the possibilities of cross-validation of both components of the indicators. For example, if within a country the proportion of ill-defined causes is high and the proportion of drug-induced causes is low, the nosologist of a specific country may be more reluctant to give one of the codes of 'drug-induced death' which may result in an underestimated prevalence of drug-induced deaths mentioned in ST5.

2.4.3. Minimum dataset for ST18 reporting and additional data of drug users

Once the cohort has been defined, for each member enrolled in the study, a minimum data set must be available. Concrete inclusion criteria of the cohort, personal identifiers (including date of birth and gender), a defined date of start and end of the observation time, the vital status and preferably a cause of death codified according to ICD-10, as well as the primary drug at enrolment is the minimal information that is necessary to provide data on mortality among drug users.

Minimal data necessary[^]:

Unique Identification number[#], personal number[*], surname[*], Date of birth, Gender (M/F)

Date of enrolment (treatment intake or otherwise specified)

Date of end of observation period
— *If alive during the follow up period: end of (periodical) follow up*
— *If death during the follow up period: date of death*
— *If lost to follow up: date of emigration*

Vital status at the end of the follow up period (according to population register)
1 Dead/2 Alive/9 Not known/Lost to follow up/Migrated

Cause of death (ICD-10)
[^]: See table below for variable names and coding
[#]: A number for this dataset (study) only, no official number.
[*]: Will not be part of the dataset used for data analyses (to be used for identification purposes only)

For computing the ST18-derived figures (e.g. person-year followed up) and reporting to the EMCDDA ([13]), the 'Patient' core variables needed are as follows:

Table 1: 'Patient' minimum dataset needed to report data through ST18

N	Label	Format	Meaning in full	Coding
Basic analysis of Mortality Rate				
1	ACCESS_ID	string	Unique identifier for the patient in this dataset	Auto number
2	BIRTH_DATE	date	Date of birth	dd/mm/yyyy
3	GENDER	numeric	Sex	1=male 2=female 9=unknown
4	PRIM_DRUG	string	Primary drug at enrolment	1=heroin 2=methadone 3=other opiates 4=cannabis 5=hypnotics and sedatives 6=cocaine 7=stimulants 8=hallucinogens 9=other substances 99=unknown
5	ENTRY_DATE	date	Date of enrolment	dd/mm/yyyy
6	END_DATE	date	End of observation	dd/mm/yyyy
7	VITAL_STAT	numeric	Vital status	1=dead 2=alive 9=unknown
8	DEATH_DATE	date	Date of death	dd/mm/yyyy
Causes of death analysis				
9	DEATH_CODE	string	Cause of death according to the ICD code	ICD codes
10	DEATH_CAUS	string	Cause of death according to text	text (up to 20 positions)

Before analysing the data, their quality and completeness has to be checked for the purpose of correcting errors where possible and of verifying any data not supplied. As the main aspect of analysis involves calculation of the observed person-time at risk of dying; all subjects should have a positive person-time (date entry < date end of follow-up or date of death). Records of subjects with negative or '0' person-years of person-time should be checked carefully. Based on the format suggested in Table 1, the minimum dataset for analysis will look as below (Table 2):

Table 2: Example of data set formatted according to the EMCDDA format showed in Table 1

ID	BIRTH_DATE	GENDER	PRIM_DRUG	ENTRY_DATE	VITAL_STAT_DATE	VITAL_STAT	DEATH_DATE	DEATH_CODE	DEATH_CAUS
1	30/06/1975	1	1	15/01/2011	15/03/2011	1	15/03/11	X42 and T402*	Heroin OD
2	30/06/1970	2	1	15/06/2011	30/06/2011	2			
3	30/06/1971	1	1	15/07/2010	15/01/2011	1	15/01/11	B182	Chronic viral HCV
4	01/08/1989	1	3	20/07/2010	30/06/2011	2			
5	01/08/1987	2	1	20/08/2010	30/06/2011	2			
6									
7									
8									

*Note that T codes should be combined with the external cause code (e.g. T402 and X42) which states that the substance was taken accidentally (accident, suicide, homicide, undetermined). Secondary codes are useful for the analysis of cause specific mortality rates and to prevent for example that injuries can not be interpreted. For pooled analysis of the cohort studies we suggest they are reported as well.

