WP2 Framework for pharmacoepidemiological studies

WG1 Databases

Study Protocol

Use of Antidepressants and risk of hip/femur fracture. A methodological comparison across data sources and epidemiological design.

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WG1 Drug AE group

Name	Role
Helga Gardarsdottir [1]	Protocol lead (from 5 Sept 2012)
Victoria Abbing [1]	Protocol backup
Marieke De Bruin [1]	Protocol reviewer
Liset van Dijk [1,2]	Protocol reviewer
Montserrat Miret [3]	Protocol reviewer
Frank de Vries [1]	Protocol reviewer
Marietta Rottenkolber [4]	Database 1 (Bavaria) lead
Joerg Hasford [4]	Database 1 (Bavaria) backup
Miguel Gil [5]	Database 2 (Bifap) lead
Consuelo Huerta [5]	Database 2 (Bifap) backup
Ulrik Hesse[6]	Database 3 (DKMA) lead
Frank de Vries[1]	Database 3 (DKMA) backup
Dan Dedman /Jenny Campbell [7]	Database 4 (GPRD) lead/backup
Olaf Klungel [1]	Database 5 (Mondriaan) lead
Liset van Dijk [1, 2]	Database 5 (Mondriaan) backup
Yolanda Alvarez [8]	Database 6 (THIN) lead
Ana Ruigomez [9]	Database 6 (THIN) backup
Mark de Groot[1] and Raymond Schlienger[10]	WG1 colead
Olaf Klungel[1] and Robert Reynolds[11]	WP2 coleads

[1] Universiteit Utrecht, Utrecht, The Netherlands (UU)
[2] Netherlands Institute for Healthcare Research, Utrecht, The Netherlands (NIVEL)
[3] Merck KGaA, Geneva, Switzerland (ME)
[4] Ludwig-Maximilians-Universität-München, Munich, Germany (LMU- Muenchen)
[5] Agencia Espanola de Medicamentos y Productos Sanitarios, Madrid, Spain (AEMPS)
[6] Lægemiddelstyrelsen (Danish Medicines Agency), Copenhagen, Denmark (DKMA)
[7] General Practice Research Database, London, United Kingdom (GPRD)
[8] European Medicines Agency, London, United Kingdom (EMA)
[9] Fundación Centro Español de Investigación Farmacoepidemiológica, Madrid, Spain (CEIFE)
[10] Novartis Pharma, Basel, Switzerland (Novartis)
[11] Pfizer Ltd, New York, USA (Pfizer)

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1 Context of the studies and objective

The studies described in this protocol are all performed within the framework of PROTECT (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium) Workpackage 2 and Workgroup 1. Primary aim of these studies is to develop, test and disseminate methodological standards for the design, conduct and analysis of Pharmacoepidemiological (PE) studies applicable to different safety issues and using different data sources. To achieve this, results from PE studies on five key adverse events (AEs) performed in different databases will be evaluated. Therefore, emphasis will be on the methodological aspects of the studies in this protocol and not on the clinical consequences of the association under investigation. The developed framework will contribute to decrease the discrepancies in results from different studies in the future and increase the usefulness and reliability of these studies for benefit-risk assessment in the EU.

This protocol describes the designs and the conduct of studies on the use of Antidepressants (AD) and hip/femur fracture, one of the five selected drug-AEs, in four databases.

2 Background

Fracture of the proximal end of the femur or hip is associated with considerable morbidity and mortality **(1)**. Hip/femur fractures impair quality of life and impose a considerable economic burden **(2)**, and occur with 20% mortality rate within the first year **(3)**. Antidepressants (AD), mainly tricyclic AD (TCAs) and selective serotonin re-uptake inhibitors (SSRIs) have been associated with fractures in several studies. A review of 13 observational studies **(4)** showed risk ratios ranging from 1.2 to 3.7 for current TCA users and a wide range of 1.5 to 8.6 for SSRI users. The majority of the studies in the aforementioned review reported increased risks of fractures in general with SSRIs use and more mixed risk outcomes for TCA use. Several mechanisms underlying this adverse effect have been postulated in the literature: e.g. through decrease in bone mineral density (BMD) **(5)** or through blocking the serotonin transporter activity (5-hydroxytryptamine re-uptake) and hence affecting bone metabolism and structure **(6)** or simply by falling **(7)** or through co-morbidities such as depression itself. Previous observational studies differ in design, conduct and analysis of the considered association with varying degree of accounting for confounders. Confounding factors such as depression and other co-morbidities, previous fractures, concomitant drug use and lifestyle factors such as smoking have usually not been accounted for in most of the studies **(4)**. In addition, small sample size, different methods used to ascertain exposure, selection bias and lack of data on compliance as well as important covariates limit the use of these results in benefit-risk analyses. Furthermore, studies evaluating different types of SSRI and TCA are few and dose-response relationship for most of the AD remains to be studied. We will study effects of cumulative exposure focusing on acute (less than 6 months) and long term exposure (at least 5 years) and doses of exposure.

3 Objectives

To assess the association between AD use and hip/femur fracture using different study designs (descriptive, cohort, nested case-control and case crossover) across different databases (Bavarian, Mondriaan, BIFAP and THIN) and to compare the results between and across databases and designs. This is to evaluate the impact of design/database /population difference in the outcome of the studies association.

4 Methods

4.1 Data sources

The databases where the proposed studies are to be implemented are described in the manuscript “Bridging differences in the outcome of PE studies: The PROTECT project” (submitted for publication). Here we give relevant characteristics of these databases.

4.2 The Health Improvement Network (THIN)

The Health Improvement Network (THIN) is a collaboration between two companies; In Practice Systems Ltd. (INPS), developer of Vision software used by general practices in the UK, and EPIC, provider of access to data for use in medical research. THIN data are collected during routine medical practice and regularly delivered to a central database. THIN data collection prospectively started in 2003, although all prior computerized data were extracted from each practice since they started medical record computerization. It currently contains the electronic medical records of almost 8 million patients (more than 3 million active patients) collected from over 386 general practices in the UK. THIN database consequently covers more than 5.7% of the UK population. Patient data are arranged in five standardised files per practice: patient, medical, therapy, additional health data and a file to enable data linkage containing postcodes. Additional data can be collected using the Additional Information Service which includes: questionnaires completed anonymously by the patient or general practitioner, copies of patient-related correspondence, a specified intervention (e.g. a laboratory test to confirm a diagnosis) and death certificates.

4.3 Mondriaan

The Dutch Mondriaan project is a private-public collaboration funded by the Dutch TOP Institute Pharma. Under the umbrella of Mondriaan, the participating databases currently include: the Dutch General Practitioner (LINH) database, The Almere Health Care (ZGA) database, The General Practitioners of Utrecht (HNU) database and The Leidsche Rijn Julius Health Centre (LRJG) database. The cumulative number of persons having data in Mondriaan reached around 1.4 million comprising mainly of general practitioner (GP) data complemented by pharmacy dispensing data and linkages to survey data. The four databases within Mondriaan have different starting dates and scope of data. LINH is the Netherlands Information Network of General Practice and it holds a longitudinal data on morbidity, prescription, and referrals. The GPs record data on all patient contacts, including diagnoses, referrals and prescriptions. The ZGA is a GP and pharmacy database. The HNU is a GP database set up in 1995 and includes data dating till the end of 2005. The LRJG is a GP database with a linkage to additional survey records. Survey information is periodically up-dated through follow-up, including information on a wide range of health and lifestyle related variables.

4.4 BIFAP

BIFAP (Base de Datos para la Investigación Farmacoepidemiológica en Atencion Primaria), a computerised database of medical records of Primary Care) (14) is a non-profit research project operated by the Spanish Medicines Agency (AEMPS), a public agency belonging to the Spanish Department of Health, with the collaboration of the Spanish Centre for Pharmacoepidemiological Research (CEIFE). The project has started in 2001 having the goal to achieve a pool of collaborators in the range of 1000 general practitioners and paediatricians. Currently, 1190 physicians (995 GPs and 195 paediatricians) from 9 different autonomous communities in Spain collaborate with BIFAP and send their data to BIFAP every 6 months. BIFAP database includes clinical and prescription data from around 3.1 million patients covering around 6.8% of the Spanish population. The AEMPS has renewed its funding to BIFAP for project consolidation, for validation of information included in the databases, in addition to performing epidemiological studies.

4.5 Bavaria database

The Bavarian statutory health insurance physicians' association is based on accounting information of the Bavarian physicians. This German database includes a population-based data on diagnosis and medical services, covering 10.5 million people. It is a pharmacy (claims) database linked to outpatient treatment data through general practitioners and specialists. The database exists since 2001 and covers 84% of the Bavarian population excluding those with private insurance. A population-based study on asthma treatment resistance is done using this database(15).

4.6 National Databases (Denmark)

The Danish registries include computerized medical records of general practitioners and all hospital contacts, medication use, and causes of death for the entire population (5.5 million inhabitants). The National Bureau of Statistics keeps computerized records of income, degree of education, working status, and civil status. The

Ministry of Interior keeps records of all inhabitants and their migrations and date of birth and death. The information on outcomes will come from the National Hospital Discharge Register [22]. The National Hospital Discharge Register was founded in 1977. It covers all inpatient contacts from 1977 to 1994 and from 1995 also all outpatient visits to hospitals, outpatient clinics, and emergency rooms. Upon discharge, the physician codes the reason for the contact using the ICD system. The code used is at the discretion of the individual physician. The register has a nationwide coverage and an almost 100% capture of contacts. In general, the validity of registrations is high [23]. The National Health Service keeps a register of all contacts to general practitioners for reimbursement purposes. The register does not contain ICD codes for the contacts but codes for the nature of the contact (regular check-up visit, routine vaccination in children).
The Danish Medicines Agency keeps a nationwide register of all drugs sold at pharmacies throughout the country from 1996 onward (National Pharmacological Database run by the Danish Medicines Agency [24]). Any drug bought is registered with ATC code, dosage sold, and date of sale for the period January 1, 1996, to December 31, 2009. As all sales are registered to the individual who redeemed the prescription, the capture and validity are high.
All registers can be linked through the use of a person specific code (the civil person number) given to all inhabitants, and used for all of the registrations mentioned before. The validity of fracture reports in general is high (around 97%, although differences may exist between different fracture types).

4.7 General Practice Research Database (UK)

The General Practice Research Database (GPRD) comprises computerized medical records of general practitioners (GPs) from 1987 onwards. The database contains data from over 600 practices based throughout the United Kingdom, providing information on 12.5 million patients, of which 5 million are currently active. The data covers 8% of the population. GPs play a gatekeeper role in the UK health care system, as they are responsible for primary health care and specialist referrals. Patients are affiliated to a practice, which centralizes the medical information from the GPs, specialist referrals, hospitalisations and tests. The data recorded in the GPRD include demographic information, prescription details, clinical events, preventive care provided, specialist referrals, laboratory results, hospital admissions and death. Many practices are entirely paperless and have included key historical events prior to 1987 in a patient's record. The validity of a wide range of drug exposure data is routinely tested. Practices that want to contribute data to GPRD are carefully selected and trained in the software used to record medical data. Only those practices that meet quality standards are then used for research (about 10% of the practices that send data to GPRD do not meet the quality standards). Furthermore, validation studies are conducted regularly by comparing GPRD data to written notes of general practitioners. Recent additions to the database include external record linkage to other National Health Services (NHS) datasets, such as the national Hospital Episode Statistics (with extended data on all hospitalisations) and Death Certificates, increased availability of free text information via new automated system, the possibility of genetic linkage studies, prospective data collections such as questionnaires, copies of patient–based correspondence, the conduct of multi-country studies, and performing randomization studies within the database.

4.8 Period of valid data collection

Each data source has a period of valid data collection, from the left censoring date, up to the right censoring date. For the proposed studies, we will consider the study period from 1 January 2001 to 31 December 2009 for all the databases (see table 1). See figure 1 for a schematic diagram for valid data period.

4.9 THIN/Mondriaan/BIFAP

The left censoring date is the *latest* of the following:
the date that a practice was enrolled into the database and became up to research standard (THIN/BIFAP/Mondriaan),
the date that a patient enrolled into a practice
the date that the practice started computerized records (THIN)

January 1, 2001 (Mondriaan/BIFAP/THIN)

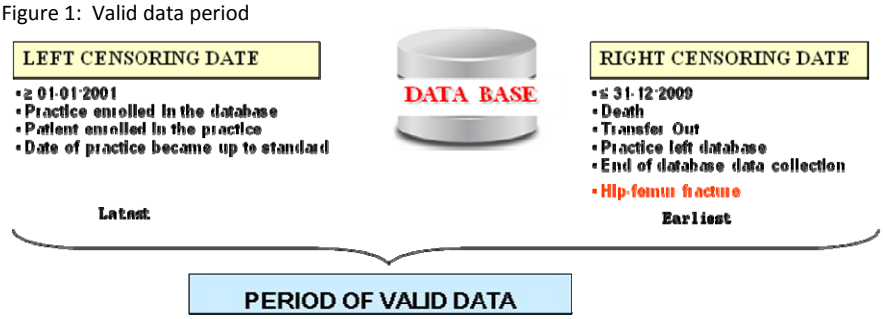
The right censoring date is the *earliest* of the following:
the date a patient died,
the date a patient was transferred out of the practice,
the end of the database data collection,
the date that the practice left the database or
the latest recorded event date (Mondriaan, BIFAP)
December 31, 2009

As deaths may not be always well recorded in Mondriaan and BIFAP; we will right censor patients in these databases on patient's latest recorded event date.

4.10 Bavarian claims

The left censoring date is the earliest event that is recorded for an individual patient (prescription, diagnosis or lab test) after January 1, 2001. The right censoring date is the latest event that is recorded for an individual patient (prescription, diagnosis or lab test) before December 31, 2009. Death is not well recorded in the Bavarian claims data.

