Association between anxiolytic or hypnotic drugs and total mortality

RESEARCH PROTOCOL

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List of ACRONYMS

ALD	Affection de Longue Durée
ANSM	Agence nationale de sécurité du Médicament et des produits de santé
ATC	Anatomical Therapeutic Chemical Classification System
BMI	Body Mass Index
CMU	Couverture Maladie Universelle
CONSORT	Consolidated Standards of Reporting Trials
CRPD	Clinical Practice Research Datalink
DDD	Defined Daily Dose
DID	DDD per thousand inhabitants per day
EGB	Echantillon Généraliste de Bénéficiaires, General Sample of Beneficiaries
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
GP	General Practitioners
GPRD	General Practice Research Database
HRs	Hazard Ratios
ICD10	International Classification of Diseases, Tenth Revision
IMD	Index of Multiple Deprivation
INSERM	Institut national de la santé et de la recherche médicale
LSOA	patient Lower Super Output Area
MHRA	Medicines and Healthcare products Regulatory Agency
NIHR	NHS National Institute for Health Research
ONS	Office of National Statistics
PMSI	Programme de médicalisation des systèmes d'information
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology
UK	United Kingdom

I. SUMMARY

Principal investigator	Lapeyre-Mestre Maryse 37, allées Jules Guesde Toulouse 31000 France maryse.lapeyre-mestre@univ-tlse3.fr
Title	Association between anxiolytic or hypnotic drugs and total Mortality
Justification/context	Anxiolytic and hypnotic drugs are widely prescribed in Europe. Benzodiazepines and related drugs are extensively represented. In a study supported by the French Medicines Agency aiming to identify accessibility and level of consumption of psychoactive drugs in Europe, we observed that in every European country, the N05BA class (benzodiazepine anxiolytics) represented more than 90 % of the total amount of anxiolytics over the ten last years . The level of consumption, estimated though sales or reimbursement data and expressed in DDD per thousand inhabitants per day (DID), varies widely across countries, from 4.87 DID in Germany to 78.20 in Portugal in 2009. Concerning hypnotics, there are mainly represented by zopiclone and zolpidem which were the two most consumed hypnotics whatever the country during the 10 last year (32.14 DID for zopiclone in Norway in 2009 or 14.80 DID for zolpidem in France in 2009). Benzodiazepines and related drugs are indicated either for the short term treatment of moderate or severe anxiety or insomnia. These compounds can produce a range of well-known and non-fatal adverse effects, due to their pharmacologic properties. They could also be involved directly in fatal outcomes, such as in mixed drug overdose or suicide attempts. Due to their effect on cognitive and motor function, they are also associated with car crashes or falls. However, the ways by which these drugs can lead to an increased mortality are not entirely elucidated, and must take account of the complex confounding, involving in particular medical history, lifestyle and socioeconomic status. Recently, Kripke et al reported that hypnotic exposure was associated with an increased risk of death. The Hazard Ratios (HRs) were also elevated in analyses at active substance level for zolpidem and temazepam. However, residual confounding (lifestyle, socioeconomic status, alcohol,..) could not be entirely excluded in this study. Increased mortality associated with anxiolytics or hypnotics has already been reported in the literature, but the studies were essentially based on self-report for drug exposure, anxiolytics and/or hypnotics were grouped as a class (often explored by the question: “how many times in the last past... have you used sleeping pills?”) and the confounding was often not taken into account. Recently, some studies did not show an increased mortality risk, after controlling for confounding factors (smoking habits, analgesics use, lifestyle, heath status including depression). A systematic review by Charlson in 2009, investigating the mortality associated with benzodiazepines, has underlined the difficulty to conclude taking account of the non medical use or inappropriate prescribing of these drugs.

Objectives	to investigate mortality associated with anxiolytic or hypnotic drug exposure • among a representative sample of French insurees • among the population covered by the CPRD
study Design	retrospective exposed unexposed cohort study
Inclusion criteria	• Patients aged 18 and more • Patients with First Registration Date or Current Registration Date > 12 months • Acceptable Patient Flag (for CPRD)
Exclusion criteria	
Exposure of interest	• all benzodiazepine derivatives • benzodiazepine derivatives used as anxiolytics • benzodiazepines derivatives used as hypnotics • benzodiazepine related hypnotic/sedative drugs • clonazepam
Other Data collected	• Basic patients demographics: Age/birthdate, Gender, marital status • Patients lifestyles details: smoking, drinking, height, weight, BMI (for CPRD) • Diagnosis, symptoms and medical history information • FDep99 index (for EGB) or Index of Multiple deprivation quintile (for CPRD) • Other prescriptions (classe of particular interest: antidepressants, antiepileptics, antipsychotics, other anxiolytics and/or hypnotics
Event of interest	• death (all-cause) (and cause-specific for CPRD)
sample Size	
Data source	• EGB (Echantillon Généraliste de Bénéficiaires, General Sample of Beneficiaries) • CPRD (Clinical Practice Research Datalink)
Duration of the study	Duration of the inclusion period Duration of each patient's participation Total duration of the study
Statistical analysis	Brief summary of the statistical methods
Expected results	The research proposed is expected to provide an up to date and consolidated estimation of the risk which can be attributed to benzodiazepines and benzodiazepine-like drugs in the total and/or cause specific mortality, taking account of the complex confounding in this area. It will then provide evidence for decision making, in particular concerning risk management and the need for regulatory change. The overall impact of this issue should be highlighted given the extensive use of benzodiazepines in European countries.

II. ABSTRACT

Benzodiazepines and related drugs are indicated either for the short-term treatment of moderate or severe anxiety or insomnia. These compounds can produce a range of well-known and non-fatal adverse effects, due to their pharmacologic properties. They could also be involved directly in fatal outcomes, such as in mixed drug overdose or suicide attempts. Due to their effect on cognitive and motor function, they are also associated with car crashes or falls. However, the ways by which these drugs can lead to an increased mortality are not entirely elucidated, and must take account of the complex confounding, involving in particular medical history, lifestyle and socioeconomic status.

This study intends to investigate the impact of anxiolytic or hypnotic drug exposure on all cause and specific mortality among cohorts obtained in a representative permanent sample of French beneficiaries of the national health insurance scheme (EGB) and through a large healthcare database (CPRD) in the United Kingdom.

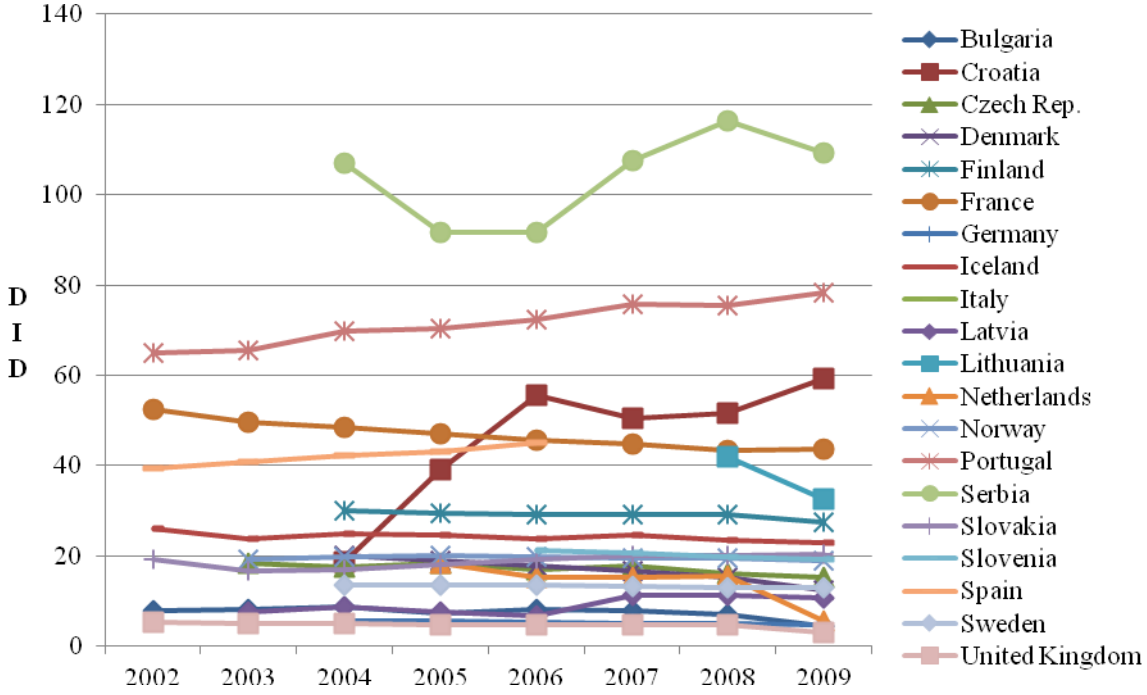
Two retrospective exposed unexposed cohort studies will be implemented among patient's records, one in the EGB, one in the CPRD. Subject 18 years or older, registered in the database for at least one year, and those in the CPRD meeting sufficient quality standard, are eligible.

Exposed patients will be those beneficing at least one prescription for any medication containing at least one benzodiazepine derivative or benzodiazepine related substance. Exposed patients will be matched to one to 10 unexposed controls according to birth year, gender, and Postal code in the EGB, and Practice in the CPRD. In the EGB, patients will be followed from 2006 to the latest available date, whereas in the CPRD, patients will be followed since 1999 to the latest available date. In the EGB, all cause and cause specific mortality will be investigated, together with patients' sociodemographics, medicines use, and co-morbidities (including medical history). In the CPRD, all cause and cause specific mortality will be investigated, together with patients' sociodemographics, life-style (alcohol consumption, smoking), medicines use, and co-morbidities (including medical history). Time to death will be described using the Kaplan-Meier survival function, and analysed using an extended Cox regression model taking account of time-dependent covariates.

III. BACKGOUND AND RATIONALE

Anxiolytic and hypnotic drugs are widely prescribed in Europe. Benzodiazepines and related drugs (named benzodiazepines) are extensively represented. In the study supported by the French Medicines Agency aiming to identify accessibility and level of consumption of psychoactive drugs in Europe, we observed that in every European country, the N05BA class (benzodiazepine anxiolytics) represented more than 90 % of the total amount of anxiolytics over the ten last years[1]. The level of consumption, estimated though sales or reimbursement data and expressed in DDD per thousand inhabitants per day (DID), varies widely across countries, from 4.87 DID in Germany to 78.20 in Portugal in 2009. Concerning hypnotics, there are mainly represented by zopiclone and zolpidem which were the two most consumed hypnotics whatever the country during the 10 last year (32.14 DID for zopiclone in Norway in 2009 or 14.80 DID for zolpidem in France in 2009).

Figure 1. Trends in benzodiazepine derivatives use (N05BA) in selected continental European and Nordic countries, in Defined Daily Doses per thousand inhabitants per day (DID), 2002-2009 (source: M. Lapeyre-Mestre; A. Palmaro. Comparaison des données d'utilisation des medicaments psychoactifs ayant un potentiel de dépendance dans les differents pays d'Europe. CEIP de Toulouse (Septembre 2011))



Benzodiazepines and related drugs are indicated either for the short term treatment of moderate or severe anxiety or insomnia. These compounds can produce a range of well-known and non-fatal adverse effects, due to their pharmacologic properties. They could also be involved directly in fatal outcomes, such as in mixed drug overdose or suicide attempts. Due to their effect on cognitive and motor function, they are also associated with car crashes or falls. However, the ways by which these drugs can lead to an increased mortality are not entirely elucidated, and must take account of the complex confounding, involving in particular medical history, lifestyle and socioeconomic status. Recently, Kripke et al[2] reported that hypnotic exposure was associated with an increased risk of death. The Hazard Ratios (HRs) were also elevated in analyses at active substance level for zolpidem and temazepam. However, residual confounding (lifestyle, socioeconomic status, alcohol,…) could not be entirely excluded in this study. Increased mortality associated with anxiolytics or hypnotics has already been reported in the literature, but the studies were

[1] M. Lapeyre-Mestre; A. Palmaro. Comparaison des données d'utilisation des medicaments psychoactifs ayant un potentiel de dépendance dans les differents pays d'Europe. CEIP de Toulouse (Septembre 2011).
[2] Kripke DF, Langer RD, Kline LE. Hypnotics' association with mortality or cancer: a matched cohort study. BMJ Open. 2012;2(1):e000850.

essentially based on self-report for drug exposure, anxiolytics and/or hypnotics were grouped as a class (often explored by the question: "*how many times in the last past... have you used sleeping pills?*") and the confounding was often not taken into account.

Recently, some studies[3,4] did not show an increased mortality risk, after controlling for confounding factors (smoking habits, analgesics use, lifestyle, heath status including depression). A systematic review by Charlson in 2009, investigating the mortality associated with benzodiazepines, has underlined the difficulty to conclude taking account of the non medical use or inappropriate prescribing of these drugs[5].

As underlined by previous literature reviews and by our recent extensive systematic review[6], data suggesting elevated overall mortality among benzodiazepine users remain limited. Short term clinical trials did not find any increase of mortality risk. A majority of observational studies found a slight increase, but the question of residual confounding should not be excluded. Except for suicide related death and for mortality in patients with respiratory disease, the level of risk is very low, except for one study, which raises many methodological questions. There is insufficient data to conduct a comparative risk assessment between different benzodiazepines, and there are too few studies that report on specific causes of death. Despite this lack of evidence, some points should be highlighted from the existing literature for future research: cohort studies on large enough population allowing analysis by specific drugs, by specific cause of mortality, using drug exposure as a time varying variable in the statistical analysis, with a sub-group of comparison of users of non-benzodiazepine anxiolytic-hypnotic drugs, and finally a minimal set of potentially confounding variables including social context, comorbidities, and co-exposure to other psychoactive drugs.

A. Hypotheses and expected results

1. Hypothesis Testing

The primary hypothesis is that the use of hypnotics or anxiolytics could be associated with increased all-cause mortality among the exposed population.
The possibility for an increased all-cause mortality associated with dose dependent or duration dependent exposure to hypnotic or anxiolytic benzodiazepines will be tested.