([13]) See Current EMCDDA questionnaire for DRD reporting — cohorts of drug users recruited in treatment services (Fonte template 18) in http://www.emcdda.europa.eu/themes/key-indicators/drd)

This core simple dataset will be sufficient to compute all derived variables (e.g. duration of follow-up, by age-band and calendar year as explained later in Figure 4) and the final results needed for ST18 (e.g. mortality rates and their confidence interval). In addition, reference population (namely the European Standard population) will allow the computation of standardised mortality rates (see text below in 3. Data Analysis, as well as SPSS® or Stata® scripts ([14])).

Additional data may tell us more about specific sub-groups with higher or lower (cause-specific) mortality. Additional data may be obtained from a core set of variables of the Treatment demand indicator (TDI) registered at treatment intake ([15]). Moreover, we suggest that data concerning the serological status on HIV, HBV and HCV are added to this set.

Additional data (TDI format) (see numbering of the TDI protocol, Item list page 43).

Treatment details
1.Treatment centre type
3. Ever previously treated

Socio-demographic information
7. Living status (with whom)
9. Living status (where)
10. Labour status
11. Highest educational level completed

Drug-related information
12. Primary drug
13. Usual route of administration
14. Frequency of use
15. Age at first use
16. Secondary drugs (Other drugs currently used)
20. Ever injected/currently (last 30 days) injecting

Infectious diseases[*]
22–23 Data on specific laboratory test performed (HIV, HCV)

* not part of the core Treatment Demand Indicator data set

Should we update the information in case of multiple intakes?

Some drug users will have multiple intakes which may allow or require updating information. However, the characteristics of drug users who do not return to treatment may change as well, but their data cannot be updated. Therefore, we do not advise to update the information selectively. Problems may arise if people are readmitted to treatment with another primary drug of abuse. In this case one individual may participate in both cohorts. For example, if an opioid cohort and another cohort is described separately, the person may appear in both cohorts; but this would require two (or more) separate data files, one per cohort.

If only one cohort is analysed, a double appearance of one individual is inappropriate. We propose a hierarchical approach in which the opioid cohort is prioritised. This means once a person participates within an opiate cohort, a person remains participating in this cohort. When a person

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([14]) http://www.emcdda.europa.eu/themes/key-indicators/drd
([15]) See current version of the TDI questionnaire (ST34) in http://www.emcdda.europa.eu/themes/key-indicators/tdi and the protocol, available from http://www.emcdda.europa.eu/publications/manuals/tdi-protocol-3.0

changes from another cohort to an opioid cohort, his/her observation-time should be censored (stopped) within the non-opioid cohort at the date of entrance in the opioid cohort. This person is considered to start attributing person-time to the opioid cohort from that date onwards.

3. Data analysis: rates, confidence intervals and adjustment for differences in age distribution

3.1. Crude mortality rate

The crude mortality rate is defined as the quotient of the sum of all deaths and the sum of all person-times usually counted in years or fractions of years.

$$\text{Mortality rate} = \Sigma \text{ deaths} / \Sigma \text{ person-time.}$$

This rate is often expressed as the number of deaths per 1 000 person-years by multiplying by 1 000.

The calculated mortality rate is subject to 'chance' events during follow up and can be considered as an estimate (also expressed as 'point estimate') of the 'true' mortality rate. To give an indication of the (statistical) precision of this point estimate a 95 % confidence interval (95 % CI) can be calculated. If there are no biases and the study should be repeated for an innumerable number of times, 95 % of the confidence intervals will contain the 'true' value.

As an example, Table 3 and Figure 3 show the confidence intervals of similar point estimations of mortality rates (20/1 000py) with a cohort size varying from 100 to 100 000. A similar mortality rate within a larger cohort implies that the observed number of deaths is higher and subsequently the standard error (SE) is lower. Eventually the 95 % CI varies from 5/1 000 py to 80/1 000py in a cohort with 100 person-years at risk and 2 deaths from 19/1 000py to 21/1 000py within a cohort with 100 000py and 2 000 deaths. Note that the 95 % CI of the mortality rate can never reach a value below zero ([16]).