Figure 1: Valid data period



5 Study Designs

The PE studies exploring methodological issues related to the use of AD and hip/femur fracture will be conducted in different databases using different designs. The studies (designs and databases) have been prioritized and are listed in Table 1. The databases are: The Dutch Mondriaan, The British THIN, The German Bavarian Claims and The Spanish BIFAP databases.

Table 1. List of study designs to be conducted in each datasource

Study designs	Datasource
Descriptive	Bavaria
Descriptive	BIFAP
Descriptive	DKMA

Descriptive	GPRD
Descriptive	Mondriaan
Descriptive	THIN
Cohort	Bavaria
Cohort	BIFAP
Cohort	Mondriaan
Cohort	THIN
Nested case control	Bavaria
Nested case control	BIFAP
Nested case control	Mondriaan
Nested case control	THIN
Case crossover	BIFAP
Case crossover	Mondriaan
Case crossover	THIN

5.1 Descriptive studies

The descriptive studies are based on the guidelines for descriptive studies issued on November 2nd 2011

5.2 Study population and period

The study population will consist of all patients included in the period of valid data collection (section 4.2 and Figure 1). The study period will be defined from January 1, 2001 to December 31, 2009. Information on the use of AD and occurrence of hip/femur fracture will be obtained from individual databases comprising of medical records of GPs and/or claims data where prescription and diagnosis data are recorded.

5.3 Exposure description

Exposure to AD (Annex I , Table 2) will be described in terms of age in ten –year categories (0-9, 10-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80-89, 90+) and gender across the 9-year time period (1 January 2001 until 31 December 2009) for the participating databases. Therefore exposure will be defined as follows:

Period prevalence of ever drug use for the 9 years (2001-2009).

Period prevalence for each year from 2001 to 2009.

Point prevalence for each year, from 2001 to 2009, at 1 June of the calendar year stratified by age and gender.

Prevalence of ever use by indication for each year from 2001 to 2009. Indication will be classified as (see Annex II Table 5 for codes):

anxiety alone and anxiety /panic related disorders such as, panic disorders, agoraphobia, stress related symptoms and fear

sleep disorders

depression

others

unknown

Prevalence of ever use by number of prescriptions for each year from 2001 to 2009. The following categories will be used: 1 prescription, 2-4 prescriptions, 5-11 prescriptions and >12 prescriptions.

Definitions:

For 1 and 2: Period prevalence for the 9 years, and for each year from 2001 to 2009, will be calculated by age and sex.

The numerator will be:

The total number of patients with at least one prescription during the whole period (2001-2009) and in each year. and the total number of patients present at mid-year (June) in the denominator. When a prescription overlaps over two consecutive years, it will only be counted once, corresponding to the year in which the prescription was filled.

The denominators will be:

Preferred : number of people present in the database at midyear (June 1)

If possible (extra): number of person-years in the study period, overall and each age and sex specific categories.

Alternative 1 (if preferred is not possible): If mid-year is not possible, number of people at 1 January.

Alternative 2 (if alternative 1 is not possible): Total number of people in geographically defined catchment area.

Results will be per 10,000 patients (and per 10,000 person-years).

For 3: Point prevalence will be calculated using the number of patients in the database at June 1 of each year.

The numerator will be:
Current users of AD on this day. For this descriptive study a current user will be patient with a prescription of AD within 90 days before June 1 of each year, assuming duration of a supply as 90 days.
Results will be per 10,000 patients.

The prevalence rates for AD will be calculated for the following groups separately (see section 9.1 table 1 for drug codes): SSRIs, TCAs and SSRI or TCAs.

For 4: The indication is defined in association with the first prescription in the year of interest (independent of potential changes of the indication throughout the year). Indication is estimated only once (first prescription issued) per year. It will be defined and calculated as follows:

1. Period prevalence by year from 2001 to 2009 stratified by indication.

The numerator will be:
Ever users of AD in each category of indication associated to the fist prescription in the year of interest.

The denominators will be:

Preferred: number of people that are present in the database at mid-year (June 1).
if possible (extra): number of person-years in the study period.
Alternative 1 (if preferred is not possible) : If mid-year is not possible, number of people at 1 Jan.
Alternative 2 (if preferred is not possible) : Total number of people in geographically defined catchment area.

Results will be per 10,000 patients (and per 10,000 person-years if denominator 2 is used).

2. *Point prevalence* by year from 2001 to 2009 stratified by indication
will be calculated using the number of patients in the database at June 1 of each year.

The numerator will be:

Current users on this day stratified by indication. For this descriptive study, current user will be considered as patients with a prescription of AD within 90 days before June 1 of each year, assuming duration of a supply as 90 days.

Definition for categories of indication:
Prevalence of AD ever used by indication will be assessed using the specific link between indication and prescriptions if it exists, and if not, this will be assessed by searching for specific codes or free text any time before of the prescription of interest (first prescription in the year of interest or "current" prescriptions at June 1 for point prevalence). Classification of indication for the descriptive study will be done according to the following categories (see codes under anxiety disorders, sleep disorders, depression and other in Annex II, Table 5)**:**

Anxiety disorders (alone or with any other indication but without depression)
Sleep disorders (alone or with any other indication but neither anxiety nor depression)
Depression (with any, or both, of the following: anxiety and sleep disorders)
Depression (alone or with any indication under "Others")
Others
Unknown

For 5: Period prevalence for each year from 2001 to 2009 stratified by number of prescriptions.

The numerator will be:
Ever users of AD in each category in the year of interest. The following categories will be used for number of prescriptions: 1 only, 2-4, 5-9, >or =10. When a prescription overlaps over two consecutive years, it will only be counted once, corresponding to the year in which the prescription was filled.

The denominators will be:

Preferred: number of people that are present in the database at mid-year (1 July).
If possible (extra): number of person-years in the study period.
Alternative 1(if preferred not possible): If mid-year is not possible, number of people at 1 Jan.
Alternative 2 (if alternative 1 not possible): Total number of people in geographically defined catchment area

Results will be per 10,000 patients (and per 10,000 person-years if denominator 2 is used).

5.4 Outcome description

Prevalence of the (lifetime) hip/femur fracture by sex and age over the first year

Prevalence for hip/femur fractures (Annex I, Tables 3 and 4) will be described in terms of gender and age in ten-year categories (0-9, 10-19, 20-29, 30-39, 40-49, 50-59, 60-69,70-79, 80-89, 90+).

The first year for reporting prevalence is the calendar year that starts after at least one year of valid data collection. For example: period prevalence of the lifetime outcome should be reported for the period from Jan 1, 2002 to Dec 31, 2002, assuming that the database came 'up to research standards' before Jan 1, 2002..

Prevalence of the (lifetime) hip/femur fractures for the selected reporting year by age and sex.

The numerator will include both, hip/femur fractures first ever recorded in the selected calendar year and hip/femur fractures previously recorded in the database, stratified by gender and age in ten year categories.

The denominators will be:

Preferred: number of people that are present in the database at mid-year (June 1).
Alternative1 : If mid-year is not possible, number of people at 1 Jan.
Alternative 2: Total number of people in geographically defined catchment area.

Results will be per 10,000 patients.

(Cumulative) incidence of hip/femur fracture by sex and age per year

Incidence for hip/femur fractures (Annex I, Tables 3 and 4).will be described in terms of gender and age in ten-year categories (0-9, 10-19, 20-29, 30-39, 40-49, 50-59, 60-69,70-79, 80-89, 90+). Yearly incidence of first time ("first ever") hip/femur fractures in patients within databases will be calculated starting in 1 January after the year for prevalence computation.

The numerator will be:

First time ("first ever") recorded cases of hip/femur fracture in each year. The age of a patient will be computed as the age at midyear when the outcome occurs.

The denominators will be:

Preferred: number of people that are present in the database at start (1 January) of the corresponding year for calculate incidence and who do not have a recorded history of the event of interest prior to Jan 1 of this year. Age of patients will be compute at midyear.
If possible (extra): total person-year of patients who do not have a recorded history of the event of interest prior to Jan 1 of this year. Age of patients will be compute at midyear.

Results will be per 10,000 patients (or 10,000 person-years if denominator 2 is used).

5.5 Analytical studies

In order to harmonize the different observational study design, the study population, the exposure and the case definition will be included in this paragraph in a general section, as they are common to all the designs. Individual designs in later sections will add specific parts relevant to each of the designs.

5.6 Study population and study period

From the source population that comprised all patients included in the period of valid data collection, all patients who have at least one year of enrolment with the GP, are ≥ 18 years and have at least one

antidepressant prescription (see Annex I, Table 2 for drug codes) will be selected. The date of the AD prescription will be the index date.

Patients with a prescription of AD within 6 months before index date will be excluded to restrict the analysis to new users only.

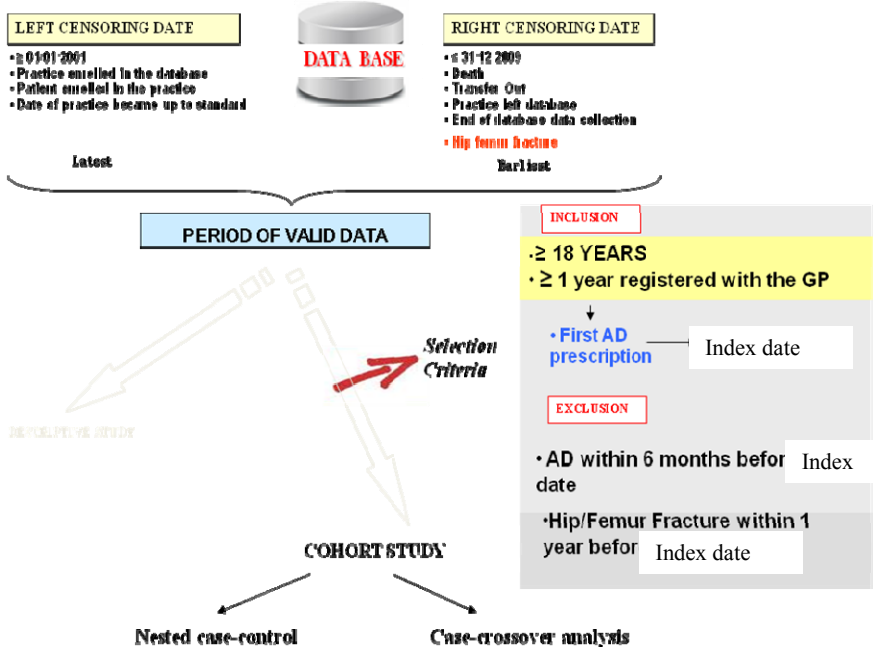
The remaining patients after inclusion and exclusion criteria will define the study cohort. Patients with missing information on sex and age will be excluded. The number of excluded patients with the accompanying recorded reason for exclusion will be reported in a flowchart.

See section 4.2 for description of the valid data period and figure 2 for description of the study population for the analytical studies

The study period will be defined from 1 January 2001 to 31 December 2009.
Information on the use of AD and occurrence of hip/femur fracture will be obtained from individual databases comprising of medical records of GPs and or claims data where prescription and diagnosis data are recorded.

Three designs will be adopted to study the association of AD and hip/femur fracture. Below are the common descriptions of exposure, outcome and confounding factors, followed by design-specific methods.

Figure 2. Period of valid data collection and study population for the analytical studies.



5.7 Outcome definition

The outcome of interest includes hip/femur fractures as follows.

Hip/femur fracture*: all patients* of the study population with a record/diagnosis of a first fracture of the hip or femur during the study period regardless of whether they have a history of past fractures. When the

patient has a history of hip or hip/femur fracture, a minimum of 12 months should have elapsed between the two episodes for a current fracture to be considered a new event.
Patients with hip or femur fractures who, after the review of their automated clinical records, are shown to have had the fracture as a result of major trauma (e.g., car accident one month before) should be ignored as event of interest and their follow-up will be stopped at the time of the fracture (right-censored).
Hip/femur fractures will be searched in different databases according to respective coding systems mentioned below (section 9.2 tables 1 and 2 for specific codes).

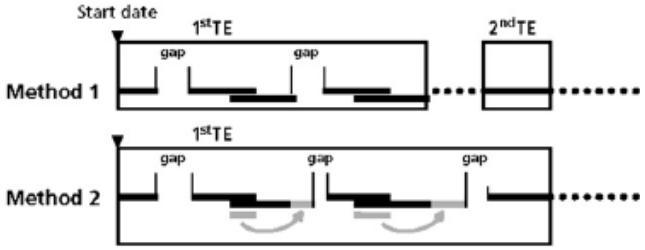
Bavarian database: International Classification of Diseases version 10 (ICD10) (Annex I, Table 2)
THIN database: READ codes. (Annex I tables 3 and 4)
BIFAP and Mondriaan: The International Classification of Primary Care (ICPC-2) (Annex I, Table 2)

5.8 Exposure definition

The duration of antidepressant (see section 9.1 table 1 for drug codes) use will be determined by calculating length of treatment episodes. Treatment episodes will be defined as a series of subsequent prescriptions for AD, independent of switching of type and dose change and should be constructed according to the method of Gardarsdottir et al **(8).**:

In case a subsequent antidepressant prescription with the same drug is collected before the theoretical end date of a previous antidepressant prescription, the number of overlapping days is added to the theoretical end date of the subsequent antidepressant prescription (see figure 3, method 2). If the subsequent prescription is within the same treatment episode included another antidepressant (SSRI or TCA), the patient is considered to have switched therapy and the remaining tablet days from the prior prescription are disregarded (see figure 3, method 1).

Figure 3. Constructing drug treatment episodes based on estimated duration of a dispensed prescription and gaps of a defined length



TE: treatment episode

A new treatment episode will be considered when an interval of 90 days or more occurs between the theoretical end date of a prescription and the dispensing date of the next prescription for the same patient.