2. Hypothesis Generating

In a first approach, all benzodiazepines could be considered as a class. However, we could also hypothesize that the risk could differ according to individual drugs, and that increased observed mortality could be associated with the consumption of selected individual anxiolytics or hypnotics. However, analyses that will be performed at active substance level will be considered as secondary and hypothesis-generating (the literature review does not allow to identify any specific substance risk).

B. Justification of the methodological approach adopted

This study will be conducted in two European countries and will allow bringing evidence on the mortality associated with anxiolytic or hypnotics drugs (France because the high level of anxiolytic and hypnotic drug use in the general population, and UK because of the availability of a large general population based database comprising drug prescription, mortality and lifestyle characteristics).
When designing a retrospective study on electronic databases, the choice of the data source is determinant, and should ensure that all the information needed could be retrieved with high level of completeness and

[3] Hausken AM, Skurtveit S, Tverdal A. Use of anxiolytic or hypnotic drugs and total mortality in a general middle-aged population. Pharmacoepidemiol Drug Saf. 2007 Aug;16(8):913-8.
[4] Belleville G. Mortality hazard associated with anxiolytic and hypnotic drug use in the National Population Health Survey. Can J Psychiatry. 2010 Sep;55(9):558-67.
[5] Charlson F, Degenhardt L, McLaren J, Hall W, Lynskey M. A systematic review of research examining benzodiazepine-related mortality. Pharmacoepidemiol Drug Saf. 2009 Feb;18(2):93-103.
[6] Gardette V, Micallef-Roll J, Gane A, Rueter M, Lapeyre-Mestre M. Association between benzodiazepines and related drugs and mortality: a systematic review. To be submitted.

quality through the source chosen. With reference to the tender issue, drug exposure and mortality outcomes were required, together with several covariates related to patient lifestyle, medical history or socio economics characteristics. However, little data information system collect routinely all these aspects and can provide all this information for a same patient. Prescription databases, sometimes with national coverage, provide useful and complete information on drug exposure, as illustrated by the Nordic countries experience. These databases could comprise medical information for selected beneficiaries (chronic disease, etc.), and can be linked to death registries. However, this kind of record does not routinely collect socio economic or lifestyle characteristics. At the opposite, some existing cohort studies could provide exhaustive information about lifestyle, income or related information for the participants, sometimes with large population coverage. However, if the death could be recorded, this type of data source often fails to record precisely information on drug exposure.

In France, the General Sample of Beneficiaries was retained, as the level of exposure to anxiolytics and hypnotics is particularly high among the population covered.

The limitation of traditional prescription databases led us to choose also the CPRD, which could advantageously provide information on lifestyle, including smoking, drinking or Body Mass Index (BMI) of the patient, together with an Index of Multiple Deprivation (IMD) taking account of economic, social and housing issues.

C. Expected results

The research proposed is expected to provide an up to date and consolidated estimation of the risk which can be attributed to hypnotic and anxiolytic medications in the total and/or cause specific mortality, taking account of the complex confounding in this area. It will then provide evidence for decision making, in particular concerning risk management and the need for regulatory change. The overall impact of this issue should be highlighted given the extensive use of benzodiazepines in European countries.

IV. OBJECTIVES

The aim of this project will be to investigate mortality associated with anxiolytic or hypnotic drug exposure in France and in the UK.

We will address this aim doing two cohort studies, using drug exposure as a time varying variable in the statistical analysis, with a sub-group of comparison of users of non-benzodiazepine anxiolytic-hypnotic drugs, and finally a minimal set of potentially confounding variables including social context, comorbidities, and co-exposure to other psychoactive drugs.

For France, it will be addressed among a representative sample of the French beneficiaries of the national health insurance scheme: the *Echantillon Généraliste de Bénéficiaires* EGB (General Sample of Beneficiaries) database.

For the UK, it will be addressed among the population covered by the Clinical Practice Research Datalink CPRD.

V. POPULATION AND METHODS

A. Study design

A retrospective exposed unexposed cohort study will be designed:

- using data from a random sample of French beneficiaries (EGB) from January 1st, 2006 to June 30, 2012
- using data from cross-linked CPRD database in UK from 1999 to the latest available date

All beneficiaries receiving at least one prescription for any medication containing at least one active substance referred
Table 1 will be included and followed from the date of first prescription until whichever the end of the study period or the date of death. Beneficiaries will have to be incident: no previous reimbursement for those substances for at least one year.
In parallel, all medical consults (specifically with psychiatrists), age, gender, marital status, socio economic status, lifestyle (for CPRD), medical history comorbidities (according to ICD10 codes or via the medication consumed as a proxy for several comorbidities), and other prescriptions will be collected as potential confounding factors.

More precisely, for the CPRD, the CPRD GP Database linked to Office of National Statistics (ONS) mortality data and Index of Multiple Deprivation (IMD) data at the patient Lower Super Output Area (LSOA) level will be used for the purpose of the study.

B. Source and study population

1. Description of the data source: EGB and CPRD

The *Echantillon Généraliste de Bénéficiaires* EGB (General Sample of Beneficiaries), a permanent representative sample of French beneficiaries affiliated with the French health insurance system, covering approximately 660,000 beneficiaries[7], will be used[8] [9]. EGB is obtained by 1/97th random sampling with control for distribution of age, gender and area of residence.

This database has been linked since 2008 with another large-scale information system containing data from hospitalization stays (PMSI). Retrospective collection of data from PMSI has permitted link with these data since 2005.
Use of databases of the French health insurance system is valid and useful[10,11]. This particularly database has been yet used in pharmacoepidemiological studies[12,13,14].

The EGB includes records the following data:

[7] Tuppin P, de Roquefeuil L, Weill A, Ricordeau P, Merlière Y. French national health insurance information system and the permanent beneficiaries sample. Rev Epidemiol Sante Publique. 2010 août;58(4):286-90.
[8] Martin-Latry K, Begaud B. Pharmacoepidemiological research using French reimbursement databases: yes we can! Pharmacoepidemiol Drug Saf. 2010 Mar;19(3):256-65.
[9] Tuppin P, de Roquefeuil L, Weill A, Ricordeau P, Merliere Y. French national health insurance information system and the permanent beneficiaries sample. Rev Epidemiol Sante Publique. 2010 Aug;58(4):286-90.
[10] Martin-Latry K, Bégaud B. Pharmacoepidemiological research using French reimbursement databases: yes we can! Pharmacoepidemiol Drug Saf. 2010 mars;19(3):256-65.
[11] Latry P, Molimard M, Bégaud B, Martin-Latry K. How reimbursement databases can be used to support drug utilisation studies: example using the main French national health insurance system database. Eur. J. Clin. Pharmacol. 2010 juill;66(7):743-8.
[12] Bongue B, Laroche ML, Gutton S, Colvez A, Guéguen R, Moulin JJ, et al. Potentially inappropriate drug prescription in the elderly in France: a population-based study from the French National Insurance Healthcare system. Eur. J. Clin. Pharmacol. 2011 déc;67(12):1291-9.
[13] Pariente A, Pinet M, Moride Y, Merlière Y, Moore N, Fourrier-Réglat A. Factors associated with persistence of cholinesterase inhibitor treatments in the elderly. Pharmacoepidemiol Drug Saf. 2010 juill;19(7):680-6.
[14] Blin P, Lassalle R, Dureau-Pournin C, Ambrosino B, Bernard MA, Abouelfath A, et al. Insulin glargine and risk of cancer: a cohort study in the French National Healthcare Insurance Database. Diabetologia. 2012 mars;55(3):644-53.

- Demographic data (gender, age, area of residence)
- All reimbursed medical expenses (visits, medications, etc.)
- Dates of prescription
- Medication dispensed, route and dosage
- Date of dispensing
- Quantity dispensed
- 31 major chronic diseases fully covered: "Affection de Longue Durée" (ALD), coded according to the International Classification of Diseases (ICD)-10
- Date of death (provided indirectly by the National Institute of Statistics and Economic Research (INSEE), the cause is not recorded)
- Affiliation to the CMU (*couverture maladie universelle*), the universal health care coverage scheme, attributed to the unemployed and low income insurees, and which can be used as a proxy of the income level
- Data of hospitalization (dates, durations, technical acts and, particularly, diagnoses according to ICD-10)
- Data on prescriber (specialty)

The Clinical Practice Research Datalink (CPRD), previously GPRD[15,16,17], is a research database funded by the NHS National Institute for Health Research (NIHR) and the Medicines and Healthcare products Regulatory Agency (MHRA). This register contains data from over 10 million patients linked to an overall total of 500 general practices in UK (corresponding to ≈1500 General Practitioners). It covers approximately 8% of the UK population through representative sample of the England and Wales population.

The information is recorded by General Practitioners (GP), as part of their usual medical practice and contains anonymised, longitudinal medical records of patients registered with participating primary care practices in UK. This comprises records of clinical events (medical diagnoses), referrals to specialists and secondary care settings, prescriptions issued in primary care, records of immunisations and vaccinations, diagnostic testing, lifestyle information (smoking and alcohol status), and all other types of care administered as part of routine GP practice.

This database has been widely used for research purposes, particularly in the area of Drug utilisation, Pharmacovigilance and Pharmacoepidemiology[18,19,20] .

More precisely, the CPRD GP Database linked to Office of National Statistics (ONS) mortality data and Index of Multiple Deprivation (IMD) data at the patient Lower Super Output Area (LSOA) level will be used for the purpose of the study.

2. Description of source population

EGB database covers a permanent representative sample of French beneficiaries of the national health insurance scheme. The national health insurance scheme covered more than 90% of French population. EGB is a 1/97th representative sample covering approximately 660,000 beneficiaries. These beneficiaries are salaried workers, agricultural workers and farmers, self-employed and retirees and patients with

[15] Walley T, Mantgani A. The UK General Practice Research Database. Lancet. 1997 Oct 11;350(9084):1097-9.
[16] Garcia Rodriguez LA, Perez Gutthann S. Use of the UK General Practice Research Database for pharmacoepidemiology. Br J Clin Pharmacol. 1998 May;45(5):419-25.
[17] Wood L, Martinez C. The general practice research database: role in pharmacovigilance. Drug Saf. 2004;27(12):871-81
[18] Charlton RA, Cunnington MC, de Vries CS, Weil JG. Data resources for investigating drug exposure during pregnancy and associated outcomes: the General Practice Research Database (GPRD) as an alternative to pregnancy registries. Drug Saf. 2008;31(1):39-51.
[19] Delaney JA, Moodie EE, Suissa S. Validating the effects of drug treatment on blood pressure in the General Practice Research Database. Pharmacoepidemiol Drug Saf. 2008 Jun;17(6):535-45.
[20] Devine S, West SL, Andrews E, Tennis P, Eaton S, Thorp J, et al. Validation of neural tube defects in the full featured--general practice research database. Pharmacoepidemiol Drug Saf. 2008 May;17(5):434-44.

universal coverage (attributed to the unemployed and low income insurees). Some population is not represented in EGB: public sector employees, students, migrants[21].

The CPRD covers about 5% of the UK population. The population covered is considered representative of the general population of UK with respect to age, sex, and geographic distribution.

3. Definition of target population

The French and the UK adult population, including both genders, will be targeted. In order to minimize selection bias and improves the generalizability of further results, no exclusion criteria based on clinical on other proper characteristics of the patients will be applied.

4. Study population

a) Inclusion criteria

- Patients aged 18 and more
- Patients with First Registration Date or Current Registration Date > 12 months
- Acceptable Patient Flag (patients records meeting sufficient quality standard for research) (for CPRD)
- Patients whose practice consented for linkage scheme (ONS mortality data available) (for CPRD)

b) Exclusion criteria

No exclusion criteria will be applied

5. Methods of selection

For EGB, we will insure extraction of data. For CPRD, extraction of data will be insured by the CPRD.

Exposed patients will be matched to 1 to 10 unexposed controls according to index date (date of first benzodiazepine prescribing), birth year (+/- 5years), gender, and area of residence (for EGB) or practice (for CPRD).
Control patients must also be registered in the database for at least 12 months, and they should not have been prescribed any of the studied drugs for the whole study period. Data of control patients must also meet sufficient quality standard (for CPRD).
Index date for the matched controls will be the date of the first reimbursement claim in the database during the study period (for EGB) or of the first prescribing record of the corresponding patient exposed in the database (for CPRD).

a) Exposed group

Exposed patients will be those:

- with at least one recorded prescription for any of benzodiazepines or related drugs during the follow up (referred in appendix 1)
- with no recorded prescription for any of these drugs during the previous 12 months («incident users »)

This 12-month period used to define incident users does not constitute a risk period for the outcome.

[21] Tuppin P, de Roquefeuil L, Weill A, Ricordeau P, Merlière Y. French national health insurance information system and the permanent beneficiaries sample. Rev Epidemiol Sante Publique. 2010 août;58(4):286-90.

The choice of a sufficiently long period (12 months) will enable to deal with depletion of susceptible bias, in avoiding recruitment of patients with previous exposure without outcome occurrence and who would be less likely to present the outcome during the study period.

Similarly, this 12 months period will permit to deal with a potential for selection bias, in avoiding selection of patients with previous repeated exposure, as past history of exposure to benzodiazepines could for instance be associated with a bad prognosis.

b) Control group 1: exposed to antidepressants or non-benzodiazepine anxiolytics or hypnotics

The first control group will comprise eligible patients:

- with at least one prescribing of antidepressants or other non-benzodiazepine anxiolytics or hypnotics after index date of the case
- with no recorded prescription for any antidepressants nor other non-benzodiazepine anxiolytics or hypnotics during the previous 12 months (« new or incident users »)

- with no recorded prescription of any benzodiazepine or related drugs during all the follow up (after index date of the corresponding exposed patient)

c) Control group 2: never exposed

A second control group will comprise eligible patients:

- with no recorded prescription for any of the cited drugs (no benzodiazepine or related nor antidepressants nor non benzodiazepine anxiolytics or hypnotics) at any time of the follow up (after index date of the case)
- with no recorded prescription for any of the cited drugs (no benzodiazepine or related nor antidepressants nor non-benzodiazepine anxiolytics or hypnotics) at any time of the follow up (after index date of the corresponding exposed patient)

C. Exposure definition and measurement

1. Drug exposure data available through the data source

Our literature review highlights the lack of accurate data concerning the exact time of exposure and the date of death. Moreover, only few studies have been taken in account the potential dose-effect relationship or the specific pharmacokinetic properties of drugs. In the data source, the following variables related to drug exposure are available, for all prescriptions during the specified period, mentioning:

- Product identification (multilexcode)
- Date of prescription
- Product dose
- Total quantity
- Number of individual product packs prescribed
- Pack size or type of the prescribed product
- Number of treatment days prescribed
- Repeat prescription details (whether the treatment is part of a repeat schedule, etc.)