Table 3: Calculation of mortality rate and 95 % confidence interval,
for different numbers of deaths and person-years:

	A	B	C	D	E	F	G	H	I	J
1	# Death	# person-years	MR	ln (MR)	SE	1.96*SE	95 % CI (ln (MR))		95 % CI (MR)	
2	=a2	=b2	=a2/b2	=ln(c2)	=1/sqrt(a2)	=1.96*e2	=d2-f2	=d2+f2	=EXP(g2)	=EXP(h2)
3	2 000	100 000	0.02	-3.912	0.022	0.044	-3.956	-3.868	0.019	0.021
4	200	10000	0.02	-3.912	0.071	0.139	-4.051	-3.773	0.017	0.023
5	20	1000	0.02	-3.912	0.224	0.438	-4.350	-3.474	0.013	0.031
6	2	100	0.02	-3.912	0.707	1.386	-5.298	-2.526	0.005	0.080
7										
8										
9				MR	95 % Confidence Interval					
10				=c2*1000	=i2*1000	=j2*1000				
11	Mortality rate (deaths per 1 000py)			20	19	21				
12	Mortality rate (deaths per 1 000py)			20	17	23				
13	Mortality rate (deaths per 1 000py)			20	13	31				
14	Mortality rate (deaths per 1 000py)			20	5	80				

([16]) To calculate the 95 % CI of the mortality rate (MR), the MR is converted into its natural logarithm (ln(MR)). The standard error (SE) of the ln(MR) is calculated as '1/√D' in which 'D' is the number of deaths. The 95 % confidence limits of the ln(MR) are calculated by adding or subtracting 1.96* SE to the ln(MR). Eventually, the exponent of the calculated confidence limits of ln(MR) are the 95 % CI of the MR (see Table 3).

Figure 3: Mortality rate (MR) and versus ln(MR)
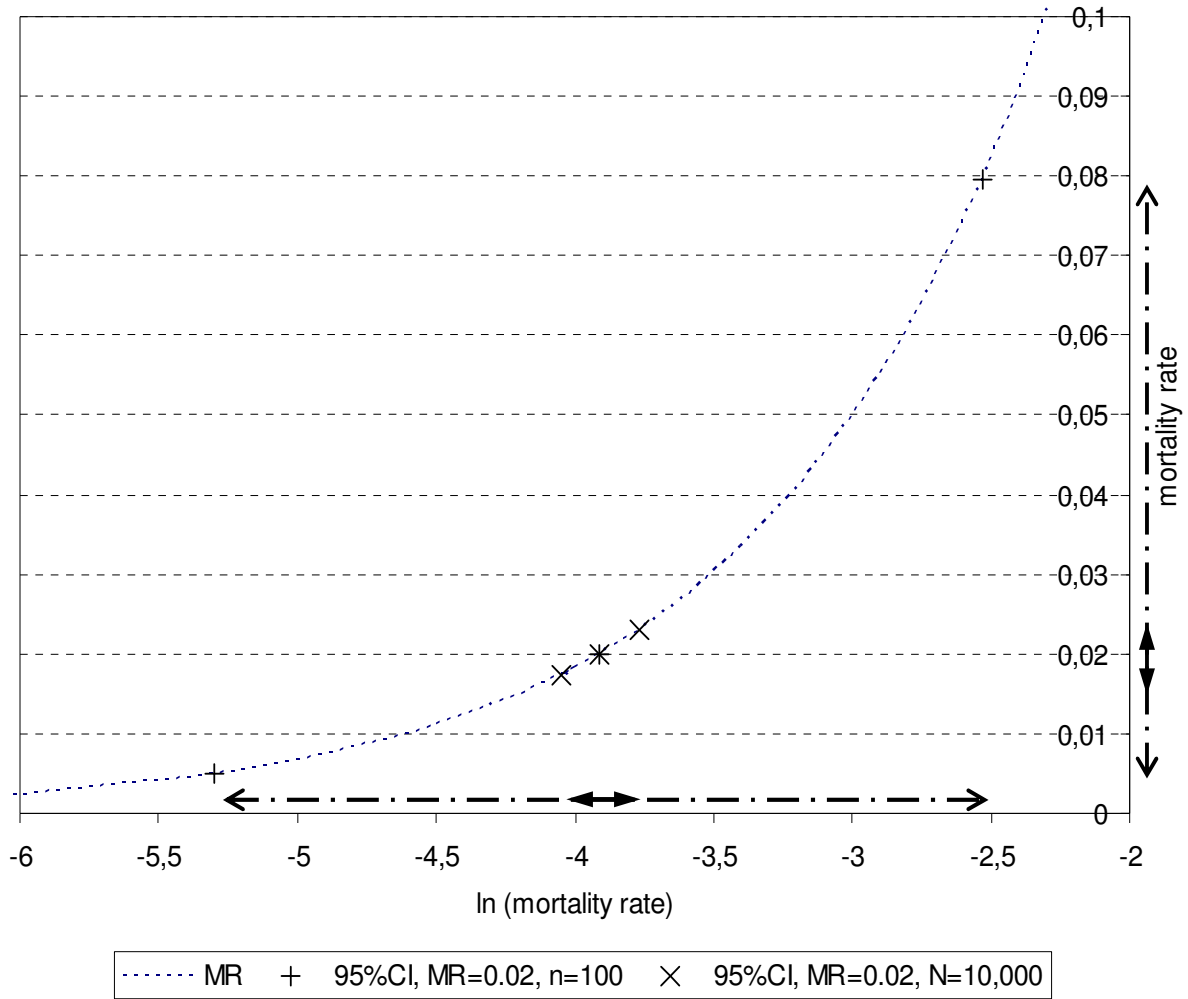
Note: The 95 %CI based on the MR with 100 person-years and 2 deaths is indicated with '+'. The much narrower 95 % CI based on a MR with 10 000 person-years and 200 deaths is indicated with an X.