In case of missing data on the estimated duration of use, information of the dosing scheme and/or number of prescribed units from the most recent previous prescription (with available data) of the patient will be used to calculate the estimated prescription length. In case this is not possible, the population-mode duration of use [specific for the type (ATC code) and strength of the antidepressant] of the database of interest will be imputed. An overview of all prescriptions with imputed population modes of duration [stratified according to age (20-year categories) and sex] will be reported.

The total exposure time of patients will be divided into periods of current, recent and past use with patients switching between these periods according to drug use:

Current use will be defined when the prescription of AD lasts until 30 days after the estimated end date of the supply. **Recent use** will encompass the period between 1- 60 days after the period of current use. When the gap between two treatment episodes is more than 90 days, a patient will automatically become a **past user**,

from the estimated end date of the treatment episode. The period of past use will be stratified into periods of 182 days, until the patient becomes a current user again, or until the end of valid data collection.
During follow-up the patient is allowed to switch between treatment categories of current use, based on the following characteristics:

Type of medication use (according to ATC and according to group (SSRI or TCA)

Dose: Prescribed daily dose (categorized as <0.5 DDD, ≥0.5 and < 1.0 DDD, ≥1.0 DDD)
Cumulative dose (DDD) of current drug within the current treatment episode treated as continuous as well as categorical variable (DDD < 180, ≥180 and < 365 and ≥365 DDD)
Cumulative dose (DDD) of previous (other) AD (SSRI or TCA) in the same treatment episode treated as continuous as well as categorical variable (DDD<180, ≥ 180 and < 365 and ≥ 365 DDD
Cumulative dose (DDD) of AD (SSRI or TCA) in previous treatment episodes treated as continuous as well as categorical variable (DDD <180, ≥ 180 and < 365 and ≥ 365 DDD)

Comment [v1]: Highlighted area is rephrased for the sake of clarity.

Duration: Among current users the duration of drug use will be calculated by summing the duration(days) of each consecutive prescription of antidepressant within the treatment episode. Four categories will be considered: 0-30 days, 31-180 days, 181-365 days and >365 days. Exposure will be considered to be continuous in case of a gap between consecutive prescriptions of 90 days or less.

Comment [v2]: Calculation of the duration is added since it was missing in the previous version

Indication: Depression /Anxiety/Sleeping disorders/Other/Unknown
The indication is assessed in the physician-patient contact file during the period from 90 days before to 90 days after prescription date. If multiple indications are identified during this period, the indication closest to the prescription date is taken. If no indication is identified in this period, the indication is taken from the most recent previous prescription with available indication.

5.9 Potential confounders

Potential confounders will be measured in a time varying analysis as follows:
All variables will be measured at baseline (in the 6 months prior to inclusion of the patient in the cohort)
Co-morbidity and co-medication variables will be measured/updated every 6 months.

Confounders will be analyzed in four different models:

Basic confounders: age (continuous variable) and sex
Well-established risk factors for fracture available in the datasets: weight, height, BMI, any previous fracture (except fracture due to major trauma), current smoking, alcohol use, glucocorticoids use and rheumatoid arthritis.
Risk factors immediately related to the outcome (and therefore likely to end up in the causal pathway): history of osteoporosis , history of other bone diseases (Paget's disease, osteogenesis imperfect), previous use of bisphosphonate or any of the other bone protecting drugs: raloxifene, Strontium ranelate, Parathyroid hormone, Calcium & vitamin D, Calcitonin, Calcitriol.
Other risk factors that have been associated with fracture in the past:

Over the counter drugs: can be determined in BIFAP database but not in Mondriaan, Bavarian. In THIN only for osteoporotic patients this information can be identified.

Drugs: benzodiazepines, AD other that TCAs or SSRIs, Antipsychotics/lithium, Anti-Parkinson drugs, Anticonvulsants, Inhaled glucocorticoids, Bronchodilators (including Beta-2-adrenoceptors agonist and Anticholinergics), Anti-arrhythmics, Sedating antihistamines, Antihypertensive drugs (including ACE inhibitors, Angiotensin II antagonists, Beta blocking agents, Calcium channel blockers, Other antihypertensives), Diuretics, Estrogen-containing hormone replacement therapy (HRT), Thyroid hormones, Antithyroid drugs, Disease-modifying anti-rheumatic drug (DMARD), Thiazolidinediones, Other antidiabetics, Antiemetic (Metoclopramide), Anticoagulants, Morphine/opiate, Two or more prescriptions for a non-steroidal anti-inflammatory drug (NSAIDs), Statins, Proton pump inhibitors and Aromatase Inhibitors.

Disease history: anaemia, seizures, syncope, ischaemic heart disease, cerebrovascular disease, malignant neoplasms, inflammatory bowel disease, obstructive airway disease, liver disease, impaired renal function, mental disorders and dementia and/or Alzheimer

Use of health services: number of visits to the GP in the last year (<1, 1-10, >10)

All codes for confounding variables are found in Annex III Tables 6 to 56.

5.10 Analysis

For each study design, at least 3 models will be run in the primary analysis:

1) adjusted analysis by age and sex, (Model "a"),
2) adjusted analysis with age, sex and all potential confounders under "b" (Model "a"+"b"),
3) adjusted analysis with age, sex and all potential confounders under "b","c", (Model "a"+"b"+"c"),
4) adjusted analysis with age, sex and all potential confounders under "b "c"and "d" (Model "a"+"b"+"c"+"d").

Note: The strategy 4) can only be applied if as a rule of thumb there are at least 10 events per independent variable in the model. If the number of variables in the model is too large (< 10 events per variable), a selection procedure will be applied, including only potential confounders that result in a + or - 5% change in the beta-coefficient of the drug exposure of interest when the individual potential confounder is added to an "a"+"b"+"c" adjusted model. If this still results in too many variables, only the potential confounders that change this beta-coefficient most will be included until the maximum number of variables allowed in the model is reached.

Statistical analyses will be conducted using statistical software available for each database study.

5.11 Cohort

5.12 Follow-up

The date of the first prescription of an AD (index date) will define the start of follow-up. Each patient will then be followed until the first date on which a hip/femur fracture occurs (Annex I, Tables 3 and 4) or until the end of valid data collection, whichever comes first (see Section 4.2 and Figure 2).

5.13 Analysis

In the retrospective cohort analysis, incidence rates of hip/femur fractures (IR) will be calculated by dividing the number of fractures (numerator) by the person-time period (denominator) separately in current, recent and past users. Crude incidence rate ratio (IRR) and 95% Confidence Intervals (95% CI) will be calculated by dividing the IR in the current and recent users by the incidence rate in the past users. Past use will be the reference category. Poisson regression analysis will be used to estimate age and gender adjusted IRR.
Time-dependent Cox proportional hazards models will also be used to calculate HR and 95% CIs. Potential confounders will be the same described in Paragraph 5.2.4 Potential confounders, and these will be entered in the model according to the procedures described under Paragraph 5.2.5 Analysis.

5.14 Nested case-control

A nested-case control study will be conducted within the previously defined cohort.

5.15 Case definition

All patients, included within the cohort study (see Figure 2), with a record/diagnosis of a new event of hip/femur fracture (Annex I, Tables 3 and 4), will be identified. The date of diagnosis of the hip/femur fracture will be considered the outcome day**.**

5.16 Selection of controls

The date for the each control will be the same as the date of fracture for the matched case (outcome day). Each case of hip/femur fracture will be matched by age (± 5 years age-band) and sex to up to ten controls using the risk set sampling method under the assumption that control patients will be not allowed to have a hip or femur fracture at the date of their matched case but they may be eligible to become cases after this date. If there are difficulties in achieving the desirable number of controls the age-band of ± 5 years might be extended to ±10 years.
In case that practice was included in the matching (for GPRD) and there were difficulties in achieving the desirable number of controls, the practice will not be included as a matching variable.

5.17 Exposure definition

Refer to section 5.2.3

5.18 Analysis

Conditional logistic regression analysis will be used to estimate the risk of hip/femur fracture associated with the current use of AD as compared to past use and adjusting for confounding variables. The risks will be calculated in terms of odds ratios (OR) with corresponding 95% confidence interval (CI).

Potential confounders will be the same described in Paragraph 5.2.4, except for the matching variables.

The analysis strategy and selection of confounders will be performed as described in Paragraph 5.2.5.

5.19 Case-crossover

Case-crossover design **(10)** is similar to case control design but only among cases with control moments from the same patient. Cases and index dates are the same as in the nested case-control design.

5.20 Study population

The study population will comprise all cases of hip/femur fracture as for the nested case-control design.

5.21 Analysis

For each case, the cumulative exposure will be assessed in the 6 months before the index date (at-risk period). For each case up to 4 control moments will be defined at 6 six months intervals starting immediately prior to the at-risk period. Cumulative exposure will also be assessed in these 'control' person moments.

Conditional logistic regression analysis will be used to estimate the risk of hip and /or femur fracture with the use of AD (SSRI or TCA) and the various confounding variables. The risks will be calculated in terms of odds ratios (OR) with corresponding 95% confidence interval (CI). Adjusted OR for hip and/or hip/femur fracture will be estimated by comparing current antidepressant use with past use (of any SSRI or TCA) using conditional regression analysis. Confounders that may change over the time will be entered in the model according to the procedures described under 'potential confounders'.

6 Instrumental variable analysis

A method that potentially controls for both observed and unobserved confounding is instrumental variable (IV) analysis [Martens 2006, Hernan 2006]. An IV is a variable that is strongly related to exposure, and only related to the outcome through exposure. Hence, an IV should neither directly nor indirectly through (unobserved) confounders be associated with the outcome. Importantly, if the IV is independent of observed confounders, it

is assumed to be independent of unobserved confounders. This is in analogy with the comparability of observed and unobserved prognostic variables between the intervention and control group achieved by randomization in a trial.

A key example of instrumental variable approach in pharmacoepidemiology for the assessment of gastrointestinal complications in relation to COX-2 inhibitors compared to non-selective non-steroidal anti-inflammatory drugs (NSAIDs) has illustrated this approach [Brookhart 2006]. It may however not be possible to identify valid IVs for every pharmacoepidemiologic research question [Groenwold 2010].

We aim to apply IV analysis to assess the unconfounded association between prescriptions for AD and hip/femur fracture. Several potential IVs will be evaluated, including physician preference (e.g. as indicated by the prescription to the previous patient with a prescription for the same indication), regional variation (e.g. different regions or countries, possibly with different prescribing guidelines), and calendar time (e.g., periods prior to and after establishment of new guidelines) [Brookhart 2007, Chen 2010]. These variables may be related to prescriptions for AD, yet are unlikely to be directly related to fracture risk, nor indirectly through the potential confounder(s) listed in the paragraph "potential confounders". Estimation will be conducted via a two-stage instrumental variable model [Rassen 2009]. This analysis will be a separate from the main analyses described in this proposal and focuses on the (methodological) application of IV analysis in pharmacoepidemiology.

7 Limitations

Limitations related to the data source:

A major limitation is related to data availability and completeness within each data source. Information on important factors such as socioeconomic status is not always recorded in most databases. Moreover missing data on weight, height, alcohol and smoking might be an issue in some of the databases. Information on hospitalization is available to a different extent in the different databases. This information is recorded in the databases by adding the specialist reports or through linkage to hospital data. Nevertheless, information on fractures of elderly patients residing in nursing homes is often not available. Moreover, information on falls, physical status or cognitive impairment, also considered of special interest in elderly patients for this drug-event pair, are usually not recorded in the databases. At last, information on the indication motivating the drug prescription might also be incomplete.

Limitations related to methodology:

Immeasurable factors, such as those factors determining exposure to a drug may be important. Selection bias is possible to occur when the disease that prompted the decision to treat may itself increase the risk of the outcome of interest, or the perceived risk of the outcome may influence the selection of the drug (indication or channelling bias).

The most relevant assumptions for case-crossover design applied to study of hip fracture in association with exposure to AD are:

1) AD use has a prompt effect on hip fracture hence it has short induction time (so bone effect is neglected here).
2) The effect of AD use does not persist (no carry over effect), hence it has a transient effect.

Misclassification of the exposure is a potential concern in pharmacoepidemiological studies using databases since we only use prescription data and do not have information on dispensing or actual drug intake. In addition, drugs prescribed by physician other than GPs could be missed. Since data were obtained from medical records, the exposure misclassification is probably non-differential and therefore we may expect a distortion of the risk towards the null value.

Over the counter medication is not expected to influence exposure since medical prescriptions are required in Europe for all ADs.

Regarding the outcome, cases of hip/femur fractures will only be identified by detection of specific recorded codes or texts for hip/femur fractures in the databases. No additional criteria will be required, as the diagnosis is straightforward and no major errors are expected. Likely, no validation of cases by requesting information or confirmation from the GPs will be done. In addition, hip/femur fractures have been widely studied in primary health care databases and data are likely to be complete.