Index date will be the date of the first prescription record in the database during the study period. Exposed patients are those with at least one prescription of medication containing the selected active substances

during the study period.
For drug exposure the dosage and the duration of the treatment sequences (periods of drug exposure interruption will be taken in account, see paragraph 5) will be collected.

The following variables related to drug exposure are available through the EGB dataset, for all prescriptions during the specified period, mentioning:

- Date of prescription
- Date of dispensing
- Product identification (CIP code and ATC code in the EGB; Multilex code in the CPRD)
- Number of individual product packs dispended

2. Coding system for medicines in the EGB

Identification of the specialities of interest will be provided by ATC codes.

The corresponding CIP (Presentation Identifying Code) code is a fixed 8- (till 2009) or 13-digits (since 2009) code assigned to all approved drugs will be available.

A CIP code identifies unambiguously
- The active substance
- Product dose
- Route
- Pack size

3. Coding system for medicines in the CPRD

Identification of the specialities of interest will be provided by Multilex codes.
Exposed patients will be eligible patients with at least one prescription during the study period for selected drugs corresponding to the Multilex codes listed APPENDIX 1: Exposure of interest

4. Products of interest

We will include all drugs with a valid marketing authorisation in UK and in France as anxiolytic and/or hypnotic drug:

- all benzodiazepine derivatives
- benzodiazepine derivatives used as anxiolytics
- benzodiazepines derivatives used as hypnotics
- benzodiazepine related hypnotic/sedative drugs

Exposed patients will be eligible patients with at least one prescription during the study period for drugs belonging to corresponding ATC codes (N05BA; N05CD; N05CF) and for selected drugs corresponding to the Multilex codes listed APPENDIX 1: Exposure of interest.

Two other benzodiazepines clonazepam and tetrazepam are available in UK (clonazepam) and in France (clonazepam and tetrazepam) are outside these codes and are classified as an anti-epileptic (clonazepam ATC Code N03AE01) or a muscle relaxant (tetrazepam ATC Code M03 BX07).

Tetrazepam will not be included in the list of benzodiazepines and benzodiazepine related hypnotic drugs since it is widely used for short term period and as muscle relaxant. However, clonazepam is highly off-label prescribed for psychiatric disorders in France and in the UK[22]. Thus, clonazepam will not be

[22] Agence Nationale de Sécurité du Médicament et des Produits de Santé. Rapport d'expertise. Etat des lieux de la consommation des benzodiazépines en France. Janvier 2012.
http://ansm.sante.fr/var/ansm_site/storage/original/application/3f1dc4756b5bc091879c9c254d95e05c.pdf

considered in the main analysis, but we let us the possibility to make a sensitivity analysis including or not this product in the list of the benzodiazepines and derivatives used as anxiolytic or hypnotic drugs (APPENDIX 2).

5. Doses and duration of treatment

a) In the EGB

The real duration of the treatment, as mentioned is the treatment is unknown. Some hypothesises need to be formulated to obtain the better estimate.
Procedure for the treatment of duration of exposure or dose will be implemented at active substance level. Thus, dose and period for specialities containing the same active substance or for the same fixed combination will be considered as additive.

The maximal duration for a single prescription in France is 30 days. Even in the case of renewable prescription, the quantity dispensed is for one month. To continue their treatment, patient have to return to a pharmacy to be dispended the quantity for the next 30 days. The date of dispensing, identification of the speciality and quantity dispended is then automatically recorded and transmitted to health insurance information system to enable reimbursement. If the next record for the same substance exceeds fixed number of days, the treatment is considered interrupted. Sensitivity analyses will be further performed with fixed duration of 35, 60, 90 and 120 days. In the same way as unrestricted drugs, specialities undergoing limitations of prescription duration will be considered as stopped if the date of the next dispensing records for a same substance exceeds the recommended duration plus a fixed margin.
The dose will be derived from the CIP codes (PHA_PRS_IDE), indicating package dose and size, and from the variable indicating the number of individual product packs dispended (PHA_ACT_QSN).

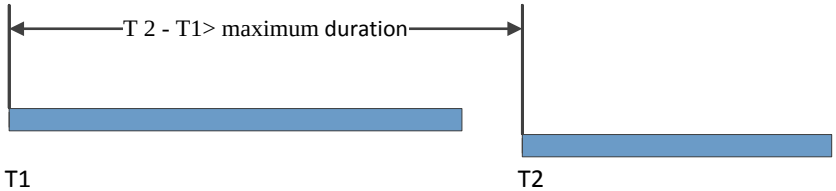
Dose will be calculated as describe above.

$$Dose\ received(mg) = strength\ (mg) * number\ of\ units * number\ of\ product\ packs\ dispended$$

$$Dose\ received(DDD) = \frac{strength\ (mg) * number\ of\ units * number\ product\ packs\ dispended}{DDD\ for\ the\ active\ subtance\ (mg)}$$

A patient will be considered as exposed for all the estimated duration of the prescription.

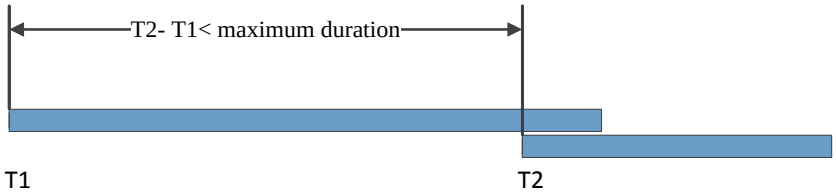
(1) No overlapping: delay between two consecutive dispensing records exceeds a fixed maximum duration (sensitivity analyses for 35, 60, 90 and 120 days)



The beneficiary is considered exposed between T1 and T1+ fixed maximum duration, and not exposed between T1+ fixed maximum duration and T2.

(2) Overlapping: delay between two consecutive dispensing is inferior to a fixed maximum duration (sensitivity analyses for 35, 60, 90 and 120 days)

The beneficiary is considered exposed between T1 and T2. The duration is computed as the delay between T1 and T2.



The dose related to prescription issued at T1 will be added to dose received after T2 even if periods are overlapping. Overlaps will be studied using doctor-shopping indicator[23].The doctor-shopping indicator, proposed by Pradel et al., will be used to take into account simultaneous use of several physicians by a patient in order to obtain prescriptions. In this approach, 3 doses are calculated: dose delivered, dose prescribed and doctor-shopping dose. The dose delivered corresponds to the daily dose delivered to the patient. The dose prescribed corresponds to the daily dose that would have been delivered to the patient if he/she had only one physician. The doctor-shopping dose corresponds to the daily dose obtained by the prescriptions of several physicians in a same period of time. The doctor-shopping indicator is obtained by dividing the doctor-shopping dose by the dose delivered. If the doctor-shopping indicator is greater than zero, we considered that the patient exhibited doctor-shopping behavior (binary variable).

(3) Specialty with prescription limitation

– Overlapping prescription or delay < recommended duration + tolerance margin:
Duration of exposure is the difference between T2 and T1 + recommended duration+ tolerance margin.

– Delay between consecutive dispensing > recommended duration + tolerance margin: Duration of exposure T1 + recommended duration+ tolerance margin.

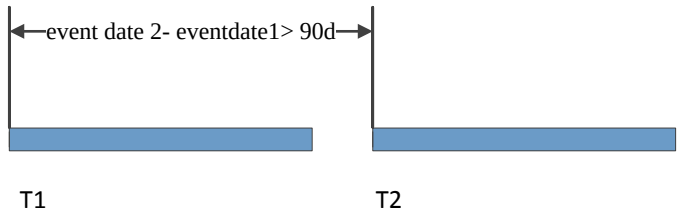
b) In the CPRD

The maximal duration for a single prescription in UK is 90 days.
So, for a fixed active substance, a length > 90 days between two prescription events is an indicator of treatment discontinuation.

Procedure for the treatment of duration of exposure or dose will be implemented at active substance level. Thus, dose and period for specialities containing the same active substance or for the same fixed combination will be considered as additive.

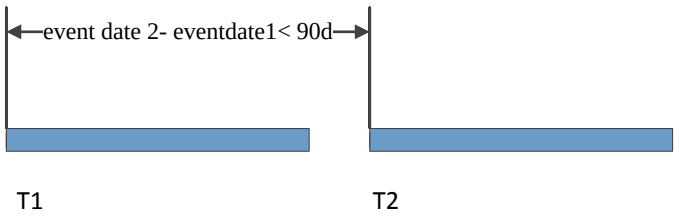
Accumulated dose will be computed as the sum of exposure durations for the same active substance or for the same fixed combination. Accumulated doses will also be converted in number of DDD.

(1) Treatment discontinuation:



[23] Pradel V, Delga C, Rouby F, Micallef J, Lapeyre-Mestre M. Assessment of abuse potential of benzodiazepines from a prescription database using 'doctor shopping' as an indicator. Cns Drugs.24(7):611-20.

(2) Treatment not discontinued between T1 and T2: prescription duration?



The duration of the exposure for a single prescription could be handled in different ways

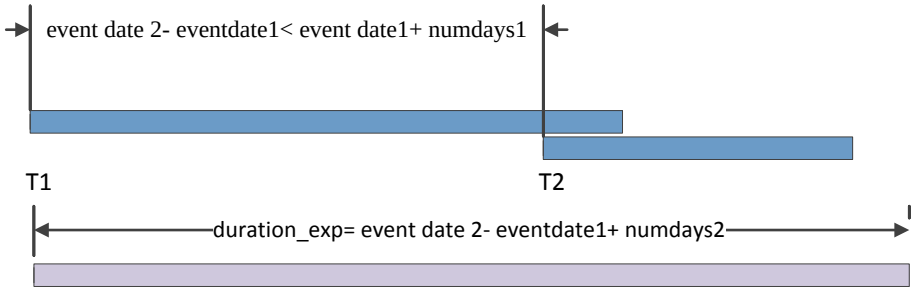
Prescription duration can be obtained is either

- A number of days of prescription as indicated by the GP (*numdays* variable)
- The total quantity prescribed (*qty*) divided by the number of treatment days prescribed (*ndd*)

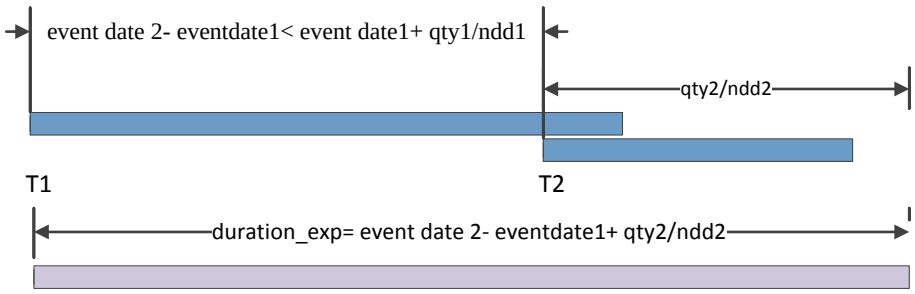
(a) Case 1: delay between prescriptions is inferior to estimated duration derived from quantity and dose

(i) Variable "Numdays" is available

- No treatment discontinuation between Event date 1 and event date 2
- Duration of exposure will be computed as the difference between even date 2 and event date 1 plus numdays for event date2:



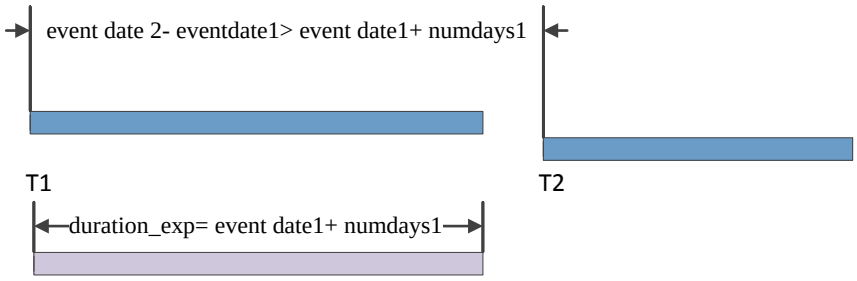
(ii) Variable "numdays" is missing



(b) Case 2: delay between prescriptions is superior to estimated duration derived from quantity and dose

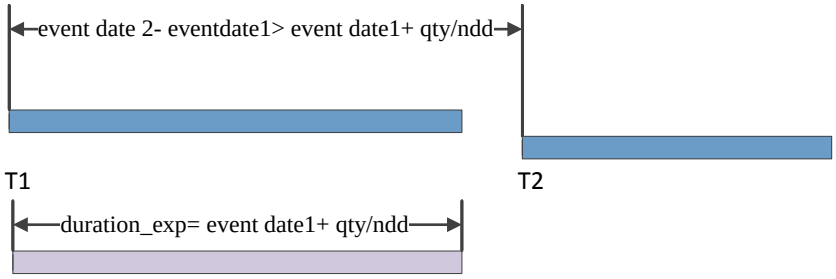
(i) Variable "numdays" is available

- Treatment has been discontinued between event date 1 and event date 2
- Duration of exposure will be obtained by adding the number of days of prescription as indicated by the GP to the event date 1



(ii) Variable "numdays" is missing

- Duration of exposure will be obtained by adding the estimated prescription duration derived from quantity and dose event date 1 in days to the event date 1



D. Definition of the risk period following exposure

As stated in the previous paragraphs, duration of exposure will be directly derived from prescription date and quantities and will include a tolerance margin reflecting the possibility for a patient to refill its prescribing some days after its theoretical ends.

The definition of a risk period for the outcome will include the duration of exposure (implicitly referring to drug intake) , but also a period following the last drug intake in which the product is still considered active and in which the patient will be considered at risk for the outcome.
This period depends on the pharmacological properties of the active substance, and will be defined for each of the studied substances.