3.2.   Adjustment for differences in age and gender distribution

We may want to compare mortality figures among a population of drug users with other drug using populations or with the general population, bearing in mind that age and gender distributions across the populations may differ and mortality rates generally increase with age and are generally higher among males than females. For a valid comparison, we would like to adjust for differences in the age and gender distribution. There are different ways to do this ([17]):

— stratification and standardisation
— multivariate analyses.

([17]) The most simple method to adjust for confounding is limitation of the study population to a certain age and gender e.g. comparison of mortality rates among males from 30–40 yrs of age only.

3.2.1. Stratification

In order to generate stratified mortality rates (mortality rates for each age and gender category), both the observed number of deaths and observed person-time at risk has to be recalculated separately for each category. As the study period proceeds, an individual grows older and may contribute person-time to several age groups. Similarly, a person may contribute person-time to multiple calendar years ([18]).

As an example, Figure 4 shows a hypothetical individual entering the study during 2011 at the age of 28, and leaving the study in 2014 when dying, aged 31. He contributes observation-time to four different categories of calendar-time (annual) and to two five-year age categories. Period I involves the time from entering the study (e.g. date of treatment intake) until 31 December 2011. Period II involves the complete year 2012, period III the year 2013 until the 30th birthday. Person-time of period I, II and III is attributed to the age category 25–29 years. Person-time of Period IV (up from the 30th birthday until the end of 2013) and period V (from 1 January 2014 until the date of death) is attributed to the age category 30–34 years. The death is only counted in the numerator of the mortality rate within the stratum, males, 30–34 years and the 2014 calendar-year.

*Figure 4: Individual observation-time attributed to different categories
of 5 years age-band and calendar time*
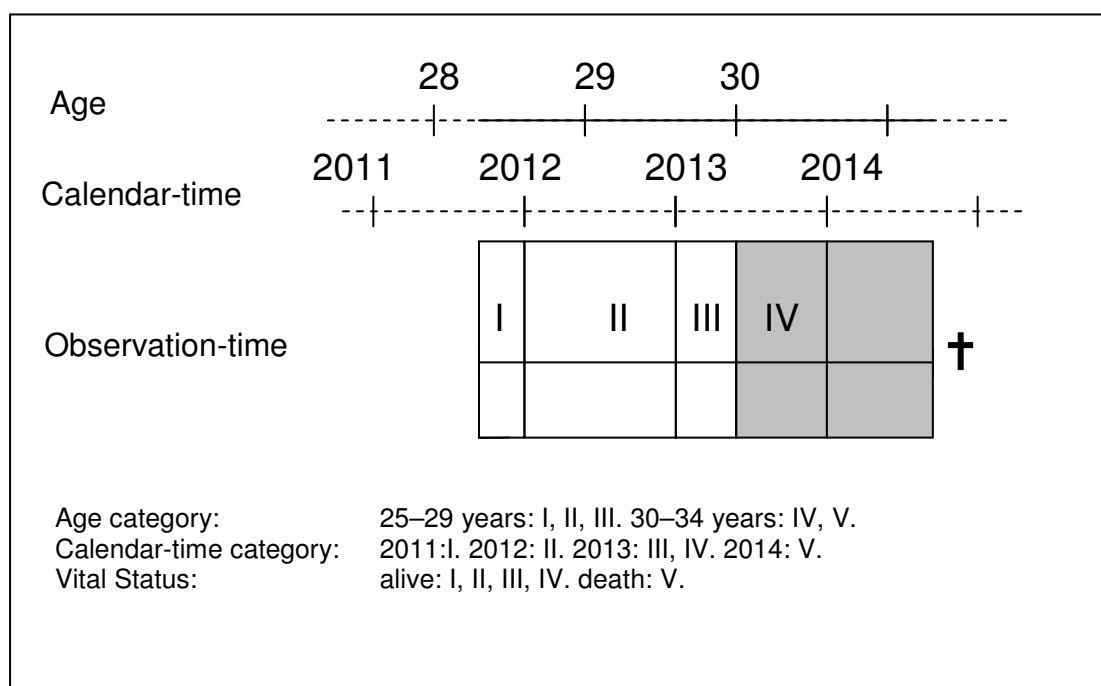
SPSS® or STATA® script, as well as an MS Excel file ([19]) can be used in order to break down the data concerning person-time and mortality in annual data, by the 5 years age category and gender, and to compute the figures needed to report ST18.