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9 Annexes

9.1 Annex I codes for exposure and outcome

9.2 Table 2 List of Antidepressants, ATC codes and DDD

Medication class	Name	ATC	DDD
TCA		N06AA	
	desipramine	N06AA01	0.1g
	imipramine	N06AA02	0.1g
	imipramine oxide	N06AA03	0.1g
	clomipramine	N06AA04	0.1g
	opipramol	N06AA05	0.15g
	trimipramine	N06AA06	0.15
	lofepramine	N06AA07	0.105g
	dibenzepin	N06AA08	0.3g
	amitriptyline	N06AA09	75mg
	nortriptyline	N06AA10	75 mg
	protriptyline	N06AA11	30 mg
	doxepin	N06AA12	0.1g
	iprindole	N06AA13	90 mg
	melitracen	N06AA14	75 mg
	butriptyline	N06AA15	75 mg
	dosulepin	N06AA16	0.15g
	amoxapine	N06AA17	0.15g
	dimetacrine	N06AA18	0.15g
	amineptine	N06AA19	
	maprotiline	N06AA21	0.1g
	Quinupramine	N06AA23	0.1g
SSRI		N06AB	
	zimeldine	N06AB02	0.2g
	fluoxetine	N06AB03	20 mg
	citalopram	N06AB04	20 mg
	paroxetine	N06AB05	20 mg
	sertraline	N06AB06	50 mg
	alaproclate	N06AB07	-
	fluvoxamine	N06AB08	0.1g
	etoperidone	N06AB09	-
	escitalopram	N06AB10	10 mg

9.3 Table 3 Read codes for hip fracture (THIN database)

icd_gr	gprdmedcode	definition	icd9	icd_gr_term	read	pegasus_code
820	278057	Closed reduction of fracture of hip	820	Hip	7K1L400	6660
820	205226	Closed reduction of fracture of femur	820	Hip	7K1L500	18962
820	307405	FRACTURE HIP	820	Hip	820 A	75586
820	305491	FRACTURE NECK OF FEMUR	820	Hip	820 B	75292
820	257232	FRACTURE TROCHANTER	820	Hip	820 T	74772
820	255857	REDUCTION CLOSED FRACTURE HIP	820	Hip	K7805H	88820
820	301763	REDUCTION OPEN FRACTURE HIP	820	Hip	K7815H	91826

820	226773	Fracture of neck of femur	820	Hip	S30..00	2225
820	217653	Hip fracture	820	Hip	S30..11	1994
820	226774	Closed fracture proximal femur, transcervical	820	Hip	S300.00	38489
820	263265	Cls # prox femur, intracapsular section, unspecified	820	Hip	S300000	39984
820	281503	Closed fracture proximal femur, transepiphyseal	820	Hip	S300100	69919
820	217654	Closed fracture proximal femur, midcervical section	820	Hip	S300200	65690
820	226775	Closed fracture proximal femur, basicervical	820	Hip	S300300	52194
820	254099	Closed fracture, base of neck of femur	820	Hip	S300311	51861
820	263266	Closed fracture head of femur	820	Hip	S300400	36391
820	272491	Cls # prox femur, subcapital, Garden grade unspec.	820	Hip	S300500	17019
820	290656	Closed fracture proximal femur, subcapital, Garden grade I	820	Hip	S300600	34351
820	235850	Closed fracture proximal femur, subcapital, Garden grade II	820	Hip	S300700	33957
820	244878	Closed fracture proximal femur, subcapital, Garden grade III	820	Hip	S300800	36599
820	235851	Closed fracture proximal femur, subcapital, Garden grade IV	820	Hip	S300900	34078
820	347222	Closed fracture of femur, upper epiphysis	820	Hip	S300A00	45779
820	272492	Closed fracture proximal femur, other transcervical	820	Hip	S300y00	49209
820	217655	Closed fracture of femur, subcapital	820	Hip	S300y11	68229
820	208671	Closed fracture proximal femur, transcervical, NOS	820	Hip	S300z00	62966
820	244879	Open fracture proximal femur, transcervical	820	Hip	S301.00	73981
820	281504	Opn # proximal femur, intracapsular section, unspecified	820	Hip	S301000	50727
820	217656	Open fracture proximal femur, transepiphyseal	820	Hip	S301100	72138
820	272494	Open fracture head, femur	820	Hip	S301400	73210
820	235852	Open fracture proximal femur,subcapital, Garden grade unspec	820	Hip	S301500	38878
820	208672	Open fracture proximal femur,subcapital, Garden grade I	820	Hip	S301600	60885
820	244881	Open fracture proximal femur,subcapital, Garden grade II	820	Hip	S301700	67394
820	263267	Open fracture proximal femur,subcapital, Garden grade III	820	Hip	S301800	23803
820	281505	Open fracture proximal femur,subcapital, Garden grade IV	820	Hip	S301900	51999
820	208673	Open fracture proximal femur, other transcervical	820	Hip	S301y00	68668
820	208674	Open fracture of femur, subcapital	820	Hip	S301y11	73234
820	208675	Closed fracture of proximal femur, pertrochanteric	820	Hip	S302.00	5301
820	272495	Cls # proximal femur, trochanteric	820	Hip	S302000	19117

		section, unspecified				
820	208676	Closed fracture of femur, greater trochanter	820	Hip	S302011	19387
820	290657	Closed fracture of femur, lesser trochanter	820	Hip	S302012	48337
820	263268	Closed fracture proximal femur, intertrochanteric, two part	820	Hip	S302100	45141
820	208677	Closed fracture proximal femur, subtrochanteric	820	Hip	S302200	29145
820	217657	Cls # proximal femur, intertrochanteric, comminuted	820	Hip	S302300	51216
820	217658	Closed fracture of femur, intertrochanteric	820	Hip	S302400	8648
820	217659	Cls # of proximal femur, pertrochanteric section, NOS	820	Hip	S302z00	44735
820	244883	Open fracture of proximal femur, pertrochanteric	820	Hip	S303.00	61733
820	208678	Open fracture of femur, greater trochanter	820	Hip	S303011	96644
820	290658	Open fracture proximal femur, subtrochanteric	820	Hip	S303200	71282
820	281506	Open fracture of femur, intertrochanteric	820	Hip	S303400	39396
820	299941	Open fracture of proximal femur, pertrochanteric, NOS	820	Hip	S303z00	70479
820	208679	Pertrochanteric fracture	820	Hip	S304.00	28965
820	217661	Closed fracture of unspecified proximal femur	820	Hip	S30w.00	24276
820	217662	Open fracture of unspecified proximal femur	820	Hip	S30x.00	58642
820	208680	Closed fracture of neck of femur NOS	820	Hip	S30y.00	18273
820	290659	Hip fracture NOS	820	Hip	S30y.11	10570
820	281507	Open fracture of neck of femur NOS	820	Hip	S30z.00	38054
820	254180	Fracture-dislocation or subluxation hip	820	Hip	S4E..00	24587
820	290757	Closed fracture-dislocation, hip joint	820	Hip	S4E0.00	40267
820	226856	Open fracture-dislocation, hip joint	820	Hip	S4E1.00	58720
820	235915	Closed fracture-subluxation, hip joint	820	Hip	S4E2.00	93374
		OPEN FRACTURE PROXIMAL FEMUR, MIDCERVICAL SECTION			S301200	
		OPEN FRACTURE PROXIMAL FEMUR, BASICERVICAL			S301300	
		OPEN FRACTURE BASE OF NECK OF FEMUR			S301311	
		OPEN FRACTURE OF FEMUR, UPPER EPIPHYSIS			S301A00	
		OPEN FRACTURE PROXIMAL FEMUR, TRANSCERVICAL, NOS			S301z00	
		OPEN FRACTURE OF FEMUR, LESSER TROCHANTER			S303012	
		OPEN FRACTURE PROXIMAL FEMUR, INTERTROCHANTERIC, TWO PART			S303100	
		OPEN FRACTURE PROXIMAL FEMUR, INTERTROCHANTERIC, COMMINUTED			S303300	
		SUBTROCHANTERIC FRACTURE			S305.00	

		OPEN FRACTURE-SUBLUXATION, HIP JOINT			S4E3.00	

9.4 Table 4 ICD-10 and ICPC codes for Hip/femur fracture

ICD-10	TITLE
S72	FRACTURE OF FEMUR Fracture of hip NOS
S72.0	FRACTURE OF NECK OF FEMUR
S72.1	PERTROCHANTERIC FRACTURE Intertrochanteric fracture Trochanteric fracture
S72.2	SUBTROCHANTERIC FRACTURE
S72.3	FRACTURE OF SHAFT OF FEMUR
S72.4	FRACTURE OF LOWER END OF FEMUR
S72.7	MULTIPLE FRACTURES OF FEMUR
S72.8	FRACTURES OF OTHER PARTS OF FEMUR
S72.9	FRACTURE OF FEMUR, PART UNSPECIFIED
ICPC-2	TITLE
L75	FRACTURE: FEMUR

9.5 Annex II codes for antidepressant indications

9.6 Table 5: Antidepressant indications in ICPC/ICD codes

Indication	ICPC-2 Code	Title
Depression	P03	Feeling depressed
	P76	Depressive disorders
Anxiety/panic disorder	P01	Feeling anxious/nervous/tense
Panic disorders	P74	Anxiety disorders/anxiety state
Insomnia/ sleep disorders	P06	Sleep disturbance
Other indications		
Indication unknown		

Antidepressant indications ICD 10 codes

Indication	ICD-10 Code	Title
Depression	R45.2, R45.3	Unhappiness, demoralization and apathy
	F32, F33, F34.1, F34.8, F34.9, F38, F39, F41.2, F53.0	Depressive episode, recurrent depressive disorder, dysthymia, other persistent mood [affective] disorders, persistent mood [affective] disorder unspecified, other mood [affective] disorders, unspecified mood [affective] disorder, mixed anxiety and depressive disorder, mild mental and behavioral disorders associated with the puerperium, not elsewhere classified
Anxiety	R45.0	Nervousness
	F41.0, F41.1, F41.3, F41.8, F41.9	Panic disorder [episodic paroxysmal anxiety], generalized anxiety disorder, other mixed anxiety disorders, other specified anxiety disorders, anxiety disorder, unspecified
Panic disorders	F41.0	Panic disorder [episodic paroxysmal anxiety]
Insomnia/ sleep disorders	F51, G47	Nonorganic sleep disorders, sleep disorders
Other indications		
Indication unknown		

9.7 Annex III codes for potential confounders

9.8 Well established risk factors (codes for confounder group under b)

9.8.1.1 Table 6. Weight, height, BMI, smoking and alcohol

Weight	in kg recorded in the last year.
Height	in cm recorded any time.
BMI	Calculated as weight in kilograms divided by height squared in meters. Categories: < 18.5; 18.5-24.9; 25.0-29.9; ≥ 30 Reference category: 18.5-24.9
Current smoking	Enter no use/use/ unknown. Reference category: No use
Alcohol	Enter no use/use/ unknown. Reference category: No use

Prior history of fractures (vertebral and non-vertebral)
Variable "previous fractures" include all codes described below (tibia/fibula, radius/ulna, and other fractures), and also femur fractures (see codes in Annex I, Tables 3 and 4). Variable value: yes or no. Reference category: No

9.8.1.2 Table 7: Fracture: radius/ulna

ICPC codes	
L72	Fracture: radius/ulna
ICD-10 codes	
S52	Fracture of forearm

Fracture: tibia/fibula

ICPC codes	
L73	Fracture: tibia/fibula
ICD-10 codes	
S82.1	Fracture of upper end of tibia
S82.2	Fracture of shaft of tibia
S82.3	Fracture of lower end of tibia
S82.4	Fracture of fibula alone
S82.5	Fracture of medial malleolus
S82.6	Fracture of lateral malleolus
S82.7	Multiple fractures of lower leg
S82.8	Fractures of other parts of lower leg
S82.9	Fracture of lower leg, part unspecified

Fracture: hand/foot bone

ICPC codes	
L74	Fracture: hand/foot bone
ICD-10 codes	
S62	Fracture at wrist and hand level
S92	Fracture of foot, except ankle

Fracture: femur

ICPC codes	
L75	Fracture: femur
ICD-10 codes	
S72	Fracture of femur

Fracture: other

ICPC codes	
L76	Fracture: other
ICD-10 codes	
S02.2	Fracture of nasal bones

S02.3	Fracture of orbital floor
S02.4	Fracture of malar and maxillary bones
S02.6	Fracture of mandible
S02.7	Multiple fractures involving skull and facial bones
S02.8	Fractures of other skull and facial bones
S02.9	Fracture of skull and facial bones, part unspecified
S12	Fracture of neck
S22	Fracture of rib(s), sternum and thoracic spine
S32	Fracture of lumbar spine and pelvis
S42	Fracture of shoulder and upper arm
S82.0	Fracture of patella
T08	Fracture of spine, level unspecified
T10	Fracture of upper limb, level unspecified
T12	Fracture of lower limb, level unspecified
T14.2	Fracture of unspecified body region

9.8.1.3 Table 8: Glucocorticoids

ATC code	
H02AB	Glucocorticoids

Variable value:
Yes: exposed to oral glucocorticoids for > 3 months at a dose of prednisolone of 5mg daily or more (or equivalent doses of other glucocorticoids)
No: exposed but lesser than 3 months or < 5mg daily of prednisolone (or equivalence) or not exposed (Reference category)

Equivalent anti-inflammatory doses of corticosteroids to Prednisolone 5 mg (Fte: British National Formulary. BMJ Group and RPS Publishing BNF, London 2009)	= Cortisone acetate 25 mg
	= Deflazacort 6 mg
	= Dexamethasone 750 micrograms
	= Hydrocortisone 20 mg
	= Methylprednisolone 4 mg
	= Triamcinolone 4 mg

9.8.1.4 Table 9: Rheumatoid artritis

ICPC-2	TITLE
L88	Rheumatoid/seropositive arthritis

ICD-10	TITLE
M05	Seropositive rheumatoid arthritis
M06	Other rheumatoid arthritis
M08	Juvenile arthritis

9.9 Risk factors immediately related to the outcome

9.9.1.1 Table 10: Osteoporosis

Value labels: yes or no. Reference category: No

ICPC-2	TITLE
L95	Osteoporosis
ICD-10	TITLE
M81	Osteoporosis without pathological fracture
M82	Osteoporosis in diseases classified elsewhere
M82*	Osteoporosis in diseases classified elsewhere

9.9.1.2 Table 11: Paget disease

Value labels: yes or no. Reference category: No

ICPC-2	TITLE
L99	NO SPECIFIC CODE (Musculoskeletal disease)
ICD-10	TITLE
M88	Paget´ disease of bone