E. EVENT OF INTEREST

1. Main outcome

All cause death will be the main outcome

a) Ascertainment of the outcome

The EGB database includes the date of death, which is provided by the National Institute of Statistics and Economic Research (INSEE), but the cause is not recorded[24]. However, information concerning exclusively death occurring in hospital can be accessed through the linkage of EGB with the PMSI, a managerial tool based on the systematic record of standardized medical and administrative information for each admission occurring in all hospitals in France (public and private).

Additional information can be accessed through this linkage, namely medical information (main cause of admission (principal diagnosis), related medical conditions (associated diagnoses), duration of the stay, and modes of admission and discharge. Death during hospitalization can be ascertained with the mode of discharge mode of discharge "9" for death. The cause of death is not routinely recorded as such.
Then, the part of deaths occurring in hospital with a recoded cause could not be estimated.

CPRD is linked Office for National Statistics (ONS) complete central Mortality data among all the patients present in the CPRD, approximately 50% has records linked to ONS mortality data, allowing to attain the sample size required. Through linked data, we could have access to the date of death together with the causes of death.

Patient deaths can be ascertained using several ways: transferred out patient with a "Transfer out reason" specified as "death", a "Clinical" or "Referral" event with a Read/OXMIS code indicating a death category including "Statement of Death" or record in the death administration structured data.
The Date of death of patient (*deathdate* variable in the Patient file) is based on high sensitivity algorithm elaborated by the CPRD CPRD

The CPRD comprises codes related to "statement of death" and codes indicating deaths. More precisely, the following fields are available:

- GPRD medical code
- Read/OXMIS code
- Read/OXMIS medical term
- Statement of Death/Death Category , including the death category of interest

"Statement of Death" codes of interest are Read or OXMIS codes detailed in APPENDIX 3 : Clinical event of interest.

2. Secondary outcomes

Cause specific death will also be investigated. Actually, most of the available studies did not distinguish the different causes of death. Only few studies have explored specific risk of suicide-death in vulnerable population (psychiatric or elderly), of cardiovascular death (post-myocardial infarction population), of pulmonary death (asthmatic population or elderly) or of drug-dependence death (opiate maintained population). The investigation of specific causes of death (cardiac, pulmonary, cancer...) will be done according to the results for the primary outcome (all cause death) and the repartition of the recorded causes of death in the cohort.

[24] P. Blin, R. Lassalle, C. Dureau-Pournin, B. Ambrosino and M. A. Bernard, et al.Insulin glargine and risk of cancer: a cohort study in the French National Healthcare Insurance Database. Diabetologia, 2012, Volume 55, Number 3, Pages 644-653

VI. DATA COLLECTION

A. Covariates

In order to consider the potential for confounding in the final analysis, the covariates referring to patients' sociodemographics, life-style (alcohol consumption, smoking) and co-morbidities (including medical history) below will also be collected. Availability of covariates could differ according to the data sources. All the covariates of interest will be collected without particular limitation in both data sources, and the heterogeneity in the set of covariates will be dealt as part of the statistical analysis.

1. Basic patients demographics: birthyear, gender, marital status

In EGB, variables are (marital status non available):

Identification code for the patient	BEN_NIR_IDT
Year of birth	BEN_ NAI_ANN
Gender	BEN_SEX_CODE

Birthyear, gender, marital status are available in the CPRD.

2. Patients lifestyles details: smoking, drinking, height, weight, body mass index (BMI)

Not available in the EGB. Available in the CPRD.

3. Diagnosis, symptoms and medical history information

a) Diagnosis, symptoms and medical history information of interest

In France, psychiatric disorders are part of the 31 major chronic diseases fully covered and recorded in the **EGB** database.

Table 1 . List of long-term disease (ALD) conditions

Disease
1 Disabling stroke
2 Aplastic anaemia and other chronic cytopenias
3 Chronic arteriopathies with ischaemic manifestations
4 Complex schistosomiasis
5 Severe heart failure, arrythmias, valvular cardiomyopathy, congenital cardiomyopathy
6 Active chronic diseases of the liver and cirrhoses
7 Primary severe immunodeficiency requiring long-term treatment, infection by HIV virus
8 Diabetes type 1, diabetes type 2
9 Severe forms of neurological and muscular conditions (of which myopathy), serious epilepsy
10 Chronic severe constitutional and acquired haemoglobinopathies, haemolysis
11 Haemophilia and constitutional conditions of severe haemostasis
12 Severe arterial hypertension
13 Coronary heart disease
14 COPD 29 Active TB, leprosy
15 Alzheimer's disease and other dementias
16 Parkinson's disease
17 Hereditary metabolic conditions requiring long-term specialized treatment

18 Cystic fibrosis
19 Chronic nephropathy and primary nephrotic syndrome
20 Paraplegia
21 Polyarteritis nodosa, acute disseminated erythematous lupus, generalized progressive scleroderma
22 Severe evolutive rheumatoid polyarthritis
23 Long-term psychiatric conditions
24 Ulcerative colitis and evolutive Crohn's disease
25 Multiple sclerosis
26 Evolutive structural scoliosis (the angle of which is equal to or over 25 degrees) until rachidian maturation
27 Severe ankylosing spondylarthritis
28 Organ transplant sequelae
29 Active TB, leprosy
30 Malignant tumours, malignant lymphatic or haematopoietic tissue

The list of the affections covered and the corresponding ICD 10 codes, according to the 2010 version, are provided in the table below. Diagnoses are also coded according to the ICD. All diagnosis related to abuse disorders are coded accordingly.

Table 2 . List of the affections covered under ALD 25 : Long-term psychiatric conditions

Term	ICD 10 (2010 version)
Mental retardation	**F70 Mild mental retardation** **F71 Moderate mental retardation** **F72 Severe mental retardation** **F73 Profound mental retardation** **F79 Unspecified mental retardation**
developmental disorders	**F80 Specific developmental disorders of speech and language** **F81 Specific developmental disorders of scholastic skills** **F82 Specific developmental disorder of motor function** **F83 Mixed specific developmental disorders** **F84 Pervasive developmental disorders**
Personality disorders	**F60 Specific personality disorders**
Mixed disorders of conduct and emotions	**F92 Mixed disorders of conduct and emotions**
Schizophrenia, schizotypal and delusional disorders	**F29 Unspecified nonorganic psychosis**
Depressive episode	**F32 Depressive episode**
anxiety disorders	**F41 Other anxiety disorders**

Detail of hospital stays and consultations, the type specialist or department is available directly or through linkage with PMSI data.

Other somatic conditions identified, thanks to ICD 10 codes, will be:

- Cardiac diseases (Severe heart failure, arrythmias, valvular cardiomyopathy, congenital cardiomyopathy, Coronary heart disease),
- Cancers (Malignant tumours, malignant lymphatic or haematopoietic tissue),
- Neurological conditions and epilepsy (Severe forms of neurological and muscular conditions (of which myopathy), serious epilepsy)
- pulmonary disease (COPD 29 Active TB, leprosy)

Number of medications reimbursed will be calculated as well as number of days of hospitalizations.

In the CPRD, information of interest is detailed below, and will be obtained through the clinical details module. Symptoms, signs and diagnoses are coded using Read or OXMIS codes.

- Psychiatric disorders
- Somatic comorbidities:
  - cardiac,
  - cancers,
  - epilepsy
  - pulmonary disease
  - renal and urinary disease...

- Significant event in the person's life
  - death of a close family member, divorce)

- Charlson score of comorbidities[25]
- Number of medications
- Significant event in the person's life
- Hospitalizations (days of hospitalization)

Significant events in the person life (statement of death of a relative for instance) are available through clinical details in the CPRD.

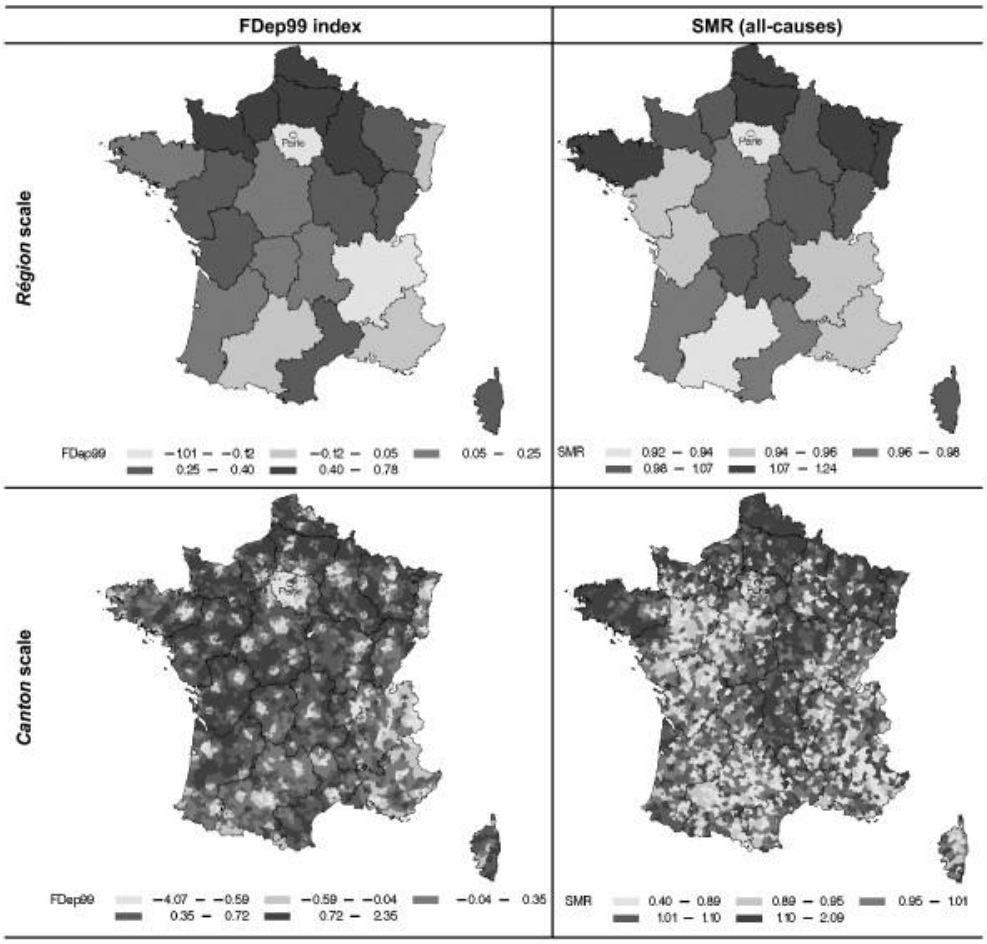
b) Creation of a medical code list

A list of all medical codes of interest will be created according to the coding system for Diagnosis, symptoms and medical history information.

4. Socio-economic factors

Income is not available through the **EGB** database. However, the affiliation to the CMU (*couverture maladie universelle*) is recorded. This universal health care coverage scheme is attributed to the unenmployed and low-income insurees, and can be used as a proxy of the income level.
Several deprivation indices have been developed. For France, specific indices have recently been proposed. The FDep99 index was built with the aim of being representative for the whole of France and taking urban-rural comparability issues into account [26] [27]. The commune is the smallest administrative unit in France (36,000 U). The socio-economic data were derived from 1999 population census[28] and from the tax authority's 2001 household income data (INSEE). On the basis of this index, a strong association between mortality and deprivation over the period 1997–2001 was observed on the Commune scale, as shown in the figure below[29].

[25] Charlson ME, Pompei P, Ales K, MacKenzie CR: A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chron Dis 1987, 40:373-383
[26] Windenberger F, Rican S, Jougla E, Rey G. Spatiotemporal association between deprivation and mortality: trends in France during the nineties. Eur J Public Health. 2012 Jun;22(3):347-53.
[27] Pornet C, Delpierre C, Dejardin O, Grosclaude P, Launay L, Guittet L, Lang T, Launoy G.Construction of an adaptable European transnational ecological deprivation index: the French version. J Epidemiol Community Health. 2012 Nov;66(11):982-9.
[28] National Institute for Statistics and Economic Studies (INSEES)
[29] Rey G, Jougla E, Fouillet A, Hémon D. Ecological association between a deprivation index and mortality in France over the period 1997 - 2001: variations with spatial scale, degree of urbanicity, age, gender and cause of death. BMC Public Health. 2009 Jan 22;9:33.



Aggregate levels of this deprivation index would be obtained at the regional or department levels, and would be applied to data available in the EGB database (the area of subject's residence is an available data in demographic part).
In the EGB database, commune of residence of the subject is an available data which will allow to estimate an aggregate deprivation index at the department level.

In the CPRD, we will use the index of Multiple deprivation quintile[30]. The Index of Multiple Deprivation (IMD) socio-economic status (SES) is available for all patients belonging to English practices that have consented to linkage. The SES quintile is calculated on the basis of lower level super output area (LSOA).

5. Other prescription of interest

Main classes of interest are represented by antidepressants, antipsychotics, antiepileptics, and other non-benzodiazepine anxiolytic or hypnotic drugs.

6. Propensity score

To reduce the potential for indication bias, a propensity score based on patient's characteristics present in the 12 months before index date (psychiatric comorbidities or previous hospital stay, cancer, cardiovascular diseases, or other identified factor suspected to be a motive for benzodiazepine prescribing...) will be calculated for each patients.

[30] Payne RA, Abel GA. UK indices of multiple deprivation - a way to make comparisons across constituent countries easier. Health Stat Q. Spring(53):22-37.

B. Study calendar

In the EGB database, the patients would be selected from 01/01/2007 to latest date available (6 months before the end of the study period) and followed-up until the most recent available date. We chose to limit the EGB study period from 01/01/2006 because we have been advised by the Health Insurance that data provided for the year 2005 must be incomplete[31].

In the CPRD database, the patients would be selected from 1999 (date of zaleplon first approval in UK) to latest date available (6 months before the end of the study period) and followed-up until the most recent available date.