([18]) Note that in ST18, mortality rates are calculated for each calendar year, by gender.
([19]) All available from http://www.emcdda.europa.eu/themes/key-indicators/drd

Table 4: Zagreb Cohort, data stratified by 5 years age categories and gender

	Male	Female	Obs. Males	Obs. Females	MR Males	MR Females
15–19	200.4	132.0	3	0	0.015	0.000
20–24	2358.5	915.4	26	1	0.011	0.001
25–29	4773.8	1180.9	42	7	0.009	0.006
30–34	2968.0	577.1	38	1	0.013	0.002
35–39	1069.6	310.9	14	3	0.013	0.010
40–44	659.6	210.9	12	3	0.018	0.014
45–49	342.9	121.6	18	1	0.052	0.008
Total 15–49	12372.7	3448.8	153	16	0.012	0.005

Table 4 shows the stratified observation-time, number of deaths and mortality rates observed among the Zagreb treatment cohort 15–49 years (EMCDDA, 2011). The crude rate in this 15–49 age group is (169/15821.5=10.7/1000py).

3.2.2. Standardisation

There are different measures that summarise the stratified rates observed in a given measure. This section presents the direct standardised rate and the standardised mortality ratio.

3.2.2.1. Direct standardised rates

Purpose

Direct standardised rates can be calculated by applying the observed rates (stratified by age and sex) among the drug cohort population to an external reference population with a known age and sex distribution. As an external population either the population of the country, city or region or the European Standard Population can be used ([20]).
This calculation controls for the effect of the age and gender distribution of the cohort, replacing it with a common referent age and gender distribution (that of the EU). As a summary of the cohort mortality, this is very difficult to interpret, but it is useful in comparing mortality across different cohorts when age and gender considerations are removed.

Table 5: Direct standardised rates using the European Standard Population (ESP)

	European Standard Population (ESP)		Observed mortality rate		'Expected' mortality within ESP	
	Males	Females	Males	Females	Males	Females
15–19	7 000	7 000	0.015	0.000	104.8	0.0
20–24	7 000	7 000	0.011	0.001	77.2	7.6
25–29	7 000	7 000	0.009	0.006	61.6	41.5
30–34	7 000	7 000	0.013	0.002	89.6	12.1
35–39	7 000	7 000	0.013	0.010	91.6	67.5
40–44	7 000	7 000	0.018	0.014	127.3	99.6
45–49	7 000	7 000	0.052	0.008	367.4	57.6
Total 15–49	49 000	49 000	0.012	0.005	919.6	285.9
			Direct standardised rates			
Males	(919.6/49 000)*1 000=19/1 000py					
Females	(285.9/49 000)*1 000=6/1 000py					
Total	(1 205.5/98 000)*1 000=12/1 000py					

([20]) The current standardised European population is available from
http://www.euphix.org/object_document/o5338n27620.html

Table 5 provides an example of the direct standardised rates, obtained by applying the stratified rates of the Croatian cohort to the European Standard Population. The expected mortality within this calculation equals the number of deaths that would have been expected if the age and gender distribution of the drug users' cohort (15–49 years) would have been equal to that of the standardised European population [21]. Note that the reference population only supplies the age and gender distribution and no mortality data in this calculation.