9.9.1.3 Table 12 Biphosphonates

ATC code	
M05BA01	etidronic acid
M05BA02	clodronic acid
M05BA03	pamidronic acid
M05BA04	alendronic acid
M05BA05	tiludronic acid
M05BA06	ibandronic acid

9.9.1.4 Table 13 Raloxifene

ATC code	
G03XC01	raloxifene

9.9.1.5 Table 14: Parathyroid hormones and analogues

ATC code	
H05AA	Parathyroid hormones and analogues

9.9.1.6 Table 15: Strontium ranelate

ATC code	
M05BX03	Strontium ranelate

9.9.1.7 Table 16 Vitamin D and analogues

ATC code	
A11CC	Vitamin D and analogues
A11CC04	calcitriol
A11CC05	colecalciferol
	calcium+ colecalciferol
A11CC06	calcifediol

9.9.1.8 Table 17 Calcitonin preparations

ATC code	
H05BA	Calcitonin preparations

9.10 Other risk factors that have been associated with fracture in the past

9.10.1.1 List of benzodiazepines, names, administrative route and Half-life

9.10.1.2 Table 18 ANXIOLYTICS

ATC code	Name	Adm.R	Half-life*
N05BA01	diazepam	O	Long (>24)
		P	
		R	
N05BA02	chlordiazepoxide	O	Long (>24)
		P	
N05BA03	medazepam	O	Long (>24)
N05BA04	oxazepam	O	Intermediate (8-24)
N05BA05	potassium clorazepate	O	Long (>24)
N05BA06	lorazepam	O	Intermediate (8-24)
		SL	
N05BA07	adinazolam		Short (<8)
N05BA08	bromazepam	O	Intermediate (8-24)
N05BA09	clobazam	O	Intermediate (8-24)
N05BA10	ketazolam		Intermediate (8-24)
N05BA11	prazepam	O	Long (>24)
N05BA12	alprazolam	O	Intermediate (8-24)
N05BA13	halazepam	O	Long (>24)
N05BA14	pinazepam		Intermediate (8-24)
N05BA15	camazepam	O	Intermediate (8-24)

N05BA16	nordazepam	O	Long (24)
N05BA17	fludiazepam	O	Long (>24)
N05BA19	etizolam		Short (<8)
N05BA21	clotiazepam		Short (<8)
N05BA56	lorazepam, combinations		

* Half life definitions: Short (<8); Intermediate (8-24), Long (>24)

9.10.1.3 Table 18.1 HYPNOTICS AND SEDATIVES

ATC code	Name	AdmR	Half-life *
N05CD01	flurazepam	O	Long (>24)
N05CD02	nitrazepam	O	Long(>24)
N05CD03	flunitrazepam	O	Intermediate (8-24)
		P	
N05CD04	estazolam	O	Intermediate (8-24)
N05CD05	triazolam	O	Short(<8)
		SL	
N05CD06	lormetazepam	O	Intermediate(8-24)
N05CD07	temazepam	O	Intermediate(8-24)
N05CD08	midazolam	O	Short(<8)
		P	
N05CD09	brotizolam	O	Short (<8)
N05CD10	quazepam	O	Long(>24)
N05CD11	loprazolam	O	Intermediate(8-24)

9.10.1.4 Table 18.2 Benzodiazepine related drugs

ATC code	Name	Half-life*
N05CF01	zopiclone*	Short (<8)
N05CF02	zolpidem*	Short (<8)
N05CF03	zapeplon	Short (<8)

* Half life definitions: Short (<8); Intermediate (8-24), Long (>24)

ATC code	Name	AdmR
N05CM	Other Hypnotics and Sedatives	
N05CM02	Clomethiazole	O
		P

9.10.1.5 List of other medications

9.10.1.6 Table 19 Anti-Parkinson drugs

ATC code	
N04	Anti-Parkinson drugs
N04A	Anticholinergic agents
N04AA	Tertiary amines
N04AB	Ethers chemically close to antihistamines
N04AC	Ethers of tropine or tropine derivatives
N04B	Dopaminergic agents
N04BA	Dopa and dopa derivatives
N04BB	Adamantane derivatives
N04BC	Dopamine agonists

N04BD	Monoamine oxidase B inhibitors
N04BX	Other dopaminergic agents

9.10.1.7 Table 20 Antiepileptic drugs (anticonvulsants)

ATC code	
N03A	Antiepileptics
N03AA	Barbiturates and derivatives
N03AB	Hydantoin derivatives
N03AC	Oxazolidine derivatives
N03AD	Succinimide derivatives
N03AE	Benzodiazepine derivatives
N03AF	Carboxamide derivatives
N03AG	Fatty acid derivatives
N03AX	Other antiepileptics

9.10.1.8 Table 21: Inhaled glucocorticoids

ATC code	
R03BA	Glucocorticoids
R03BA01	beclometasone
R03BA02	bud esonide
R03BA03	flunisolide
R03BA04	betamethasone
R03BA05	fluticasone
R03BA06	triamcinolone
R03BA07	mometasone
R03BA08	ciclesonide

9.10.1.9 Table 22 Beta-2-adrenoreceptor agonists (inhaled and systemic)

ATC code	
R03A	Adrenergics, inhalants
R03AC	Selective beta-2-adrenoreceptor agonists
R03AK	Adrenergics and other drugs for obstructive airway diseases
R03C	Adrenergics for systemic use
R03CC	Selective beta-2-adrenoreceptor agonists

9.10.1.10 Table 23 Antiarrhythmics

ATC code	
C01B	Antiarrhythmics, class I and III

C01BA	Antiarrhythmics, class Ia
C01BB	Antiarrhythmics, class Ib
C01BC	Antiarrhythmics, class Ic
C01BD	Antiarrhythmics, class III

9.10.1.11 Table 24 Sedating antihistamines

ATC code	
N05BB	Diphenylmethane derivatives (*sedating*)

9.10.1.12 Table 25 ACE inhibitors

ATC code	
C09	Agents acting on the renin-angiotensin system
C09A	ACE inhibitors, plain
C09AA	ACE inhibitors, plain
C09B	ACE inhibitors, combinations
C09BA	ACE inhibitors and diuretics
C09BB	ACE inhibitors and calcium channel blockers

9.10.1.13 Table 26 Angiotensin II antagonists

ATC code	
C09	Agents acting on the renin-angiotensin system
C09C	Angiotensin II antagonists, plain
C09CA	Angiotensin II antagonists, plain
C09D	Angiotensin II antagonists, combinations
C09DA	Angiotensin II antagonists and diuretics
C09DB	Angiotensin II antagonists and calcium channel blockers
C09DX	Angiotensin II antagonists, other combinations

9.10.1.14 TABLE 27 Beta blocking agents

ATC code	
C07A	Beta blocking agents
C07AA	Beta blocking agents, non-selective
C07AB	Beta blocking agents, selective
C07AG	Alpha and beta blocking agents
C07B	Beta blocking agents and thiazides
C07BA	Beta blocking agents, non-selective, and thiazides

C07BB	Beta blocking agents, selective, and thiazides
C07BG	Alpha and beta blocking agents and thiazides
C07C	Beta blocking agents and other diuretics
C07CA	Beta blocking agents, non-selective, and other diuretics
C07CB	Beta blocking agents, selective, and other diuretics
C07CG	Alpha and beta blocking agents and other diuretics
C07D	Beta blocking agents, thiazides and other diuretics
C07DA	Beta blocking agents, non-selective, thiazides and other diuretics
C07DB	Beta blocking agents, selective, thiazides and other diuretics
C07F	Beta blocking agents and other antihypertensives
C07FA	Beta blocking agents, non-selective, and other antihypertensives
C07FB	Beta blocking agents, selective, and other antihypertensives

9.10.1.15 Table 28 Calcium channel blockers

ATC code	
C08	Agents acting on the renin-angiotensin system
C08C	Selective calcium channel blockers with mainly vascular effects
C08CA	Dihydropyridine derivatives
C08CX	Other selective calcium channel blockers with mainly vascular effects
C08D	Selective calcium channel blockers with direct cardiac effects
C08DA	Phenylalkylamine derivatives
C08DB	Benzothiazepine derivatives
C08E	Non-selective calcium channel blockers
C08EA	Phenylalkylamine derivatives
C08EX	Other non-selective calcium channel blockers
C08G	Calcium channel blockers and diuretics
C08GA	Calcium channel blockers and diuretics

9.10.1.16 Table 29 Other antihypertensives

ATC code	
C02A	Antiadrenergic agents, centrally acting
C02AA	Rauwolfia alkaloids
C02AB	Methyldopa
C02AC	Imidazoline receptor agonists
C02C	Antiadrenergic agents, peripherally acting
C02CA	Alpha-adrenoreceptor antagonists

C02CC	Guanidine derivatives
C02D	Arteriolar smooth muscle, agents acting on
C02DA	Thiazide derivatives
C02DB	Hydrazinophthalazine derivatives
C02DC	Pyrimidine derivatives
C02DD	Nitroferricyanide derivatives
C02DG	Guanidine derivatives
C02K	Other non-selective calcium channel blockers
C02KA	Alkaloids, excluding rauwolfia
C02KB	Tyrosine hydroxylase inhibitors
C02KC	MAO inhibitors
C02KD	Serotonin antagonists
C02KX	Other antihypertensives
C02L	Calcium channel blockers and diuretics
C02LA	Rauwolfia alkaloids and diuretics in combination
C02LB	Methyldopa and diuretics in combination
C02LC	Imidazoline receptor agonists in combination with diuretics
C02LE	Alpha-adrenoreceptor antagonists and diuretics
C02LF	Guanidine derivatives and diuretics
C02LG	Hydrazinophthalazine derivatives and diuretics
C02LK	Alkaloids, excluding rauwolfia, in combination with diuretics
C02LL	MAO inhibitors and diuretics
C02LN	Serotonin antagonists and diuretics
C02LX	Other antihypertensives and diuretics

9.10.1.17 Table 30 Diuretics

ATC code	
C03A	Low-ceiling diuretics, thiazides
C03AA	Thiazides, plain
C03AB	Thiazides and potassium in combination
C03AH	Thiazides, combinations with psycholeptics and/or analgesics
C03AX	Thiazides, combinations with other drugs
C03B	Low-ceiling diuretics, excluding thiazides
C03BA	Sulfonamides, plain
C03BB	Sulfonamides and potassium in combination

C03BC	Mercurial diuretics
C03BD	Xanthine derivatives
C03BK	Sulfonamides, combinations with other drugs
C03BX	Other low-ceiling diuretics
C03C	High-ceiling diuretics
C03CA	Sulfonamides, plain
C03CB	Sulfonamides and potassium in combination
C03CC	Aryloxyacetic acid derivatives
C03CD	Pyrazolone derivatives
C03CX	Other high-ceiling diuretics
C03D	Potassium-sparing agents
C03DA	Aldosterone antagonists
C03DB	Other potassium-sparing agents
C03E	Diuretics and potassium-sparing agents in combination
C03EA	Low-ceiling diuretics and potassium-sparing agents
C03EB	High-ceiling diuretics and potassium-sparing agents
C03X	Other diuretics
C03XA	Vasopressin antagonists

9.10.1.18 Table 31 Hormone replacement therapy

ATC code	
G03C	Estrogens
G03CA	Natural and semi synthetic estrogens, plain
G03CX	Other estrogens
G03D	Progestogens
G03DA	Pregnen-(4) derivatives
G03DC	Estren derivatives
G03F	Progestogens and estrogens in combination
G03FA	Progestogens and estrogens, fixed combinations
G03FB	Progestogens and estrogens, sequential preparations

9.10.1.19 Table 32 Thyroid hormones

ATC code	
H03A	Thyroid preparations
H03AA	Thyroid hormones

9.10.1.20 Table 33 Antityroid drugs

ATC code	
H03B	Antithyroid preparations
H03BA	Thiouracils
H03BB	Sulphur-containing imidazole derivatives
H03BC	Perchlorates
H03BX	Other antithyroid preparations

9.10.1.21 Table 34 Drugs disease-modifying anti-rheumatic drug (DMARD)

ATC code	
Gold	
M01CB03	Auranofin
M01CB02	Sodium aurothiomalate
Penicillamine	
M01CC01	Penicillamine
Antimalarials	
P01BA01	Chloroquine
P01BA02	Hydroxychloroquine sulphate
Drugs affecting the immune response	
L04AX01	Azathioprine
L04AD01	Cyclosporine
L04AA13	Leflunomide
L01BA01/L01AX03	Methotrexate
Cytokine modulators	
L04AA24	Abatacept
L04AB04	Adalimumab
L04AC03	Anakinra
L04AB01	Etanercept
L04AB02	Infliximab
L01XC02	Rituximab
Sulfasalazine	
A07EC01	Sulfasalazine

9.10.1.22 Table 35 Thiazolidinediones

ATC code	

A10BG	Thiazolidinediones

9.10.1.23 Table 36 other antidiabetic drugs

ATC code	
A10A	Insulins and analogues
A10AB	Insulins and analogues for injection, fast-acting
A10AC	Insulins and analogues for injection, intermediate-acting
A10AD	Insulins and analogues for injection, intermediate-acting combined with fast-acting
A10AE	Insulins and analogues for injection, long-acting
A10AF	Insulins and analogues for inhalation
A10B	Blood glucose lowering drugs, excluding insulins
A10BA	Biguanides
A10BB	Sulfonamides, urea derivatives
A10BC	Sulfonamides (heterocyclic)
A10BD	Combinations of oral blood glucose lowering drugs
A10BF	Alpha glucosidase inhibitors
A10BG	Thiazolidinediones
A10BH	Dipeptidyl peptidase 4 (DPP-4) inhibitors
A10BX	Other blood glucose lowering drugs, excluding insulins
A10X	Other drugs used in diabetes
A10XA	Aldose reductase inhibitors