Total duration of the study: 12 months

Study start	September 2012
DELIVERABLE 1: literature review	January 2013
DELIVERABLE 2a: preliminary protocol	January 2013
Revision of the preliminary protocol	
Submission of the CPRD study protocol to ISAC	
Final protocol: application for an ENCePP seal	
DELIVERABLE 2b: Final protocol	February 2013
Data extraction	
Data management	
Data analysis	
Consultation of the agency about results	
Writing draft Interim study report	
Dissemination of the draft Interim report	
DELIVERABLE 3a: Interim report	June 2013
Writing draft final study report	
Dissemination of the draft final report	
Review of the draft final report	
DELIVERABLE 3a: final report	September 2013

[31] Personal information obtained during the official training to EGB *Caisse Nationale d'Assurance Maladie des Travailleurs Salariés*, 17, 18, 19 October 201: problem of loading data in 2005 would have occurred during merging databases.

VII. STATISTICS

A. Sample size calculation

The French EGB has been queried to assess data on benzodiazepines utilization from July 1st 2006 to June 30th 2011. Tetrazepam, bromazepam and zolpidem were the 3 most benzodiazepines used in 2009 and 2010. Prevalence of exposure was estimated to 19.5% of French population (corresponding to ≈ 120,000 subjects in the EGB), and was stable from 2006 to 2011(men: 15% vs. women 24.7%).

A preliminary review within the CPRD was requested in line with the tender preparation, in order to identify exposed patients that could be included within the nested cohort. This request identified 1 157 405 patients that met the inclusion criteria (record of specified codes within the study period (from 01/01/1999 to 12/07/2012), 12 months of registration prior to the index date, at least 18 years of old at index date). Among these patients, 50% are expected to have data linked ONS mortality data, so the number of potential cases will be reduced by approximately 50%. This first review enables to confirm the large potential for recruitment through this data source.

The sample size will be determined in order to detect an increased risk of mortality of 2, with a power of 80% and a 5% risk, in comparison with non-exposed controls. Since the cumulative risk of death observed in the Kripke[32] study was less than 0.5% in the non-exposed cohort, the size of the exposed cohort in the CPRD should be at least 15000. According to the existing literature, it is not established whether it is appropriate to consider all benzodiazepines and related drugs as a class or whether there are differing risks associated with individual drugs. Thus, drugs most frequently used will be analyzed specifically.

At the date of writing, a further request was sent to CPRD knowledge centre to identify eligible patients with a least one control identified. This request will lead to a better estimate of sample size requirement.

B. Treatment of missing data

In EGB, there are no missing data regarding drug exposure. Quality controls are performed before charging data on the database by Cnam-TS.

In CPRD, missing data is anticipated as with any study performed on such database. Concerning some potential confounding factors with a particular interest, missing value will be considered as a specific modality of the variable (for BMI, smoking and alcohol status, marital or professional status...).

C. Statistical analyses

A description of the baseline characteristics of the group will be performed. Death occurrence will be compared among both groups between using bivariate comparison. The Kaplan-Meier survival function will be used to describe the occurrence of death in both groups over the study period.

Exposure to benzodiazepines will be computed as a time-dependent covariate and categorised according to the following categories:

Benzodiazepines derivatives could be related to death occurrence

- time dependent response
- dose-dependent response

The term “Benzodiazepines” is used in reference to all the products of interest mentioned page 20. By default, clonazepam and tetrazepam will be excluded from this list and not included in the main analyses. However, further sensitivity analyses will include these products with other benzodiazepines and derivatives

[32] Kripke DF, Langer RD, Kline LE. Hypnotics' association with mortality or cancer: a matched cohort study. BMJ Open. 2012;2(1):e000850.

First, to assess the impact exposure on mortality, a categorical time dependent variable for different duration of exposure will be created.

To assess the variation of death occurrence with increasing exposure, the cumulative dose of will be considered as a continuous time-dependent covariate. The cumulative dose will be calculated from the index date until either the end of the study or death. Doses will be estimated in defined daily doses and will be considered as additive.

For each active substance (hypothesis generating), dosage will be categorized according to the following categories: high, medium and low dosage, taking into account the dose in the product information for each drug.

Table 3. Set of covariates to be entered in the cox models

<table>
<tr><th>EGB</th><th>CPRD</th></tr>
<tr><td colspan="2">Covariates in common in both databases</td></tr>
<tr><td colspan="2">Fixed covariates:

❖ Patient
➢ gender,
➢ age /birth year
➢ Propensity score

Time-varying covariates:

❖ Patient
➢ other drugs (medical use)
➢ Number of medications

❖ Clinical
➢ Psychiatric disorders
➢ Somatic comorbidities:
▪ cardiac,
▪ cancers,
▪ epilepsy
▪ pulmonary disease
▪ Renal and urinary disease...

➢ Charlson score of comorbidities
➢ Hospitalizations (days of hospitalization)</td></tr>
<tr><td>Covariate available exclusively within EGB</td><td>Covariate available exclusively within CPRD</td></tr>
<tr><td>Fixed covariates:

❖ Patient
➢ FDep99 (or FDep2008 if available)</td><td>Fixed covariates:

❖ Patient
➢ Marital status
➢ IMD quintile
➢ Height, weight, BMI</td></tr>
</table>

Time-varying covariates:	**Time-varying covariates:** ❖ Patient ➢ Alcohol consumption, ➢ Smoking ➢ other substances (non-medical use) ❖ Clinical ➢ Significant event in the person's life ▪ death of a close family member, divorce)

The role of potential confounding or explanatory variables will be taken into account by the extended Cox regression model. Independent variables will be included according to their relevance and reference into the literature.

In a first step, time-dependent Cox analyses will be conducted in each database using the complete set of available covariates referred Table 3, including both variables in common and specific to the databases.

In a further step, in order to examine the consistency of findings on patterns of benzodiazepine-associated mortality in the two countries (France and the United Kingdom) in spite of differences in covariate availability, time-dependent Cox analyses will be performed using only the common set of covariates (comprising exclusively variables in common in both databases).

A univariate analysis will be first performed to select the variables with a p value<0.2, followed by a multivariate approach using the Cox proportional hazard regression model with time dependent covariates, with stratification on the matched pairs. Continuous variables will be tested for linearity. Relevant interactions between covariates will be checked. Proportional hazards assumption will be tested for all covariates.The estimation of the crude and adjusted Hazard Ratio and their 95% confidence interval will be provided.

The mortality associated to the overall benzodiazepines derivatives and related drugs will be analysed as hypothesis testing. The same analyses will be conducted for each individual drug, but the resulting findings will only be used to generate further hypothesis focused on selected active substances.

Patterns of benzodiazepines use are prone to vary along time, thus it seems natural and appropriate to consider that in an appropriate statistical model. In the final protocol, we will explore the opportunity to perform a time-dependent Cox model to investigate the relation between benzodiazepines and mortality. Moreover, if mortality related to these drugs may be obtained by multiple causal pathways, including acute lethality, it is crucial to take account of the variation in drug use in a specific time window before death. Statistical analyses will be performed using SAS 9.2® (Sas Institute Inc, Cary NC, USA)

D. Linkage of the results of the two sources

The results obtained from the France and the UK will be discursively interpreted. No attempt will be made to synthesize the results using quantitative methods. We expected that descriptive data, comparison of the exposed and unexposed groups show the same tendency. The main analysis will include the complete set of available covariates in each database. In order to examine the consistency of findings on patterns of benzodiazepine-associated mortality in the two countries despite differences in variables availability, a time-dependent Cox analysis will also be performed using only available variables in common in both databases.

VIII. PATIENT / USER GROUP INVOLVEMENT

Involvement of patients or user groups is not planned in any stage of the study

IX. LIMITATIONS OF THE STUDY DESIGN, DATA SOURCES AND ANALYTIC METHODS

A. Potential for selection bias

The potential for selection bias is minimized due to the absence of restrictive inclusion criteria and the sampling thought a database

B. Potential for information bias

Concerning data sources, the potential for missing data for variables of interest is attenuated by the selection of the study population among patient's records who met a sufficient quality standard for research.

C. Potential for measurement bias

In the EGB, the possibility for a patient to get the product of interest elsewhere is limited as benzodiazepines are exclusively prescription medicines but reimbursement can be not requested by the beneficiary or the package can be not eligible for reimbursement.

In the CPRD, the possibility for a patient to get the product of interest elsewhere could lead to an underestimation of the real level of exposure. However, General practitioner ensures almost all the prescribing practice and all the drugs of interest are prescription only medicines. Moreover, prescription issued privately will also be covered by the dataset. The ascertainment of death is considered to be accurate for patients whose practice consented to linkage with ONS mortality data

The extended Cox model chosen take account of time to event data, and is adapted with time dependent covariates, reflecting different level of status or exposure during the study period. Handling of missing data will be performed using conventional methods for censured data.

X. REPORTING: PLAN FOR DISSEMINATION OF REPORTS

During the conduct of the study, periodic contacts with the Agency will be done to discuss global and specific results. By no later than 10 months following the start of the project, an interim report on study results of the epidemiological study (deliverable 3a) will be produced and transmitted to the agency.

The final report of the epidemiological study (deliverable 3b) will be sent on the 12th month. The final report will take the form of a detailed study report (hard copy and electronic form), accompanied of a research manuscript, suitable for submission in a research journal. The focus, the choice of the journal, and the overall direction of the manuscript will be discussed with the Agency since the interim report transmission. Preliminary version of the report should enable to identify potential issues for selected active substances, considered as hypothesis generating. In this case, the Agency will be requested for previous report, study findings, or information obtained from the marketing holders for the identified substances, in order to collect the best existing evidence and facilitate the interpretation and the generation of secondary and focused hypotheses.

XI. QUALITY CONTROL

Audit and inspection

In accordance with the Agency's Financial Regulation, the European Court of Auditors shall be entitled to access, inspect and audit the records related to this study The Agency or an outside body of its choice shall have the same rights as the European Court of Auditors for the purpose of access, inspection and audit of the Records
The European Anti Fraud Office may carry out on-the-spot checks and inspections in accordance with Council Regulation (Euratom, EC) No 2185/96 and Parliament and Council Regulation (EC) No 1073/1999

XII. ETHICAL AND REGULATORY CONSIDERATIONS

Confidentiality

All data are anonymous in the two databases. Data extracted from the EGB will be done according to rules given by the *Commission Nationale Informatique et Libertés CNIL*. The database is built in order not to be able to join sensitive data. Thanks to that, identification of subjects from this data is not possible Data received from the CPRD do not contain any information that could enable to identify the subjects.

Agreement with data providers ans data sharing

Access to EGB data is limited to authorized users only. Consequently, data obtained in this study could not be shared with other parties.

Access to CPRD data requires examination of the study protocol and qualification of the research team by an expert advisory body (ISAC, Independent Scientific Advisory Committee). Datasets obtained through this process must be dedicated to the purpose stated in the study protocol, and could not be shared with other parties.

Amendments to the protocol

Any substantial modification, i.e. any modification of a nature likely to have a significant impact on the conditions of validity and the results of the study, on interpretation of the scientific documents which provide support for the study or the methods for conducting it, is the subject of a written amendment to be submitted to the European Medicines Agency. Non-substantial modifications, i.e. those not having a significant impact on any aspect of the study whatsoever, are communicated to the Agency for information

purposes.

XIII. DATA STORAGE

Datasets will be stored on a secured server.

XIV. RULES FOR PUBLICATION

This study will follow the requirements for publication of the study results for ENCePP Seal Studies. In particular, publication will be undertaken in accordance with ENCEPP rules for transparency[33]. Publications or dissemination of the study results will be submitted to prior written authorization of the European Medicines Agency.
Publication or dissemination of information relating to this study will require prior written authorisation from the Agency and will mention the amount paid by the Agency. It will be stated that the opinions expressed are those of the Unit INSERM 1027 only and do not represent the Agency's official position.

[33] http://www.encepp.eu/encepp_studies/index.shtml

XV. Appendices

APPENDIX 1: Exposure of interest

Table 1. Detail of chemical subgroups and active substances of interest for substances considered in the main analysis

drugsubstance	productname	bnfcode	multilexcode
alprazolam	alprazolam tablets 250micrograms	4010200	4948001
	alprazolam tablets 500micrograms	4010200	4948002
	XANAX tablets 250micrograms [PHARMACIA]	4010200	2098001
	XANAX tablets 500micrograms [PHARMACIA]	4010200	2098002
bromazepam	bromazepam tablets 1.5mg	4010200	4054001
	bromazepam tablets 3mg	4010200	4054002
	LEXOTAN tablets 1.5mg [ROCHE]	4010200	523001
	LEXOTAN tablets 3mg [ROCHE]	4010200	523002
chlordiazepoxide hydrochloride	chlordiazepoxide capsules 10mg	4010200	3190002
	CHLORDIAZEPOXIDE capsules 10mg [ACTAVIS]	4010200	2222010
	CHLORDIAZEPOXIDE capsules 10mg [APS]	4010200	1809010
	CHLORDIAZEPOXIDE capsules 10mg [DDSA]	4010200	1352010
	CHLORDIAZEPOXIDE capsules 10mg [IVAX]	4010200	1760011
	chlordiazepoxide capsules 5mg	4010200	3190001
	CHLORDIAZEPOXIDE capsules 5mg [ACTAVIS]	4010200	2222009
	CHLORDIAZEPOXIDE capsules 5mg [APS]	4010200	1809009
	CHLORDIAZEPOXIDE capsules 5mg [DDSA]	4010200	1352009
	CHLORDIAZEPOXIDE capsules 5mg [HILLCROSS]	4010200	699009