Table 6 shows the formulas of the excel file [22] that can be used to calculate the direct standardised rates (age category 15–49). The expected number of deaths are given in cell number H28 (males) and I28 (females). The direct standardised rates of males and females are shown in I-4 and I-5 respectively.

Problems

Local or national populations can be used as a referent population to calculate direct standardised rates. However, if different referent populations are used for different cohorts comparison of mortality rates across different cohorts of drug users may still be compromised because of the differences in age distributions of the various referent populations. When reporting the direct standardised rates to the EMCDDA, the use of the European Standard Population is preferable.

Direct standardised rates may give misleading (inflated) results if deaths occur within strata with a limited amount of person-time. Therefore, is advised when calculating the direct standardised rates to merge the age bands of the strata until a substantial amount of observation-time (> 100 py) is collected.

As strata with a limited amount of observation-time occurs in the older age bands in which the risk of mortality is generally higher, the strata of the older age bands may be very influential compared with a non-standardised rate. Therefore, the direct standardised rates are calculated within the age group from 15 to 49 years.

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[21] Compare with the crude mortality rates in Table 4.
[22] Available from http://www.emcdda.europa.eu/themes/key-indicators/drd

Table 6: Excel file for calculating Standardised mortality ratios (SMR) and Direct Standardised Rates (DSR)

	A	B	C	D	E	F	G	H	I
1	Site:								
2									
3	legenda:					SMR	95% Low	95% Up	Direct stand. Rate /
4		data of the cohort (ENTER YOUR DATA)			Males	=E17/E28	=EXP(F33)	=EXP(G33)	=(H28/G28)*1000
5		data of reference population			Females	=F17/F28	=EXP(F34)	=EXP(G34)	=(I28/G28)*1000
6		results needed for ST18			Total	=(E17+F17)/(E28+F28)	=EXP(F35)	=EXP(G35)	=((H28+I28)/(G28*2))*1000
7		formula (DO NOT CHANGE)							
8									
9			male	female	# death Males	# death Females	MR Males	MR females	
10		15-19					=C10/E10	=D10/F10	
11		20-24					=C11/E11	=D11/F11	
12		25-29					=C12/E12	=D12/F12	
13		30-34					=C13/E13	=D13/F13	
14		35-39					=C14/E14	=D14/F14	
15		40-44					=C15/E15	=D15/F15	
16		45-49					=C16/E16	=D16/F16	
17		Total 15-49	=SUM(C10:C16)	=SUM(D10:D16)	=SUM(E10:E16)	=SUM(F10:F16)	=C17/E17	=D17/F17	
18									
19			Mortality rate European population		Expected number of deaths (1)			Expected number of deaths (2)	
20			males	females	Males	Females	ESP	Males	Females
21		15-19	0,00047	0,00022	=C10*C21	=D10*D21	7000	=G10*G21	=H10*G21
22		20-24	0,00090	0,00030	=C11*C22	=D11*D22	7000	=G11*G22	=H11*G22
23		25-29	0,00095	0,00032	=C12*C23	=D12*D23	7000	=G12*G23	=H12*G23
24		30-34	0,00111	0,00043	=C13*C24	=D13*D24	7000	=G13*G24	=H13*G24
25		35-39	0,00152	0,00068	=C14*C25	=D14*D25	7000	=G14*G25	=H14*G25
26		40-44	0,00243	0,00114	=C15*C26	=D15*D26	7000	=G15*G26	=H15*G26
27		45-49	0,00413	0,00194	=C16*C27	=D16*D27	7000	=G16*G27	=H16*G27
28		Total 15-49			=SUM(E21:E27)	=SUM(F21:F27)	49000	=SUM(H21:H27)	=SUM(I21:I27)
29									
30		ESP: European Standard							
31									
32			Ln(SMR)	SD	SE	LN(SMR)low	LN(SMR)up		
33		Males	=ln(G5)	=1/SQRT(C17)	=1.96*D33	=C33-E33	=C33+E33		
34		Females	=ln(G6)	=1/SQRT(D17)	=1.96*D34	=C34-E34	=C34+E34		
35		Total	=ln(G7)	=1/SQRT(C17+D17)	=1.96*D35	=C35-E35	=C35+E35		
36									

Mortality rates by calendar year of follow up

	Males Person-years of observation	Males Number of deaths	Males Standardised mortality rate	Females Person-years of observation	Females Number of deaths	Females Standardised mortality rate	Total Person-years of observation	Total Number of deaths	Total Standardised mortality rate
Overall mortality rates									