9.10.1.24 Table 37 Antiemetic (Metoclopramide)

ATC code	
A03F	Propulsives
A03FA	Propulsives
A03FA01	Metoclopramide

9.10.1.25 Table 38 Anticoagulants (heparine)

ATC code	
B01AB	Heparin group

9.10.1.26 Table 39 Opioids (including Morphine)

ATC code	
N02A	Opioids
N02AA	Natural opium alkaloids

N02AB	Phenylpiperidine derivatives
N02AC	Diphenylpropylamine derivatives
N02AD	Benzomorphan derivatives
N02AE	Oripavine derivatives
N02AF	Morphinan derivatives
N02AG	Opioids in combination with antispasmodics
N02AX	Other opioids

9.10.1.27 Table 40 Non-steroidal Anti-inflammatory drugs (two or more prescriptions)

ATC code	
M01A	ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STEROIDS
M01AA	Butylpyrazolidines
M01AB	Acetic acid derivatives and related substances
M01AC	Oxicams
M01AE	Propionic acid derivatives
M01AG	Fenamates
M01AH	Coxibs
M01AX	Other antinflammatory and antirheumatic agents, non-steroids

9.10.1.28 Table 41 Statins

ATC code	
C10AA01	simvastatin
C10AA02	lovastatin
C10AA03	pravastatin
C10AA04	fluvastatin
C10AA05	atorvastatin
C10AA06	cerivastatin
C10AA07	rosuvastatin
C10AA08	pitavastatin

9.10.1.29 Table 42 Proton Pum Inhibitors

ATC code	
A02BC01	omeprazole
A02BC02	pantoprazole
A02BC03	lansoprazole
A02BC04	rabeprazole
A02BC05	esomeprazole

9.10.1.30 Table 43 Aromatase inhibitors

ATC code	
L02BG	Enzyme inhibitors

L02BG01	aminoglutethimide
L02BG02	formestane
L02BG03	anastrozole
L02BG04	letrozole
L02BG05	vorozole
L02BG06	exemestane

9.10.1.31 List of diseases

9.10.1.32 Table 44 Anaemia

Variable value: yes or no. Reference category: No

ICPC codes	
B80	Iron Deficiency anaemia
B81	Anaemia, Vitamin B12/folate def
B82	Anemia other inespecify
ICD-10 codes	
D50-D53	Nutritional anaemias

9.10.1.33 Table 45 Seizures/epilepsies

(Value labels: yes or no. Reference category: No)
Please see codes under Annex II, Table 5, Indication of Benzodiazepines.

ICPC codes	
N07	Seizures
ICD-10	
F44.4	Dissociative motor disorders
F44.5	Dissociative convulsions
F80.3	Acquired aphasia with epilepsy [Landau-Kleffner]
G40.0	Localization-related (focal)(partial) idiopathic epilepsy and epileptic syndromes with seizures of localized onset
G40.1	Localization-related (focal)(partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures
G40.2	Localization-related (focal)(partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures
G40.3	Generalized idiopathic epilepsy and epileptic syndromes
G40.4	Other generalized epilepsy and epileptic syndromes
G40.5	Special epileptic syndromes
G40.6	Grand mal seizures, unspecified (with or without petit mal)
G40.7	Petit mal, unspecified, without grand mal seizures
G40.9	Epilepsy, unspecified
R56	Convulsions, not elsewhere classified

9.10.1.34 Table 46 Syncope

Value labels: yes or no. Reference category: No

ICPC codes	
A06	Syncope
ICD-10	
R55 x	Syncope and collapse

9.10.1.35 Table 47 Cardiovascular diseases

Value labels: yes or no. Reference category: No

ICPC codes	
K74	Ischaemic heart disease with angina
K75	Acute Myocardial Infarction
K76	Ischaemic heart disease without angina
ICD-10 codes	
I20-I25	Ischaemic heart diseases

9.10.1.36 Table 48 Peripheral atherosclerosis

ICPC codes	
K92	Atherosclerosis/PVD
ICD-10 codes	

9.10.1.37 Table 49 Cerebrovascular disease

Value labels: yes or no. Reference category: No

ICPC codes	
K90	Stroke/Cerebrovascular accident
K91	Cerebrovascular Disease
ICD-10 codes	
G46	Vascular syndromes of brain in cerebrovascular diseases
I60	Subarachnoid haemorrhage
I61	Intracerebral haemorrhage
I62	Other nontraumatic intracranial haemorrhage
I63	Cerebral infarction
I64	Stroke, not specified as haemorrhage or infarction

9.10.1.38 Table 50 Malignant neoplasma

Value labels: yes or no. Reference category: No

ICPC codes	
A79	Malignancy NOS
B72	Hodgkin's disease/lymphoma
B73	Leukaemia
B74	Malignant neoplasm blood other
D74	Malignant neoplasm stomach
D75	Malignant neoplasm colon/rectum
D76	Malignant neoplasm pancreas
D77	Malignant neoplasm digest other/NOS
F74	Neoplasm of the eye/adnexa
H75	Neoplasm of ear
K72	Neoplasm cardiovascular
L71	Malignant neoplasm musculoskeletal
N74	Malignant neoplasm nervous system
R84	Malignant neoplasm bronchus/lung
R85	Malignant neoplasm respiratory, other
S77	Malignant neoplasm of the skin
T71	Malignant neoplasm thyroid
U75	Malignant neoplasm of kidney
U76	Malignant neoplasm of bladder
U77	Malignant neoplasm urinary other
W72	Malignant neoplasm relate to pregnancy
X75	Malignant neoplasm cervix
X76	Malignant neoplasm breast female
X77	Malignant neoplasm genital other (f)
Y77	Malignant neoplasm prostate
Y78	Malignant neoplasm male genital other
ICPC/ICD-10	Corresponding ICD-10 codes
(ATC=A79)	C38.1, C38.2, C38.3, C38.8, C45.7, C45.9, C46.7, C46.8, C46.9, C76, C78, C79, C80, C97, D09.7, D09.9
(ATC=B72)	C81, C82, C83, C84, C85
(ATC=B73)	C91, C92, C93, C94, C95
(ATC=B74)	C37, C46.3, C77, C88, C90, C96
(ATC=D74)	C16
(ATC=D75)	C18, C19, C20, C21

(ATC=D76)	C25
(ATC=D77)	C00, C01, C02, C03, C04, C05, C06, C07, C08, C14.8, C15, C17, C22, C23, C24, C26, C45.1, C46.2, C48
(ATC=F74)	C69, D09.2, D31, D48.7
(ATC=H75)	C30.1, D48.9
(ATC=K72)	C38.0, C45.2, D15.1, D15.2, D48.7
(ATC=L71)	C40, C41, C49
(ATC=N74)	C47, C70, C71, C72
(ATC=R84)	C33, C34
(ATC=R85)	C09, C10, C11, C12, C13, C14.0, C14.2, C30.0, C31, C32, C38.4, C39, C45.0
(ATC=S77)	C43, C44, C46.0, C46.1
(ATC=T71)	C73
(ATC=U75)	C64, C65
(ATC=U76)	C67
(ATC=U77)	C66, C68
(ATC=W72)	C58
(ATC=X75)	C53, D06
(ATC=X76)	C50
(ATC=X77)	C51, C52, C54, C55, C56, C57
(ATC=Y77)	C61
(ATC=Y78)	C50, C60, C62, C63

9.10.1.39 Table 51 Inflammatory bowel disease

Value labels: yes or no. Reference category: No

ICPC-2	TITLE
D94	Chronic enteritis/Ulcerative colitis
ICD-10	TITLE
K50-K52	Noninfective enteritis and colitis

9.10.1.40 Table 52 Obstructive airway disease

Value labels: yes or no. Reference category: No

ICPC codes	
R79 (old R91)	Chronic bronchitis
R95	Emphysema/chronic obstructive pulmonary disease
ICD-10 codes	
J41	Simple and mucopurulent chronic bronchitis
J42	Unspecified chronic bronchitis

J43	Emphysema
J44	Other chronic obstructive pulmonary disease

9.10.1.41 Table 53 Liver disease

Value labels: yes or no. Reference category: No

ICPC codes	
D97	Liver disease NOS
ICD-10 codes	
K72	Hepatic failure, not elsewhere classified
K73	Chronic hepatitis, not elsewhere classified
K74	Fibrosis and cirrhosis of liver
K75	Other inflammatory liver diseases
K76	Other diseases of liver
K77	Liver disorders in diseases classified elsewhere

9.10.1.42 Table 54 Chronic renal failure

Value labels: yes or no. Reference category: No

ICPC-2	TITLE
	NO SPECIFIC CODE
ICD-10	TITLE
N18	Chronic renal failure

9.10.1.43 Table 55 Mental disorders

Value labels: yes or no. Reference category: No

ICPC-2	TITLE
P72	SCHIZOPHRENIA
P73	AFFECTIVE PSYCHOSIS
P75	SOMATIZATION DISOR(Value labels: yes or no. Reference category: No) DER
P76	DEPRESSIVE DISORDER
P77	SUICIDE/SUICIDE ATTEMPT
P78	NEURAESTHENIA/SURMENAGE
P79	PHOBIA/COMPULSIVE DISORDER
P80	PERSONALITY DISORDER
P81	HYPERKINETIC DISORDER
P82	POST-TRAUMATIC STRESS DISORDER

P85	MENTAL RETARDATION
P86	ANOREXIA NERVOSA/BULIMIA
P98	PSYCHOSIS NOS/OTHER
P99	PSYCHOLOGICAL DISORDERS OTHER
ICD-10	TITLE
F00-F09	Organic, including symptomatic, mental disorders

9.10.1.44 Table 56 Dementia/Alzheimer

Value labels: yes or no. Reference category: No

ICPC codes	
P70	Dementia
ICD-10 codes	
F00	Dementia in Alzheimer's disease
F01	Vascular dementia
F02	Dementia in other diseases classified elsewhere
F03	Unspecified dementia
G30	Alzheimer's disease

10 Annex IV: Amendments

Protocol: PROTECT WP2_ Final Protocol_Antidep_HIP_14NOv 2011.doc
Amendment number: *Nº 1*
Amendments suggested on: 13 April 2012 (see Reasons for amendment)
Amendments finalized on: 24 May 2012 (see Decision on the suggested amendment)
Protocol Owners:

Name	Role
Victoria Abbing [1]	Protocol lead
Marieke De Bruin [1]	Protocol backup
Liset van Dijk [1,2]	Protocol reviewer
Montserrat Miret [3]	Protocol reviewer
Gardarsdottir Helga [1]	Protocol reviewer
Frank de Vries [1]	Protocol reviewer
Marietta Rottenkolber [4]	Database 1 (Bavaria) lead
Joerg Hasford [4]	Database 1 (Bavaria) backup
Miguel Gil [5]	Database 2 (Bifap) lead
Consuelo Huerta [5]	Database 2 (Bifap) backup
Ulrik Hesse[6]	Database 3 (DKMA) lead
Frank de Vries[1]	Database 3 (DKMA) backup
Dan Dedman /Jenny Campbell [7]	Database 4 (GPRD) lead/backup
Olaf Klungel [1]	Database 5 (Mondriaan) lead
Liset van Dijk [1, 2]	Database 5 (Mondriaan) backup
Yolanda Alvarez [8]	Database 6 (THIN) lead
Ana Ruigomez [9]	Database 6 (THIN) backup

Universiteit Utrecht, Utrecht, The Netherlands (UU)
[2] Netherlands Institute for Healthcare Research, Utrecht, The Netherlands (NIVEL)
[3] Merck KGaA, Geneva, Switzerland (ME)
[4] Ludwig-Maximilians-Universität-München, Munich, Germany (LMU- Muenchen)
[5] Agencia Espanola de Medicamentos y Productos Sanitarios, Madrid, Spain (AEMPS)
[6] Lægemiddelstyrelsen (Danish Medicines Agency), Copenhagen, Denmark (DKMA)
[7] General Practice Research Database, London, United Kingdom (GPRD)
[8] European Medicines Agency, London, United Kingdom (EMA)
[9] Fundación Centro Español de Investigación Farmacoepidemiológica, Madrid, Spain (CEIFE)

Reason(s) for amendment:

This protocol amendment serves to the following purposes:

a) Inclusion criteria. Instead of the condition " at least 1 year registered at the GP" change to " at least 6 months registered at the GP ". This is because new starters of AD have a restriction of 6 months drug free period. Hence condition of patients having at least 6 months of history is enough to be included in the study population. Otherwise restriction of 1 year registry at the GP shall exclude patients without any relevant reason.
b) Harmonizing classification of indications with the benzodiazepine protocol for the analytical studies
c) Measure of potential confounders at baseline
d) Presenting codes for indication according to the amended definition. Also READ codes (which were missing) are added

Protocol Section(s) suggested for amendment

a) Clarifications of inclusion criteria

Change from:

5.2.1 Study population and study period

From the source population that comprised all patients included in the period of valid data collection, all patients who have at least one year of enrolment with the GP, are ≥ 18 years and have at least one antidepressant prescription (see Annex I, Table 2 for drug codes) will be selected. The date of the AD prescription will be the index date.

Patients with a prescription of AD within 6 months before index date will be excluded to restrict the analysis to new users only.