drugsubstance	productname	bnfcode	multilexcode
	chlordiazepoxide hydrochloride tablets 10mg	4010200	6225002
	chlordiazepoxide hydrochloride tablets 25mg	4010200	6225003
	chlordiazepoxide hydrochloride tablets 5mg	4010200	6225001
	chlordiazepoxide injection 100mg	4010200	3191003
	chlordiazepoxide tablets 10mg	4010200	3191001
	CHLORDIAZEPOXIDE tablets 10mg [DDSA]	4010200	1352011
	chlordiazepoxide tablets 25mg	4010200	3191002
	CHLORDIAZEPOXIDE tablets 25mg [DDSA]	4010200	1419009
	chlordiazepoxide tablets 5mg	4010200	3190003
	CHLORDIAZEPOXIDE tablets 5mg [DDSA]	4010200	1419010
	CHLORDIAZEPOXIDE tablets 5mg [HILLCROSS]	4010200	5332009
	LIBRIUM capsules 10mg [ICN]	4010200	525002
	LIBRIUM capsules 10mg [MEDA]	4010200	12713001
	LIBRIUM capsules 5mg [ICN]	4010200	525001
	LIBRIUM capsules 5mg [MEDA]	4010200	12712001
	LIBRIUM injection 100mg [ROCHE]	4010200	1481001
	LIBRIUM tablets 10mg [ICN]	4010200	526001
	LIBRIUM tablets 25mg [ICN]	4010200	526002
	LIBRIUM tablets 5mg [ICN]	4010200	525003
	TROPIUM capsules 5mg [DDSA]	4010200	3193001
	TROPIUM tablets 10mg [DDSA]	4010200	3194001
	TROPIUM tablets 5mg [DDSA]	4010200	3193003
chlordiazepoxide/clidinium bromide	clidinium bromide with chlordiazepoxide tablets	04010200/01020100	3343001
	LIBRAXIN tablets [ROCHE]	04010200/01020100	524001

drugsubstance	productname	bnfcode	multilexcode
clobazam	clobazam capsules	04010200/04080115	14576001
	clobazam capsules 10mg	04010200/04080115	3351001
	clobazam oral solution 25mg/5ml	04010200/04080115	17286001
	clobazam oral suspension 10mg/5ml	04010200/04080115	13542001
	clobazam oral suspension 5mg/5ml	04010200/04080115	13838001
	clobazam tablets 10mg	04010200/04080115	3351002
	FRISIUM capsules 10mg [AVENTIS]	04010200/04080115	377001
	FRISIUM tablets 10mg [AVENTIS]	04010200/04080115	377002
diazepam	ATENSINE tablets 10mg [RORER]	04010100/04010200/10020200/15010401/04080115	65003
	DIAZEMULS injection 10mg/2ml [ACTAVIS]	04010200/04080200/10020200/15010401/04080300	238001
	diazepam capsules 10mg	04010100/04010200/10020200/15010401/04080115	8717001
	diazepam capsules 2mg	04010100/04010200/10020200/15010401/04080115	3590002
	diazepam capsules 5mg	04010100/04010200/10020200/15010401/04080115	3590003
	diazepam elixir 2mg/5ml	04010100/04010200/10020200/15010401/04080115	2784001
	diazepam injection (emulsion) 10mg/2ml	04010200/04080200/10020200/15010401/04080300	7141001
	diazepam injection (solution) 10mg/2ml	04010200/04080200/10020200/15010401/04080300	7141002

drugsubstance	productname	bnfcode	multilexcode
	DIAZEPAM injection (solution) 10mg/2ml [HAMELN]	04010200/04080200/10020200/15010401/04080300	2740009
	DIAZEPAM injection 10mg/2ml [CP PHARM]	04010200/04080200/10020200/15010401/04080300	1429010
	diazepam oral solution 5mg/5ml	04010100/04010200/10020200/15010401/04080115	3590001
	diazepam rectal tubes 10mg	04010200/04080200/10020200/15010401/04080300	3592002
	DIAZEPAM rectal tubes 10mg [SANDOZ]	04010200/04080200/10020200/15010401/04080300	1350011
	diazepam rectal tubes 2.5mg	04010200/04080200/10020200/15010401/04080300	3592003
	diazepam rectal tubes 20mg	04010200/04080200/10020200/15010401/04080300	7426001
	diazepam rectal tubes 5mg	04010200/04080200/10020200/15010401/04080300	3592001
	DIAZEPAM rectal tubes 5mg [HILLCROSS]	04010200/04080200/10020200/15010401/04080300	5334009
	DIAZEPAM rectal tubes 5mg [SANDOZ]	04010200/04080200/10020200/15010401/04080300	1864009
	DIAZEPAM RECTUBES rectal tubes 10mg [CP PHARM]	04010200/04080200/10020200/15010401/04080300	294002
	DIAZEPAM RECTUBES rectal tubes 2.5mg [CP PHARM]	04010200/04080200/10020200/15010401/04080300	294003
	DIAZEPAM RECTUBES rectal tubes 20mg [CP PHARM]	04010200/04080200/10020200/15010401/04080300	8645001
	DIAZEPAM RECTUBES rectal tubes 5mg [CP PHARM]	04010200/04080200/10020200/15010401/04080300	294001
	diazepam sugar free oral solution 2mg/5ml	04010100/04010200/10020200/15010401/04080115	13950001
	DIAZEPAM sugar free oral solution 2mg/5ml [ACTAVIS]	04010100/04010200/10020200/15010401/04080115	365011
	diazepam suppository 10mg	04010200/04080200/10020200/15010401/04080300	3591002
	DIAZEPAM suppository 10mg [SINCLAIR]	04010200/04080200/10020200/15010401/04080300	1351009
	diazepam suppository 5mg	04010200/04080200/10020200/15010401/04080300	3591001

drugsubstance	productname	bnfcode	multilexcode
	diazepam suspension 10mg/5ml	04010100/04010200/10020200/15010401/04080115	7185003
	diazepam suspension 1mg/5ml	04010100/04010200/10020200/15010401/04080115	7185001
	diazepam suspension 2.5mg/5ml	04010100/04010200/10020200/15010401/04080115	7185002
	DIAZEPAM syrup 2mg/5ml [SANDOZ]	04010100/04010200/10020200/15010401/04080115	1350010
	DIAZEPAM syrup 5mg/5ml [HILLCROSS]	04010100/04010200/10020200/15010401/04080115	6151009
	DIAZEPAM syrup 5mg/5ml [SANDOZ]	04010100/04010200/10020200/15010401/04080115	1350009
	diazepam tablets 10mg	04010100/04010200/10020200/15010401/04080115	2783003
	DIAZEPAM tablets 10mg [ACTAVIS]	04010100/04010200/10020200/15010401/04080115	365010
	DIAZEPAM tablets 10mg [GEN (UK)]	04010100/04010200/10020200/15010401/04080115	4479009
	DIAZEPAM tablets 10mg [HILLCROSS]	04010100/04010200/10020200/15010401/04080115	368011
	DIAZEPAM tablets 10mg [RANBAXY]	04010100/04010200/10020200/15010401/04080115	3439011
	DIAZEPAM tablets 10mg [TEVA]	04010100/04010200/10020200/15010401/04080115	1319011
	diazepam tablets 2mg	04010100/04010200/10020200/15010401/04080115	2783001
	DIAZEPAM tablets 2mg [ACTAVIS]	04010100/04010200/10020200/15010401/04080115	2233009
	DIAZEPAM tablets 2mg [BERK]	04010100/04010200/10020200/15010401/04080115	354009
	DIAZEPAM tablets 2mg [CROSS-PHAR]	04010100/04010200/10020200/15010401/04080115	367009
	DIAZEPAM tablets 2mg [GEN (UK)]	04010100/04010200/10020200/15010401/04080115	4002009
	DIAZEPAM tablets 2mg [HILLCROSS]	04010100/04010200/10020200/15010401/04080115	368009
	DIAZEPAM tablets 2mg [IVAX]	04010100/04010200/10020200/15010401/04080115	3757009
	DIAZEPAM tablets 2mg [RANBAXY]	04010100/04010200/10020200/15010401/04080115	3439009
	DIAZEPAM tablets 2mg [REGENT]	04010100/04010200/10020200/15010401/04080115	3688009
	DIAZEPAM tablets 2mg [TEVA]	04010100/04010200/10020200/15010401/04080115	1319009
	diazepam tablets 5mg	04010100/04010200/10020200/15010401/04080115	2783002
	DIAZEPAM tablets 5mg [ACTAVIS]	04010100/04010200/10020200/15010401/04080115	365009
	DIAZEPAM tablets 5mg [BERK]	04010100/04010200/10020200/15010401/04080115	354010

drugsubstance	productname	bnfcode	multilexcode
	DIAZEPAM tablets 5mg [CROSS-PHAR]	04010100/04010200/10020200/15010401/04080115	367010
	DIAZEPAM tablets 5mg [GEN (UK)]	04010100/04010200/10020200/15010401/04080115	4003009
	DIAZEPAM tablets 5mg [HILLCROSS]	04010100/04010200/10020200/15010401/04080115	368010
	DIAZEPAM tablets 5mg [TEVA]	04010100/04010200/10020200/15010401/04080115	1319010
	EVACALM tablets 5mg [UNIMED]	04010100/04010200/10020200/15010401/04080115	2805002
	SOLIS capsules 5mg [GALEN]	04010100/04010200/10020200/15010401/04080115	2807002
	STESOLID rectal tubes 10mg [ACTAVIS]	04010200/04080200/10020200/15010401/04080300	2466002
	STESOLID rectal tubes 10mg [DUMEX]	04010200/04080200/10020200/15010401/04080300	10498001
	STESOLID rectal tubes 5mg [ACTAVIS]	04010200/04080200/10020200/15010401/04080300	2466001
	TENSIUM tablets 10mg [DDSA]	04010100/04010200/10020200/15010401/04080115	2806003
	VALCLAIR suppository 10mg [DURBIN]	04010200/04080200/10020200/15010401/04080300	7098001
	VALIUM capsules 2mg [ROCHE]	04010100/04010200/10020200/15010401/04080115	1001001
	VALIUM capsules 5mg [ROCHE]	04010100/04010200/10020200/15010401/04080115	1001002
	VALIUM injection 5mg/ml [ROCHE]	04010200/04080200/10020200/15010401/04080300	1000001
	VALIUM suppository 10mg [ROCHE]	04010200/04080200/10020200/15010401/04080300	1004002
	VALIUM suppository 5mg [ROCHE]	04010200/04080200/10020200/15010401/04080300	1004001
	VALIUM syrup 2mg/5ml [ROCHE]	04010100/04010200/10020200/15010401/04080115	1002001
	VALIUM tablets 10mg [ROCHE]	04010100/04010200/10020200/15010401/04080115	1003003
	VALIUM tablets 2mg [ROCHE]	04010100/04010200/10020200/15010401/04080115	1003001
	VALIUM tablets 5mg [ROCHE]	04010100/04010200/10020200/15010401/04080115	1003002
dipotassium clorazepate	clorazepate dipotassium capsules 15mg	4010200	3372002
	clorazepate dipotassium capsules 7.5mg	4010200	3372001
	TRANXENE capsules 15mg [BOEH INGL]	4010200	967002

drugsubstance	productname	bnfcode	multilexcode
	TRANXENE capsules 7.5mg [BOEH INGL]	4010200	967001
flunitrazepam	flunitrazepam tablets 1mg	4010100	3479001
	ROHYPNOL tablets 1mg [ROCHE]	4010100	829001
flurazepam hydrochloride	DALMANE capsules 15mg [MEDA]	4010100	210001
	DALMANE capsules 30mg [MEDA]	4010100	210002
	flurazepam capsules 15mg	4010100	3502001
	flurazepam capsules 30mg	4010100	3502002
	PAXANE capsules 30mg [STEINHARD]	4010100	3503002
ketazolam	ANXON capsules 15mg [BEECHAM]	4010200	53001
	ANXON capsules 30mg [BEECHAM]	4010200	53002
	ketazolam capsules 15mg	4010200	3959001
	ketazolam capsules 30mg	4010200	3959002
loprazolam mesilate	DORMONOCT tablets 1mg [HOECHSTMAR]	4010100	4005001
	loprazolam tablets 1mg	4010100	2361001
	LOPRAZOLAM tablets 1mg [WINTHROP]	4010100	3346009
lorazepam	ATIVAN injection 4mg/1ml [WYETH PHAR]	04010200/04080200/15010401	66001
	ATIVAN tablets 1mg [WYETH PHAR]	04010200/15010401	67001
	ATIVAN tablets 2.5mg [WYETH PHAR]	04010200/15010401	67002
	lorazepam injection 4mg/1ml	04010200/04080200/15010401	4006001
	lorazepam oral solution 1mg/5ml	04010200/15010401	15867001
	lorazepam oral suspension 1mg/5ml	04010200/15010401	15865001
	lorazepam oral suspension 500mcg/5ml	04010200/15010401	13569001
	lorazepam tablets 1mg	04010200/15010401	2786001

drugsubstance	productname	bnfcode	multilexcode
	LORAZEPAM tablets 1mg [ARROW]	04010200/15010401	4806009
	LORAZEPAM tablets 1mg [GEN (UK)]	04010200/15010401	6204009
	LORAZEPAM tablets 1mg [GENUS]	04010200/15010401	831009
	LORAZEPAM tablets 1mg [TEVA]	04010200/15010401	629009
	lorazepam tablets 2.5mg	04010200/15010401	2786002
	LORAZEPAM tablets 2.5mg [GENUS]	04010200/15010401	831010
	LORAZEPAM tablets 2.5mg [TEVA]	04010200/15010401	629010
lormetazepam	LORAMET capsules 1mg [WYETH PHAR]	4010100	1209001
	lormetazepam capsules 1mg	4010100	4007003
	lormetazepam tablets 0.5mg	4010100	4007001
	LORMETAZEPAM tablets 0.5mg [GEN (UK)]	4010100	3146009
	LORMETAZEPAM tablets 0.5mg [GENUS]	4010100	3178009
	LORMETAZEPAM tablets 0.5mg [HILLCROSS]	4010100	832009
	lormetazepam tablets 1mg	4010100	4007002
	LORMETAZEPAM tablets 1mg [GEN (UK)]	4010100	3146010
	LORMETAZEPAM tablets 1mg [GENUS]	4010100	3178010
	LORMETAZEPAM tablets 1mg [WYETH PHAR]	4010100	469010
	NOCTAMID tablets 1mg [SCHERING]	4010100	651001
medazepam	medazepam capsules 10mg	4010200	4084002
	medazepam capsules 5mg	4010200	4084001
	NOBRIUM capsules 10mg [ROCHE]	4010200	650002
	NOBRIUM capsules 5mg [ROCHE]	4010200	650001