The tables to be filled in ST18 are as follows:

Mortality rates by calendar year of follow up

	Males Person-years of observation	Males Number of deaths	Males Standardised mortality rate	Females Person-years of observation	Females Number of deaths	Females Standardised mortality rate	Total Person-years of observation	Total Number of deaths	Total Standardised mortality rate
Year 1									
Year 2									
Year 3									
Year 4									
Year 5									
Year 6									
Year 7									
Year 8									
Year 9									
Year 10									

Note: there might be a risk of bias, especially if the cohort is relatively small, the annual calculation of standardised risks may be problematic.

3.2.2.2.   Indirect Standardised mortality ratio (SMR)

Purpose

Indirect standardised rates can be calculated by applying age- and gender-specific mortality rates of the general population to the age and gender distribution of the cohort. This last procedure allows us to estimate the Standardised mortality ratio (SMR) which is also known as Excess mortality ratio (EMR).
The SMR summarises the impact of mortality in the cohort as opposed to mortality in the reference population, but retains the age and gender distribution of the cohort. It is useful in summarising the 'excess' force of mortality experienced in the cohort compared with that in the reference population.

Example

Table 7a: Calculation of 'expected' mortality by applying the reference rates of the European population ([23])

	European population		Observed person-time cohort		Expected mortality	
	Rate Females	Rate Males	Females	Males	Females	Males
15-19	0.00022	0.00047	132.0	200.4	0.09	0.03
20-24	0.00030	0.00090	915.4	2 358.5	2.12	0.27
25-29	0.00032	0.00095	1 180.9	4 773.8	4.55	0.38
30-34	0.00043	0.00111	577.1	2 968.0	3.31	0.25
35-39	0.00068	0.00152	310.9	1 069.6	1.63	0.21
40-44	0.00114	0.00243	210.9	659.6	1.60	0.24
45-49	0.00194	0.00413	121.6	342.9	1.42	0.24
Total 15-49			3 448.8	12 372.7	14.71	1.62

Table 7b: Calculation of the Standardised mortality ratio

	Obs. / Exp. SMR		95 %CI low	95 % up
Males	=153/14.71	10.4	8.9	12.2
Females	=16/1.62	9.9	6.1	16.1
Total		10.3	8.9	12.0

Note: see Euphix home page: http://www.euphix.org/object_document/o5338n27620.html

Table 7a and 7b gives an example of the calculation of the expected number of deaths among the Croatian cohort of drug users by using the reference mortality rates of the European population and the age and gender distribution of the drug users' population.
Table 6 shows the formulae of the MS Excel[®] file that can be used to calculate the standardised mortality ratio and its 95 % Confidence Intervals (age category 15–49). The expected number of deaths are given in cell number E-28 (males) and F-28 (females). The standardised mortality ratios of males and females are shown in cell number F-4 and F-5.

Problems

Used as a comparison with other cohorts, this is difficult to interpret. Identical mortality figures among different cohorts will lead to different SMRs if a different reference population is used. Moreover, if mortality ratios across different strata are not equal, the SMR does not fully adjust for differences in age and gender distribution.

([23]) Provided by Eurostat. Available from http://epp.eurostat.ec.europa.eu/portal/page/portal/statistics/search_database.

The table to be filled in ST18 is as follows:

**Expected and observed number of deaths and
SMR (Standardised mortality ratios)
(95 % Confidence Interval)**

	Observed No deaths	Reference rate	Expected No deaths	SMR	SMR Lower CI 95	SMR Upper CI 95
Overall figures Males						
Overall figures Females						
Overall figures Total						

### 3.2.3. Multivariate analysis, pooled data

The preferred way of adjusting for differences in age and gender distribution would be a direct comparison of the mortality figures in a pooled analysis. The analysis of the mortality rates could be conducted by using Poisson Regression and including as covariates both individual data and geographical indicators.
Cox regression models are applied to analyse mortality at different study sites according to age, sex, calendar year of enrolment, and other potential risk factors available.

3.3. Kaplan Meier

Another way of expressing mortality is the cumulative survival probability, generally expressed in the 5-years survival probability. The Kaplan Meier product limit method can be used to estimate cumulative risk of death at different follow-up time. The Kaplan Meier method takes into account the differences in follow up time of the population. The SPSS syntax includes a Kaplan Meier graph of the crude data. Figure 8 gives an example of the survival function using the Croatian cohort.