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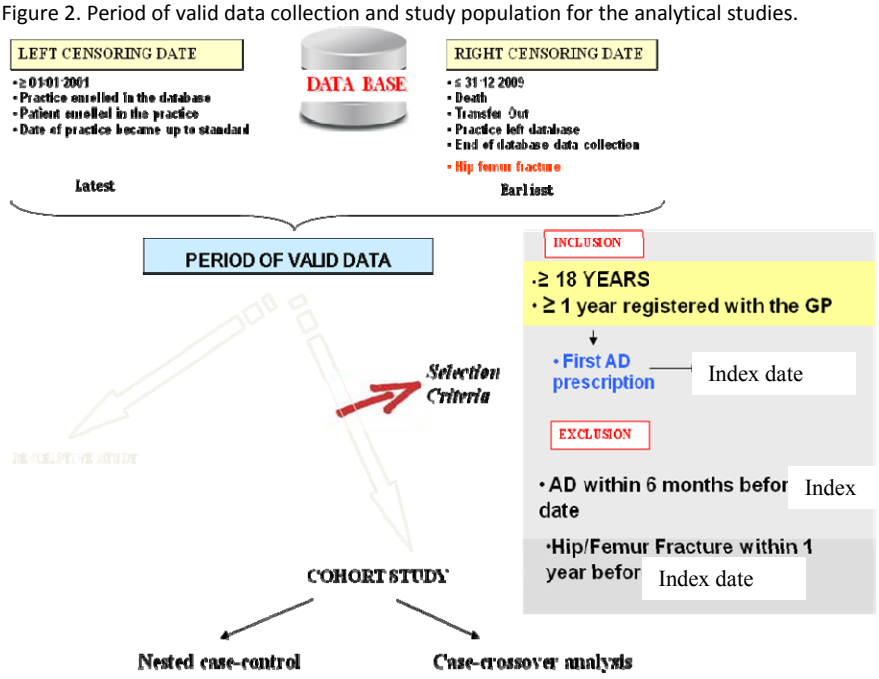
Figure 2. Period of valid data collection and study population for the analytical studies.



Change to:

5.2.1 Study population and study period

From the source population that comprised all patients included in the period of valid data collection, all patients who have at least ~~one year~~ 6 months of enrolment with the GP, are ≥ 18 years and have at least one antidepressant prescription (see Annex I, Table 2 for drug codes) will be selected. The date of the AD prescription will be the index date.

Patients with a prescription of AD within 6 months before index date will be excluded to restrict the analysis to new users only.

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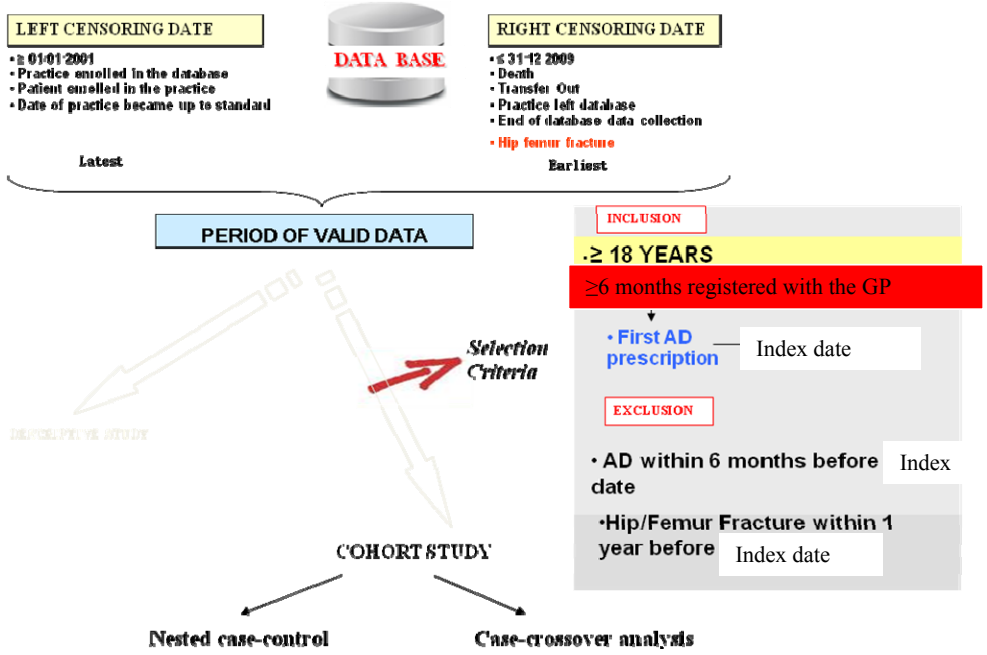
Figure 2. Period of valid data collection and study population for the analytical studies.



b) Harmonizing classification of indications with the benzodiazepine protocol for the analytical studies

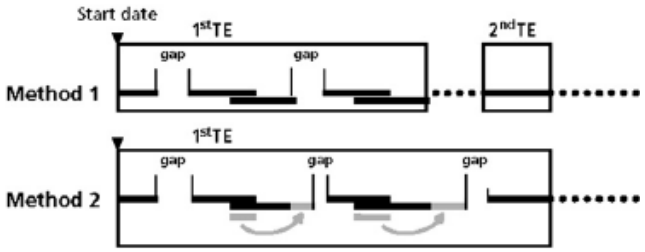
Change from

5.2.3 Exposure definition

The duration of antidepressant (see section 9.1 table 1 for drug codes) use will be determined by calculating length of treatment episodes. Treatment episodes will be defined as a series of subsequent prescriptions for AD, independent of switching of type and dose change and should be constructed according to the method of Gardarsdottir et al **(8).**:

In case a subsequent antidepressant prescription with the same drug is collected before the theoretical end date of a previous antidepressant prescription, the number of overlapping days is added to the theoretical end date of the subsequent antidepressant prescription (see figure 3, method 2). If the subsequent prescription is within the same treatment episode included another antidepressant (SSRI or TCA), the patient is considered to have switched therapy and the remaining tablet days from the prior prescription are disregarded (see figure 3, method 1).

Figure 3. Constructing drug treatment episodes based on estimated duration of a dispensed prescription and gaps of a defined length



TE: treatment episode

A new treatment episode will be considered when an interval of 90 days or more occurs between the theoretical end date of a prescription and the dispensing date of the next prescription for the same patient.

In case of missing data on the estimated duration of use, information of the dosing scheme and/or number of prescribed units from the most recent previous prescription (with available data) of the patient will be used to calculate the estimated prescription length. In case this is not possible, the population-mode duration of use [specific for the type (ATC code) and strength of the antidepressant] of the database of interest will be imputed. An overview of all prescriptions with imputed population modes of duration [stratified according to age (20-year categories) and sex] will be reported.

The total exposure time of patients will be divided into periods of current, recent and past use with patients switching between these periods according to drug use:

Current use will be defined when the prescription of AD lasts until 30 days after the estimated end date of the supply. **Recent use** will encompass the period between 1- 60 days after the period of current use. When the gap between two treatment episodes is more than 90 days, a patient will automatically become a **past user**, from the estimated end date of the treatment episode. The period of past use will be stratified into periods of 182 days, until the patient becomes a current user again, or until the end of valid data collection.
During follow-up the patient is allowed to switch between treatment categories of current use, based on the following characteristics:

Type of medication use (according to ATC and according to group (SSRI or TCA)

Dose: Prescribed daily dose (categorized as <0.5 DDD, ≥0.5 and < 1.0 DDD, ≥1.0 DDD)
Cumulative dose (DDD) of current drug within the current treatment episode treated as continuous as well as categorical variable (DDD < 180, ≥180 and < 365 and ≥365 DDD)
Cumulative dose (DDD) of previous (other) AD (SSRI or TCA) in the same treatment episode treated as continuous as well as categorical variable (DDD<180, ≥ 180 and < 365 and ≥ 365 DDD
Cumulative dose (DDD) of AD (SSRI or TCA) in previous treatment episodes treated as continuous as well as categorical variable (DDD <180, ≥ 180 and < 365 and ≥ 365 DDD

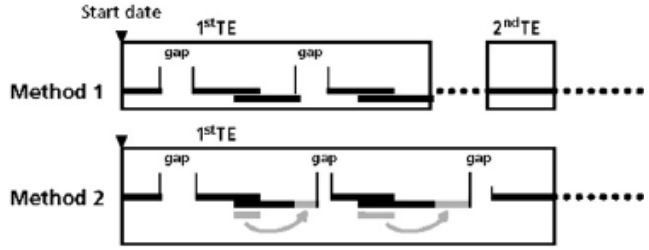
Indication: Depression /Anxiety/Sleeping disorders/Other/Unknown
The indication is assessed in the physician-patient contact file during the period from 90 days before to 90 days after prescription date. If multiple indications are identified during this period, the indication closest to the prescription date is taken. If no indication is identified in this period, the indication is taken from the most recent previous prescription with available indication.

Change to:

5.2.3 Exposure definition
The duration of antidepressant (see section 9.1 table 1 for drug codes) use will be determined by calculating length of treatment episodes. Treatment episodes will be defined as a series of subsequent prescriptions for AD, independent of switching of type and dose change and should be constructed according to the method of Gardarsdottir et al **(8).**:

In case a subsequent antidepressant prescription with the same drug is collected before the theoretical end date of a previous antidepressant prescription, the number of overlapping days is added to the theoretical end date of the subsequent antidepressant prescription (see figure 3, method 2). If the subsequent prescription is within the same treatment episode included another antidepressant (SSRI or TCA), the patient is considered to have switched therapy and the remaining tablet days from the prior prescription are disregarded (see figure 3, method 1).

Figure 3. Constructing drug treatment episodes based on estimated duration of a dispensed prescription and gaps of a defined length



TE: treatment episode

A new treatment episode will be considered when an interval of 90 days or more occurs between the theoretical end date of a prescription and the dispensing date of the next prescription for the same patient.

In case of missing data on the estimated duration of use, information of the dosing scheme and/or number of prescribed units from the most recent previous prescription (with available data) of the patient will be used to calculate the estimated prescription length. In case this is not possible, the population-mode duration of use [specific for the type (ATC code) and strength of the antidepressant] of the database of interest will be imputed. An overview of all prescriptions with imputed population modes of duration [stratified according to age (20-year categories) and sex] will be reported.

The total exposure time of patients will be divided into periods of current, recent and past use with patients switching between these periods according to drug use:

Current use will be defined when the prescription of AD lasts until 30 days after the estimated end date of the supply. **Recent use** will encompass the period between 1- 60 days after the period of current use. When the gap between two treatment episodes is more than 90 days, a patient will automatically become a **past user**, from the estimated end date of the treatment episode. The period of past use will be stratified into periods of 182 days, until the patient becomes a current user again, or until the end of valid data collection.
During follow-up the patient is allowed to switch between treatment categories of current use, based on the following characteristics:

Type of medication use (according to ATC and according to group (SSRI or TCA)

Dose: Prescribed daily dose (categorized as <0.5 DDD, ≥0.5 and < 1.0 DDD, ≥1.0 DDD)
Cumulative dose (DDD) of current drug within the current treatment episode treated as continuous as well as categorical variable (DDD < 180, ≥180 and < 365 and ≥365 DDD)
Cumulative dose (DDD) of previous (other) AD (SSRI or TCA) in the same treatment episode treated as continuous as well as categorical variable (DDD<180, ≥ 180 and < 365 and ≥ 365 DDD

Comment [v3]: This change is not part of the amendment (see in protocol section in yellow) since it is rephrased for the purpose of clarity

Duration: Among current users the duration of drug use will be calculated by summing the duration(days) of each consecutive prescription of antidepressant within the treatment episode. Four categories will be considered: 0-30 days, 31-180 days, 181-365 days and >365 days. Exposure will be considered to be continuous in case of a gap between consecutive prescriptions of 90 days or less.

Comment [v4]: This change is not part of the amendment (see in protocol section in yellow) since it is rephrased for the purpose of clarity

Indication will be categorized as follows:

a) Anxiety disorders (alone or with any other indication but without depression),
b) Sleep disorders (alone or with any other indication but neither anxiety nor depression),
c) Depression combined (with any, or both, of the following: anxiety and sleep disorders,
d) Depression (alone or with other indication under "Other"),
e) Other
f) Unknown (*Annex II, Table 5*.1 added).

Comment [v5]: This addition is done just not to have two categories with the same name "depression". No need to apply for amendment

These categories might be later summarized for their inclusion in the designs as follows:

a) Anxiety (alone or with any other indication but without depression),
b) Sleep disorders (alone with any other indication but neither anxiety nor depression),
c) Depression (alone or with any other),
d) Other and
e) Unknown..

The indication is assessed in the physician-patient contact file during the period from 90 days before to 90 days after prescription date. If multiple indications are identified during this period, the indication closest to the prescription date is taken. If no indication is identified in this period, the indication is taken from the most recent previous prescription with available indication.

c) Measurement of potential confounders at baseline

Change from
5.2.4 Potential confounders
Potential confounders will be measured in a time varying analysis as follows:
All variables will be measured at baseline (in the 6 months prior to inclusion of the patient in the cohort)
Co-morbidity and co-medication variables will be measured/updated every 6 months.