drugsubstance	productname	bnfcode	multilexcode
midazolam hydrochloride	HYPNOVEL injection 10mg/2ml [ROCHE]	15010401	1449001
	HYPNOVEL injection 10mg/5ml [ROCHE]	15010401	1449002
	midazolam injection 100mg/50ml	15010401	14283001
	midazolam injection 10mg/2ml	15010401	14288001
	MIDAZOLAM injection 10mg/2ml [ANTIGEN]	15010401	3715010
	MIDAZOLAM injection 10mg/2ml [CP PHARM]	15010401	3731010
	midazolam injection 10mg/5ml	15010401	14282001
	midazolam injection 1mg/ml	15010401	4197003
	midazolam injection 2mg/2ml	15010401	14285001
	midazolam injection 2mg/ml	15010401	4197001
	midazolam injection 50mg/10ml	15010401	14289001
	midazolam injection 50mg/50ml	15010401	14284001
	midazolam injection 5mg/5ml	15010401	14286001
	midazolam injection 5mg/ml	15010401	4197002
	midazolam injection 90mg/18ml	15010401	14290001
nitrazepam	MOGADON capsules 5mg [ROCHE]	4010100	2731001
	MOGADON tablets 5mg [ICN]	4010100	595001
	MOGADON tablets 5mg [MEDA]	4010100	12710001
	NITRADOS tablets 5mg [RORER]	4010100	645001
	nitrazepam capsules 5mg	4010100	4278001
	nitrazepam suspension 2.5mg/5ml	4010100	4279002
	nitrazepam suspension 5mg/5ml	4010100	4279003
	nitrazepam tablets 10mg	4010100	4279001
	nitrazepam tablets 5mg	4010100	2772001
	NITRAZEPAM tablets 5mg [ACTAVIS]	4010100	1529009

drugsubstance	productname	bnfcode	multilexcode
	NITRAZEPAM tablets 5mg [BERK]	4010100	279009
	NITRAZEPAM tablets 5mg [DDSA]	4010100	857009
	NITRAZEPAM tablets 5mg [GEN (UK)]	4010100	4004009
	NITRAZEPAM tablets 5mg [HILLCROSS]	4010100	282009
	NITRAZEPAM tablets 5mg [TEVA]	4010100	1324009
	NITRAZEPAM tablets 5mg [WOCKHARDT]	4010100	280009
	REMNOS tablets 10mg [DDSA]	4010100	4281001
	SOMNITE suspension 2.5mg/5ml [NORGINE]	4010100	874001
	SUREM capsules 5mg [GALEN]	4010100	2794001
oxazepam	OXANID tablets 10mg [STEINHARD]	4010200	4333001
	oxazepam capsules 30mg	4010200	4332001
	oxazepam tablets 10mg	4010200	2986001
	OXAZEPAM tablets 10mg [ACTAVIS]	4010200	1758009
	OXAZEPAM tablets 10mg [GENUS]	4010200	286009
	OXAZEPAM tablets 10mg [HILLCROSS]	4010200	283009
	OXAZEPAM tablets 10mg [IVAX]	4010200	2450010
	oxazepam tablets 15mg	4010200	2986002
	OXAZEPAM tablets 15mg [ACTAVIS]	4010200	1758010
	OXAZEPAM tablets 15mg [HILLCROSS]	4010200	283010
	OXAZEPAM tablets 15mg [IVAX]	4010200	2450009
	oxazepam tablets 30mg	4010200	2986003
prazepam	CENTRAX tablets 10mg [PARKE]	4010200	156001
temazepam	EUHYPNOS elixir 10mg/5ml [PHARMACIA]	04010100/15010401	332002

drugsubstance	productname	bnfcode	multilexcode
	EUHYPNOS FORTE capsules 20mg [PHARMACIA]	04010100/15010401	1129001
	NORMISON capsules 10mg [WYETH PHAR]	04010100/15010401	660001
	NORMISON capsules 20mg [WYETH PHAR]	04010100/15010401	660002
	temazepam capsules 10mg	04010100/15010401	4784001
	TEMAZEPAM capsules 10mg [HILLCROSS]	04010100/15010401	641009
	temazepam capsules 15mg	04010100/15010401	4784003
	temazepam capsules 20mg	04010100/15010401	4784002
	TEMAZEPAM capsules 20mg [HILLCROSS]	04010100/15010401	641010
	temazepam capsules 30mg	04010100/15010401	6514001
	temazepam gel-filled capsules 10mg	04010100/15010401	6581001
	TEMAZEPAM gel-filled capsules 10mg [BERK]	04010100/15010401	639009
	temazepam gel-filled capsules 20mg	04010100/15010401	6581003
	TEMAZEPAM gel-filled capsules 20mg [BERK]	04010100/15010401	639010
	TEMAZEPAM GELTHIX gel-filled capsules 10mg [PHARMACIA]	04010100/15010401	6583001
	TEMAZEPAM GELTHIX gel-filled capsules 15mg [PHARMACIA]	04010100/15010401	6583002
	TEMAZEPAM GELTHIX gel-filled capsules 20mg [PHARMACIA]	04010100/15010401	6583003
	TEMAZEPAM GELTHIX gel-filled capsules 30mg [PHARMACIA]	04010100/15010401	6584001
	TEMAZEPAM PLANPAK capsules [???]	04010100/15010401	5779001
	temazepam sugar free elixir 10mg/5ml	04010100/15010401	5188001

drugsubstance	productname	bnfcode	multilexcode
	TEMAZEPAM sugar free elixir 10mg/5ml [GEN (UK)]	04010100/15010401	2572009
	TEMAZEPAM sugar free elixir 10mg/5ml [HILLCROSS]	04010100/15010401	952011
	TEMAZEPAM sugar free elixir 10mg/5ml [ROSEMONT]	04010100/15010401	2049009
	temazepam tablets 10mg	04010100/15010401	5188002
	TEMAZEPAM tablets 10mg [GEN (UK)]	04010100/15010401	2826009
	TEMAZEPAM tablets 10mg [HILLCROSS]	04010100/15010401	680010
	TEMAZEPAM tablets 10mg [IVAX]	04010100/15010401	1485009
			1977009
	TEMAZEPAM tablets 10mg [PHARMACIA]	04010100/15010401	1393011
	TEMAZEPAM tablets 10mg [TEVA]	04010100/15010401	1392011
	TEMAZEPAM tablets 10mg [WYETH PHAR]	04010100/15010401	642011
	temazepam tablets 20mg	04010100/15010401	5188003
	TEMAZEPAM tablets 20mg [GEN (UK)]	04010100/15010401	2826010
	TEMAZEPAM tablets 20mg [HILLCROSS]	04010100/15010401	680011
	TEMAZEPAM tablets 20mg [IVAX]	04010100/15010401	1485010
	TEMAZEPAM tablets 20mg [PHARMACIA]	04010100/15010401	3383009
	TEMAZEPAM tablets 20mg [WYETH PHAR]	04010100/15010401	642010
triazolam	TRIAZOLAM tablets 0.25mg [BERK]	4010100	1080010
	triazolam tablets 125micrograms	4010100	4878001
	triazolam tablets 250micrograms	4010100	4878002
zaleplon	SONATA capsules 10mg [MEDA]	4010100	11725002

drugsubstance	productname	bnfcode	multilexcode
	SONATA capsules 5mg [MEDA]	4010100	11725001
	zaleplon capsules 10mg	4010100	11724002
	zaleplon capsules 5mg	4010100	11724001
zolpidem tartrate	STILNOCT tablets 10mg [SANOFI/AVE]	4010100	7296002
	STILNOCT tablets 5mg [SANOFI/AVE]	4010100	7296001
	zolpidem tablets 10mg	4010100	7295002
	ZOLPIDEM tablets 10mg [GEN (UK)]	4010100	4802009
	ZOLPIDEM tablets 10mg [HILLCROSS]	4010100	4191009
	ZOLPIDEM tablets 10mg [IVAX]	4010100	4493009
	ZOLPIDEM tablets 10mg [TEVA]	4010100	4125009
	ZOLPIDEM tablets 10mg [WINTHROP]	4010100	3963010
	zolpidem tablets 5mg	4010100	7295001
	ZOLPIDEM tablets 5mg [HILLCROSS]	4010100	4190009
	ZOLPIDEM tablets 5mg [IVAX]	4010100	4492009
	ZOLPIDEM tablets 5mg [TEVA]	4010100	4124009
	ZOLPIDEM tablets 5mg [WINTHROP]	4010100	3963009
zopiclone	ZILEZE tablets 3.75mg [OPUS]	4010100	11541001
	ZILEZE tablets 7.5mg [OPUS]	4010100	11541002
	ZIMOVANE LS tablets 3.75mg [AVENTIS]	4010100	10296001
	ZIMOVANE tablets 7.5mg [AVENTIS]	4010100	6358001
	zopiclone oral suspension 3.75mg/5ml	4010100	14097001
	zopiclone tablets 3.75mg	4010100	6361002
	ZOPICLONE tablets 3.75mg [ACTAVIS]	4010100	2837010
	ZOPICLONE tablets 3.75mg [GEN (UK)]	4010100	2972010
	ZOPICLONE tablets 3.75mg [HILLCROSS]	4010100	3142009

drugsubstance	productname	bnfcode	multilexcode
	ZOPICLONE tablets 3.75mg [IVAX]	4010100	2844009
	ZOPICLONE tablets 3.75mg [KENT]	4010100	4412009
	ZOPICLONE tablets 3.75mg [TEVA]	4010100	2923009
	zopiclone tablets 7.5mg	4010100	6361001
	ZOPICLONE tablets 7.5mg [ACTAVIS]	4010100	2837009
	ZOPICLONE tablets 7.5mg [GEN (UK)]	4010100	2972009
	ZOPICLONE tablets 7.5mg [HILLCROSS]	4010100	3142010
	ZOPICLONE tablets 7.5mg [IVAX]	4010100	2844010
	ZOPICLONE tablets 7.5mg [KENT]	4010100	3839009
	ZOPICLONE tablets 7.5mg [PLIVA]	4010100	3929009
	ZOPICLONE tablets 7.5mg [TEVA]	4010100	2923010

APPENDIX 2 : Clonazepam codes to be included in the sensitivity analysis

Appendix 2. Detail of chemical subgroups and active substances of interest for substances considered in a sensitive analysis

drugsubstance	productname	bnfcode	multilexcode
clonazepam	clonazepam concentrate for solution for injection 1mg/1ml	4080200	3365003
	clonazepam oral drops 2.5mg/ml	4080115	11576001
	clonazepam oral solution 250micrograms/5ml	4080115	14440001
	clonazepam sugar free oral solution 2mg/5ml	4080115	11576003
	CLONAZEPAM sugar free oral solution 2mg/5ml [ROSEMONT]	4080115	3428009
	clonazepam sugar free solution 500micrograms/5ml	4080115	13395001
	clonazepam suspension 500micrograms/5ml	4080115	11576002
	clonazepam tablets 2mg	4080115	3365002
	clonazepam tablets 500 micrograms	4080115	3365001
	RIVOTRIL concentrate for solution for injection 1mg/1ml [ROCHE]	4080200	1482001
	RIVOTRIL oral drops 2.5mg/ml [ROCHE]	4080115	11577001
	RIVOTRIL tablets 0.5mg [ROCHE]	4080115	823001
	RIVOTRIL tablets 2mg [ROCHE]	4080115	823002

APPENDIX 3 : Clinical event of interest

Detail of GPRD, Read oxmis terms and code for the event interest

Gprd medical code	Read oxmis code	Read oxmis term	Statement of death /death category
272392	R210000	[D]Cot death	death of baby
299832	R210100	[D]Crib death	death of baby
299833	R212.00	[D]Death less than 24 hours from onset of illness	statement of death
244769	R212z00	[D]Death less than 24 hours from onset of illness NOS	statement of death
217544	R212000	[D]Death, not instantaneous cause unknown	statement of death
235749	R212100	[D]Died, with no sign of disease	statement of death
290566	R213000	[D]Found after death, unknown cause of death	statement of death
208564	R213100	[D]Found dead	statement of death
226667	R211.00	[D]Instantaneous death	statement of death
208562	R2...12	[D]Mortality, cause unsure	statement of death
235748	R210200	[D]Nonspecific sudden infant death	death of baby
281406	R21..00	[D]Sudden death, cause unknown	statement of death
244770	R21z.00	[D]Sudden death, cause unknown NOS	statement of death
208563	R210.00	[D]Sudden infant death syndrome	death of baby
263156	R210z00	[D]Sudden infant death syndrome NOS	death of baby
235750	R213.00	[D]Unattended death	statement of death
263157	R213z00	[D]Unattended death NOS	statement of death
283173	ZV68011	[V]Issue of death certificate	statement of death
217555	RyuC.00	[X]Ill-defined and unknown causes of mortality	statement of death
253102	Lyu7500	[X]Obstetric death of unspecified cause	death of mother
272402	RyuC200	[X]Other ill-defined and unspecified causes of death	statement of death
290575	RyuC100	[X]Other sudden death, cause unknown	statement of death
217556	RyuC000	[X]Sudden infant death syndrome	death of baby
219023	U2...13	[X]Suicide	suicide
218674	TGyz400	Accidentally killed NOS	statement of death
278563	94...11	Administration after pat. died	statement of death
205711	9454	Ask for hosp death disch lett.	statement of death
278567	9452	Await hosp death disch letter	statement of death
241921	94B..00	Cause of death	statement of death
214706	947..00	Cause of death clarif. SD17/18	statement of death
307873	941..11	Certificate - death	statement of death
260298	94B..11	Condition fatal-cause of death	statement of death
219554	L0010GP	CORONER REFERRED TO	statement of death
260291	9433	Coroner report - paid for	statement of death
260290	9431	Coroner report - requested	statement of death
278565	9432	Coroner report - sent off	statement of death
251110	9441	Coroner's PM report awaited	statement of death
214704	944Z.00	Coroner's PM report NOS	statement of death
278566	9443	Coroner's PM report received	statement of death