Figure 8: Example of SPSS survival function (Zagreb cohort until 5 years after enrolment).
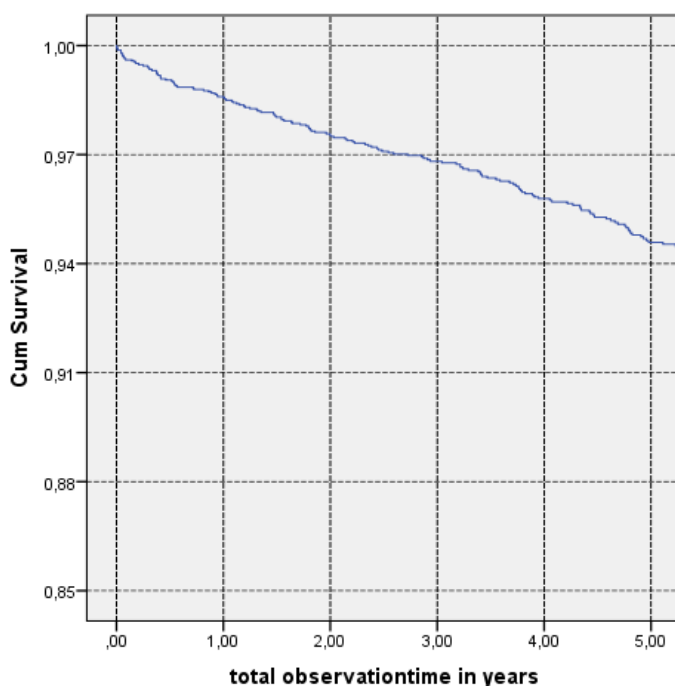
4.   Strengths and limitations

Longitudinal studies have their strength in estimating the actual mortality rate among drug users. Considering the drug induced deaths it may add to the answer of the question whether a high or low number of drug induced deaths (other indicator of mortality) is a result of a high or low prevalence of drug use or a high or low risk among drug users in a specific country. Cohort studies may unveil risk patterns that remain hidden within the national general mortality statistics. Mortality due to drug-related infectious diseases of a certain country, for example, may be low because of a high mortality rate of overdose mortality among infected drug users (phenomenon of competing risks) ([24]).

Moreover, cohort studies measure a broader range of health consequences than drug-induced death and broaden our view of the hazards that drug users encounter, especially concerning infectious diseases among injecting drug users. Therefore, the mortality figures among drug users are not only complementary to the drug-induced death component of the DRD indicator, but also to the indicators of prevalence and infectious diseases among drug users. In addition, cohort studies document other causes of death among drug users such as suicide, trauma and violence that account for a large part of the overall mortality and should be among research priorities (Darke, S. et al., 2007; EMCDDA, 2011).

Since record linkage studies require no individual follow-up procedures and face-to-face measurements to update the information at enrolment, they can be conducted with relatively limited resources.

It is however worthwhile highlighting some limitations of the study design.

Ideally, we would like to monitor:

(1) The mortality rates among a random sample of drug users within the Member States. However, by using the available sources of information, a selection of drug users will be enrolled. This hampers a straightforward comparison of the mortality figures between the different Member States. Two Member States with similar mortality figures among the drug users may give different mortality figures among treatment cohorts. Moreover, when the treatment is used to enrol drug users, the differences between two cohorts may reflect the differential effect of treatment rather than the differences in mortality risks between the Member States.

(2) The mortality rates among the current drug using population. In cohort studies follow up time is crucial. During follow up, the status of drug use may change. As the record linkage studies as proposed in this protocol uses the baseline information only, these changes will not be recorded. Therefore, during follow up, an increasing proportion of drug users will be ex-drug users.

The bias that is caused by these two effects is inevitable but its size will depend on the kind of drugs that is studied. The bias will probably be limited if a large proportion of the drug users is in contact with some kind of treatment and if the drug use is a chronic condition. Therefore, the cohort design seems to be more suitable to study mortality among opiate users than the users of for example, magic mushrooms. Moreover, the bias may be reduced by including a wide range of treatment facilities in the study (e.g. from national treatment registers) and to limit the observation period (see above, section 3.2).

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(24) 'Events that compete with the outcome of interest to remove people from the population at risk', Rothman and Greenland; modern epidemiology.

5.   References

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