251111	9442	Coroner's PM report requested	statement of death
223731	944..00	Coroner's post-mortem report	statement of death
266439	795 C	COT DEATH	death of baby
269509	9482	Crem. form part B completed	statement of death
214707	9483	Crem. form part C arranged	statement of death
205712	9484	Crem. form part C completed	statement of death
223733	948..00	Cremation certification	statement of death
214708	948Z.00	Cremation certification NOS	statement of death
342841	94E..00	Date of death	statement of death
287730	949..11	Dead - place patient died	statement of death
223734	9498	Dead on arrival at hospital	statement of death
230556	22J..12	Death	statement of death
237692	T140 F	DEATH	statement of death
296898	94...00	Death administration	statement of death
232867	94Z..00	Death administration NOS	statement of death
202781	9681D	DEATH ANAESTHETIC	statement of death
256083	T140 FH	DEATH AT HOME	statement of death
205709	9411	Death cert. Med A due	statement of death
278564	941Z.00	Death cert. Med A NOS	statement of death
241918	9412	Death cert. Med A signed	statement of death
214702	941..00	Death certificate form Med A	statement of death
253054	L39B.00	Death from sequelae of direct obstetric causes	death of mother
223678	8HG..11	Death in hospital	statement of death
283503	T140 FP	DEATH IN HOSPITAL	statement of death
214705	9451	Death notif. from hospital	statement of death
251112	946..00	Death notif.- non.hosp source	statement of death
253053	L39A.00	Death obst cse occur more 42 day less than one yr aft deliv	death of mother
266987	13M2.00	Death of infant	death of baby
260294	949..12	Deceased - place patient died	statement of death
229519	662 N	DELIVERY DEATH DUE ANAESTHETIC	death of mother
211371	661 DH	DELIVERY SUDDEN DEATH (MOTHER)	death of mother
212395	22J..13	Died	statement of death
302004	T1400M	DIED	statement of death
260295	949..13	Died - place patient died	statement of death
269465	8HG..00	Died in hospital	statement of death
284701	795 DR	DROPPED DEAD	statement of death
217383	Q016.11	Fetus affected by maternal death	death of mother
253824	Q016.00	Fetus or neonate affected by maternal death	death of mother
305437	7962	FOUND DEAD	statement of death
251118	9499	Found dead at accident site	statement of death
254742	T0y0.00	Found dead on railway right-of-way unspecified	statement of death
209258	T0y0y00	Found dead on railway unspecified - other spec person	statement of death
245503	T0y0100	Found dead on railway unspecified - passenger	statement of death
291285	T0y0200	Found dead on railway unspecified - pedestrian	statement of death
273081	T0y0z00	Found dead on railway unspecified - unspecified person	statement of death
251103	9234	FP22-death	statement of death
223732	945Z.00	Hospital death disch. NOS	statement of death
232864	945..00	Hospital death discharge notif	statement of death
340888	94D..00	Hospital notified of death	statement of death

290473	Q4z..11	Infant death	death of baby
245500	T053.00	Killed by rolling stock	statement of death
227366	T053y00	Killed by rolling stock - other specified person	statement of death
282113	T053100	Killed by rolling stock - passenger	statement of death
236409	T053300	Killed by rolling stock - pedal cyclist	statement of death
209256	T053200	Killed by rolling stock - pedestrian	statement of death
300566	T053000	Killed by rolling stock - railway employee	statement of death
291278	T053z00	Killed by rolling stock - unspecified person	statement of death
205710	9413	Med A given to family	statement of death
287729	9414	Med A not signed-coroner case	statement of death
266336	7789ND	NEONATAL DEATH	death of baby
281331	Q4z..12	Neonatal death	death of baby
244660	Q4z..13	Newborn death	death of baby
248767	22J..00	O/E - dead	statement of death
294585	22J..11	O/E - dead - condition fatal	statement of death
257956	22J5.00	O/E - dead - cot death	death of baby
239551	22J2.00	O/E - dead - expected	statement of death
248769	22J4.00	O/E - dead - sudden death	statement of death
285439	22J6.00	O/E - dead - suspicious death	statement of death
248768	22J3.00	O/E - dead - unattended death	statement of death
267185	22J1.00	O/E - dead - unexpected	statement of death
221486	22JZ.00	O/E - dead NOS	statement of death
203432	2329	O/E - death rattle	statement of death
248776	236..12	O/E - respiratory death	statement of death
253055	L39X.00	Obstetric death of unspecified cause	death of mother
203428	22J..14	Patient died	statement of death
292688	T400	PATIENT DIED	statement of death
214709	949..00	Patient died - to record place	statement of death
287731	9491	Patient died at home	statement of death
342243	949B.00	Patient died in community hospital	statement of death
344547	949C.00	Patient died in GP surgery	statement of death
223735	949A.00	Patient died in hospice	statement of death
269510	9495	Patient died in hospital	statement of death
260296	9493	Patient died in nursing home	statement of death
251116	9492	Patient died in part 3 accom.	statement of death
296900	949Z.00	Patient died in place NOS	statement of death
232866	9497	Patient died in publ.place NOS	statement of death
251117	9494	Patient died in resid.inst.NOS	statement of death
278568	9496	Patient died in street	statement of death
241920	9481	Patient for cremation	statement of death
263052	Q4z..14	Perinatal death	death of baby
214710	949..14	Place of death	statement of death
260299	94C..00	Post mortem report	statement of death
214711	94C0.00	Post mortem report received	statement of death
301899	L 917PM	POST MORTEM REPORT RECEIVED	statement of death
296484	7L1M000	Preoperative anaesthetic death	statement of death
260292	9453	Receiv hosp death disch letter	statement of death
296901	94A..11	Referral to coroner	statement of death
256003	L0010GN	REFERRED TO CORONER	statement of death
251109	943..00	Report for Coroner	statement of death
214703	943Z.00	Report for Coroner NOS	statement of death
283395	L 917WD	REPORT RECEIVED FROM CORONER	statement of death

251113	947..11	SD17 - cause of death clarif	statement of death
232865	947Z.00	SD17/18 cause of death NOS	statement of death
251115	9472	SD17/18 completed	statement of death
251114	9471	SD17/18 received-death clarif.	statement of death
241919	9473	SD17/18-no details, returned	statement of death
260293	947..12	SD18 - cause of death clarif	statement of death
296899	948..11	Stat B,C and F cremation certs	statement of death
289080	G575100	Sudden cardiac death, so described	statement of death
210633	T4002	SUDDEN DEATH	statement of death
275218	661 DN	SUDDEN DEATH CHILDBIRTH CAUSE UNKNOWN	death of mother
307376	795 B	SUDDEN DEATH INFANT SYNDROME	death of baby
305432	795 N	SUDDEN DEATH NONVIOLENT	statement of death
275223	6770AD	SUDDEN DEATH PUERPERIUM CAUSE UNKNOWN	death of mother
265290	T1400SI	SUDDEN INFANT DEATH	death of baby
294371	13M3.00	Sudden infant death	death of baby
303412	3009D	SUICIDE	suicide
264375	TK3z.00	Suicide + selfinflicted inj by hang/strangle/suffocate NOS	suicide
264374	TK3y.00	Suicide + selfinflicted inj oth mean hang/strangle/suffocate	suicide
264374	TK3y.00	Suicide + selfinflicted inj oth mean hang/strangle/suffocate	suicide
209725	TKx0z00	Suicide + selfinflicted inj-jump/lie before moving obj NOS	suicide
218755	TK3..00	Suicide + selfinflicted injury by hang/strangulate/suffocate	suicide
273558	TK31.00	Suicide + selfinflicted injury by suffocation by plastic bag	suicide
264378	TKx0.00	Suicide + selfinflicted injury-jump/lie before moving object	suicide
245970	TKx0000	Suicide + selfinflicted injury-jumping before moving object	suicide
301075	TKx0100	Suicide + selfinflicted injury-lying before moving object	suicide
291736	TK06.00	Suicide + selfinflicted poisoning by agricultural chemical	suicide
209722	TK00.00	Suicide + selfinflicted poisoning by analgesic/antipyretic	suicide
209722	TK00.00	Suicide + selfinflicted poisoning by analgesic/antipyretic	suicide
227822	TK08.00	Suicide + selfinflicted poisoning by arsenic + its compounds	suicide
264370	TK01.00	Suicide + selfinflicted poisoning by barbiturates	suicide
264370	TK01.00	Suicide + selfinflicted poisoning by barbiturates	suicide
264371	TK07.00	Suicide + selfinflicted poisoning by corrosive/caustic subst	suicide
264372	TK1z.00	Suicide + selfinflicted poisoning by domestic gases NOS	suicide
236844	TK05.00	Suicide + selfinflicted poisoning by drug or medicine NOS	suicide
236844	TK05.00	Suicide + selfinflicted poisoning by drug or medicine NOS	suicide

301069	TK10.00	Suicide + selfinflicted poisoning by gas via pipeline	suicide
218754	TK2z.00	Suicide + selfinflicted poisoning by gases and vapours NOS	suicide
236845	TK1..00	Suicide + selfinflicted poisoning by gases in domestic use	suicide
301070	TK11.00	Suicide + selfinflicted poisoning by liquified petrol gas	suicide
273557	TK20.00	Suicide + selfinflicted poisoning by motor veh exhaust gas	suicide
301067	TK02.00	Suicide + selfinflicted poisoning by oth sedatives/hypnotics	suicide
301067	TK02.00	Suicide + selfinflicted poisoning by oth sedatives/hypnotics	suicide
282596	TK04.00	Suicide + selfinflicted poisoning by other drugs/medicines	suicide
282596	TK04.00	Suicide + selfinflicted poisoning by other drugs/medicines	suicide
245968	TK2y.00	Suicide + selfinflicted poisoning by other gases and vapours	suicide
291737	TK2..00	Suicide + selfinflicted poisoning by other gases and vapours	suicide
301068	TK0z.00	Suicide + selfinflicted poisoning by solid/liquid subst NOS	suicide
273554	TK0..00	Suicide + selfinflicted poisoning by solid/liquid substances	suicide
273554	TK0..00	Suicide + selfinflicted poisoning by solid/liquid substances	suicide
282595	TK03.00	Suicide + selfinflicted poisoning tranquilliser/psychotropic	suicide
282595	TK03.00	Suicide + selfinflicted poisoning tranquilliser/psychotropic	suicide
255198	TK...14	Suicide and self harm	suicide
255198	TK...14	Suicide and self harm	suicide
301065	TK01000	Suicide and self inflicted injury by Amylobarbitone	suicide
273555	TK01100	Suicide and self inflicted injury by Barbitone	suicide
236843	TK01z00	Suicide and self inflicted injury by barbiturates	suicide
218753	TK01200	Suicide and self inflicted injury by Butabarbitone	suicide
273556	TK01300	Suicide and self inflicted injury by Pentabarbitone	suicide
255199	TK01400	Suicide and self inflicted injury by Phenobarbitone	suicide
301066	TK01500	Suicide and self inflicted injury by Quinalbarbitone	suicide
291735	TK...00	Suicide and selfinflicted injury	suicide
291735	TK...00	Suicide and selfinflicted injury	suicide
255203	TKx1.00	Suicide and selfinflicted injury by burns or fire	suicide
255203	TKx1.00	Suicide and selfinflicted injury by burns or fire	suicide
209726	TKx5.00	Suicide and selfinflicted injury by crashing motor vehicle	suicide
209727	TKx6.00	Suicide and selfinflicted injury by crashing of aircraft	suicide

291738	TK60.00	Suicide and selfinflicted injury by suicide cutting
291738	TK60.00	Suicide and selfinflicted injury by suicide cutting
264377	TK6..00	Suicide and selfinflicted injury by suicide cutting and stabbing
264377	TK6..00	Suicide and selfinflicted injury by suicide cutting and stabbing
273560	TK6z.00	Suicide and selfinflicted injury by suicide cutting and stabbing NOS
282597	TK4..00	Suicide and selfinflicted injury by suicide drowning
273561	TKx4.00	Suicide and selfinflicted injury by suicide electrocution
209723	TK55.00	Suicide and selfinflicted injury by suicide explosives
227825	TKx3.00	Suicide and selfinflicted injury by suicide extremes of cold
218756	TK5..00	Suicide and selfinflicted injury by suicide firearms and explosives
209724	TK5z.00	Suicide and selfinflicted injury by suicide firearms/explosives NOS
282598	TK50.00	Suicide and selfinflicted injury by suicide handgun
264373	TK30.00	Suicide and selfinflicted injury by suicide hanging
264373	TK30.00	Suicide and selfinflicted injury by suicide hanging
236846	TK52.00	Suicide and selfinflicted injury by suicide hunting rifle
255202	TK7..00	Suicide and selfinflicted injury by suicide jumping from high place
255200	TK53.00	Suicide and selfinflicted injury by suicide military firearms
264376	TK54.00	Suicide and selfinflicted injury by suicide other firearm
301074	TKx..00	Suicide and selfinflicted injury by suicide other means
227826	TKxz.00	Suicide and selfinflicted injury by suicide other means NOS
255205	TKxy.00	Suicide and selfinflicted injury by suicide other specified means
255204	TKx2.00	Suicide and selfinflicted injury by suicide scald
273559	TK51.00	Suicide and selfinflicted injury by suicide shotgun
273559	TK51.00	Suicide and selfinflicted injury by suicide shotgun
301073	TK61.00	Suicide and selfinflicted injury by suicide stabbing
301073	TK61.00	Suicide and selfinflicted injury by suicide stabbing
209728	TKx7.00	Suicide and selfinflicted injury suicide caustic subst, excl poison
273562	TKz..00	Suicide and selfinflicted injury suicide NOS
273562	TKz..00	Suicide and selfinflicted injury suicide NOS

301072	TK21.00	Suicide and selfinflicted poisoning by other carbon monoxide	suicide
301071	TK1y.00	Suicide and selfinflicted poisoning by other utility gas	suicide
227824	TK7z.00	Suicide+selfinflicted injury-jump from high place NOS	suicide
236847	TK72.00	Suicide+selfinflicted injury-jump from natural sites	suicide
291739	TK71.00	Suicide+selfinflicted injury-jump from oth manmade structure	suicide
227823	TK70.00	Suicide+selfinflicted injury-jump from residential premises	suicide
260297	94A..00	Unexpected death-Coroner told	statement of death
305438	7963	UNKNOWN CAUSE DEATH	statement of death
246910	T4001	VIOLENT DEATH	statement of death