Change to
5.2.4 Potential confounders
Potential confounders will be measured in a time varying analysis as follows:
All variables will be measured at baseline (~~in the 6 months prior~~ co-morbidity will be measured any time before and co-medication will be measured 6 months before to inclusion of the patient in the cohort), and
Co-morbidity and co-medication variables will be measured/updated every 6 months

d) Presenting codes for indication according to the amended definition. Also adding READ codes (which were missing)

Decision on the suggested amendments

a) Ignore the suggested amendment. Based on discussions this change of inclusion criteria was disregarded.
b) Amendment accepted
c) Amendment accepted
d) Amendment accepted

d) Added codes under amendment d) for indications in Annex II
Table 5.1 Antidepressant indications (ICPC-2, ICD-10 and READ codes)

ICPC-2 CODES

Indication	ICPC-2 Code	Title
ANXIETY/RELATED DISORDERS		
Anxiety/panic disorders	P01	Feeling anxious/nervous/tense
	P74	Anxiety disorders/anxiety state
Phobias/compulsive disorders	P79	Phobia/compulsive disorder
Stress related symptoms	P02	Acute stress reaction
	P82	Post-traumatic stress disorder
Somatisation disorders/fear		
	P75	Somatization disorders
	A13	Concern/fear medical treatment
	A25	Fear of death/dying
	A26	Fear of cancer NOS
	A27	Fear of other disease NOS
	B25	Fear of aids/HIV
	B26	Fear cancer blood/lymph
	B27	Fear blood/lymph disease other
	D26	Fear of cancer of digestive system
	D27	Fear of digestive disease other
	F27	Fear of eye disease
	H27	Fear of ear disease
	K24	Fear of heart disease
	K25	Fear of hypertension
	K27	Fear of cardiovascular disease other
	L26	Fear of cancer/musculoskeletal
	L27	Fear musculoskeletal disease other
	N26	Fear cancer neurological system
	N27	Fear of neurological disease other
	P27	Fear of mental disorder
	R26	Fear of cancer respiratory system
	R27	Fear of respiratory disease other
	S26	Fear of cancer of skin
	S27	Fear of skin disease
	T26	Fear of cancer of endocrine system
	T27	Fear endocrine/metabolic disease other
	U26	Fear of cancer of urinary system
	U27	Fear of urinary disease other
	W27	Fear complications of pregnancy
	X23	Fear sexually transmitted disease f.
	X24	Fear of sexual dysfunction female
	X25	Fear of genital cancer female
	X26	Fear of breast cancer female
	X27	Fear genital/breast disease other
	Y24	Fear of sexual dysfunction male
	Y25	Fear sexually transmitted disease f.
	Y26	Fear of genital cancer male
	Y27	Fear of genital disease male other
INSOMNIA/SLEEP DISORDERS		
	P06	Sleep disturbance
DEPRESSION	P03	Feeling depressed
	P76	Depressive disorders
OTHERS		
Alcohol withdrawal	P15	Chronic alcohol abuse
	P16	Acute alcohol abuse

Muscle relaxation	L18	Muscle pain
	L19	Muscle symptom/complaint NOS
Convulsions	N07	Convulsion/seizure
	N88	Epilepsy

ICD-10 CODES

Indication	ICD-10 Code	Title
ANXIETY/RELATED DISORDERS		
Anxiety/panic disorders		
	F41	Other anxiety disorders
Phobias/compulsive disorders	F40	Phobic anxiety disorders
	F42	Obsessive-compulsive disorder
Stress related symptoms	F43	Reaction to severe stress, and adjustment disorders
Somatisation disorders/fear		
	Z71.1	Person with feared complaint in whom no diagnosis is made
	F45	Somatoform disorders
INSOMNIA/SLEEP DISORDERS		
	F51, G47	Nonorganic sleep disorders, sleep disorders
DEPRESSION		
	F31.3	Bipolar affective disorder, current episode mild or moderate depression
	F31.4	Bipolar affective disorder, current episode mild or moderate depression
	F31.5	Bipolar affective disorder, current episode severe depression with psychotic symptoms
	F32	Depressive episode
	F33	Recurrent depressive disorder
	F34	Persistent mood [affective] disorders
OTHERS		
Alcohol withdrawal	F10	Mental and behavioral disorders due to use of alcohol
Muscle relaxation	M60, M79	Myositis, other soft tissue disorders, not elsewhere classified
	M62.5, M62.6	Muscle wasting and atrophy, not elsewhere classified, muscle strain
Convulsions	R56	Convulsions, not elsewhere classified
	G40	Epilepsy
	G41	Status epilepticus
	F80.3	Acquired aphasia with epilepsy [Landau-Kleffner]

READ CODES

Indication	READ Code	Title
ANXIETY/RELATED DISORDERS		
Anxiety/panic disorders	1466.00	H/O: ANXIETY STATE
	1B13.00	ANXIOUSNESS

	1B13.11	ANXIOUSNESS - SYMPTOM
	1B13.12	ANXIOUS
	1B1V.00	C/O - PANIC ATTACK
	2258.00	O/E - ANXIOUS
	225J.00	O/E - PANIC ATTACK
	8G94.00	ANXIETY MANAGEMENT TRAINING
	8HHp.00	REFERRAL FOR GUIDED SELF-HELP FOR ANXIETY
	E200.00	ANXIETY STATES
	E200000	ANXIETY STATE UNSPECIFIED
	E200100	PANIC DISORDER
	E200111	PANIC ATTACK
	E200200	GENERALISED ANXIETY DISORDER
	E200400	CHRONIC ANXIETY
	E200500	RECURRENT ANXIETY
	E200z00	ANXIETY STATE NOS
	E202.12	PHOBIC ANXIETY
	E202100	AGORAPHOBIA WITH PANIC ATTACKS
	E280.00	ACUTE PANIC STATE DUE TO ACUTE STRESS REACTION
	E292000	SEPARATION ANXIETY DISORDER
	E292400	ADJUSTMENT REACTION WITH ANXIOUS MOOD
	E2D0.00	DISTURBANCE OF ANXIETY AND FEARFULNESS CHILDHOOD/ADOLESCENT
	E2D0000	CHILDHOOD AND ADOLESCENT OVERANXIOUSNESS DISTURBANCE
	E2D0z00	DISTURBANCE ANXIETY AND FEARFULNESS CHILDHOOD/ADOLESCENT NOS
	Eu05400	[X]ORGANIC ANXIETY DISORDER
	Eu34114	[X]PERSISTANT ANXIETY DEPRESSION
	Eu40.00	[X]PHOBIC ANXIETY DISORDERS
	Eu40012	[X]PANIC DISORDER WITH AGORAPHOBIA
	Eu40y00	[X]OTHER PHOBIC ANXIETY DISORDERS
	Eu40z00	[X]PHOBIC ANXIETY DISORDER, UNSPECIFIED
	Eu41.00	[X]OTHER ANXIETY DISORDERS
	Eu41000	[X]PANIC DISORDER [EPISODIC PAROXYSMAL ANXIETY]
	Eu41011	[X]PANIC ATTACK
	Eu41012	[X]PANIC STATE
	Eu41100	[X]GENERALIZED ANXIETY DISORDER
	Eu41111	[X]ANXIETY NEUROSIS
	Eu41112	[X]ANXIETY REACTION
	Eu41113	[X]ANXIETY STATE
	Eu41200	[X]MIXED ANXIETY AND DEPRESSIVE DISORDER
	Eu41211	[X]MILD ANXIETY DEPRESSION
	Eu41300	[X]OTHER MIXED ANXIETY DISORDERS
	Eu41y00	[X]OTHER SPECIFIED ANXIETY DISORDERS
	Eu41y11	[X]ANXIETY HYSTERIA
	Eu41z00	[X]ANXIETY DISORDER, UNSPECIFIED
	Eu41z11	[X]ANXIETY NOS
	Eu51511	[X]DREAM ANXIETY DISORDER
	Eu60600	[X]ANXIOUS [AVOIDANT] PERSONALITY DISORDER
	Eu93000	[X]SEPARATION ANXIETY DISORDER OF CHILDHOOD
	Eu93100	[X]PHOBIC ANXIETY DISORDER OF CHILDHOOD
	Eu93200	[X]SOCIAL ANXIETY DISORDER OF CHILDHOOD
	Eu93y12	[X]CHILDHOOD OVERANXIOUS DISORDER
	Z4I7.00	ACKNOWLEDGING ANXIETY
	Z4I7100	RECOGNISING ANXIETY

	Z4I7200	ALLEVIATING ANXIETY
	Z4I7211	REDUCING ANXIETY
	Z4L1.00	ANXIETY COUNSELLING
Phobias/Compulsive disorders		
	E2...00	NEUROTIC, PERSONALITY AND OTHER NONPSYCHOTIC DISORDERS
	E20..00	NEUROTIC DISORDERS
	E20z.00	NEUROTIC DISORDER NOS
	E20z.11	NERVOUS BREAKDOWN
	E21..11	NEUROTIC PERSONALITY DISORDER
	E214.00	COMPULSIVE PERSONALITY DISORDERS
	E214.11	ANANCASTIC PERSONALITY
	E214000	ANANKASTIC PERSONALITY
	E214100	OBSESSIONAL PERSONALITY
	E21y711	NEUROTIC PERSONALITY
	E202.00	PHOBIC DISORDERS
	E202.11	SOCIAL PHOBIC DISORDERS
	E202.12	PHOBIC ANXIETY
	E202000	PHOBIA UNSPECIFIED
	E202100	AGORAPHOBIA WITH PANIC ATTACKS
	E202200	AGORAPHOBIA WITHOUT MENTION OF PANIC ATTACKS
	E202300	SOCIAL PHOBIA, FEAR OF EATING IN PUBLIC
	E202400	SOCIAL PHOBIA, FEAR OF PUBLIC SPEAKING
	E202500	SOCIAL PHOBIA, FEAR OF PUBLIC WASHING
	E202600	ACROPHOBIA
	E202700	ANIMAL PHOBIA
	E202800	CLAUSTROPHOBIA
	E202900	FEAR OF CROWDS
	E202A00	FEAR OF FLYING
	E202B00	CANCER PHOBIA
	E202C00	DENTAL PHOBIA
	E202D00	FEAR OF DEATH
	E202E00	FEAR OF PREGNANCY
	E202z00	PHOBIC DISORDER NOS
	E202z11	WEIGHT FIXATION
	Eu22y11	[X]DELUSIONAL DYSMORPHOPHOBIA
	Eu40.00	[X]PHOBIC ANXIETY DISORDERS
	Eu40000	[X]AGORAPHOBIA
	Eu40011	[X]AGORAPHOBIA WITHOUT HISTORY OF PANIC DISORDER
	Eu40012	[X]PANIC DISORDER WITH AGORAPHOBIA
	Eu40100	[X]SOCIAL PHOBIAS
	Eu40111	[X]ANTHROPOPHOBIA
	Eu40112	[X]SOCIAL NEUROSIS
	Eu40200	[X]SPECIFIC (ISOLATED) PHOBIAS
	Eu40211	[X]ACROPHOBIA
	Eu40212	[X]ANIMAL PHOBIAS
	Eu40213	[X]CLAUSTROPHOBIA
	Eu40214	[X]SIMPLE PHOBIA
	Eu40300	[X]NEEDLE PHOBIA
	Eu40y00	[X]OTHER PHOBIC ANXIETY DISORDERS

	Eu40z00	[X]PHOBIC ANXIETY DISORDER, UNSPECIFIED
	Eu40z11	[X]PHOBIA NOS
	Eu40z12	[X]PHOBIC STATE NOS
	Eu42.00	[X]OBSESSIVE - COMPULSIVE DISORDER
	Eu42.11	[X]ANANKASTIC NEUROSIS
	Eu42.12	[X]OBSESSIVE-COMPULSIVE NEUROSIS
	Eu42000	[X]PREDOMINANTLY OBSESSIONAL THOUGHTS OR RUMINATIONS
	Eu42100	[X]PREDOMINANTLY COMPULSIVE ACTS [OBSESSIONAL RITUALS]
	Eu42200	[X]MIXED OBSESSIONAL THOUGHTS AND ACTS
	Eu42y00	[X]OTHER OBSESSIVE-COMPULSIVE DISORDERS
	Eu42z00	[X]OBSESSIVE-COMPULSIVE DISORDER, UNSPECIFIED
	Eu45212	[X]DYSMORPHOPHOBIA NONDELUSIONAL
	Eu45215	[X]NOSOPHOBIA
	Eu46.00	[X]OTHER NEUROTIC DISORDERS
	Eu46000	[X]NEURASTHENIA
	Eu46011	[X]FATIGUE SYNDROME
	Eu46100	[X]DEPERSONALIZATION - DEREALIZATION SYNDROME
	Eu46y00	[X]OTHER SPECIFIED NEUROTIC DISORDERS
	Eu46y11	[X]BRIQUET'S DISORDER
	Eu46y12	[X]DHAT SYNDROME
	Eu46y13	[X]OCCUPATIONAL NEUROSIS, INCLUDING WRITER'S CRAMP
	Eu46y14	[X]PSYCHASTHENIA
	Eu46y15	[X]PSYCHASTHENIA NEUROSIS
	Eu46y16	[X]PSYCHOGENIC SYNCOPE
	Eu46z00	[X]NEUROTIC DISORDER, UNSPECIFIED
	Eu46z11	[X]NEUROSIS NOS
	Eu60500	[X]ANANKASTIC PERSONALITY DISORDER
	Eu60511	[X]COMPULSIVE PERSONALITY DISORDER
	Eu60512	[X]OBSESSIONAL PERSONALITY DISORDER
	Eu60513	[X]OBSESSIVE-COMPULSIVE PERSONALITY DISORDER
	F481700	PHOTOPHOBIA
	Z481.00	PHOBIA COUNSELLING
	Z522400	DESENSITISATION - PHOBIA
	Z522700	FLOODING - AGORAPHOBIA
	E203.00	OBSESSIVE-COMPULSIVE DISORDERS
	E203.11	ANANCASTIC NEUROSIS
	E203000	COMPULSIVE NEUROSIS
	E203100	OBSESSIONAL NEUROSIS
	E203z00	OBSESSIVE-COMPULSIVE DISORDER NOS
	E204.00	NEUROTIC DEPRESSION REACTIVE TYPE
	E20y.00	OTHER NEUROTIC DISORDERS
Stress		
	05L9.00	STRESSMAN
	13H4.12	MARITAL STRESS
	13HT100	STRESS AT HOME
	13HT111	DOMESTIC STRESS
	13JM.13	STRESS AT WORK
	1B1L.00	STRESS RELATED PROBLEM
	1B1T.00	FEELING STRESSED
	67J..00	STRESS COUNSELLING

	9ON..00	STRESS MONITORING ADMIN.
	9ON..11	STRESS CLINIC ADMINISTRATION
	9ON1.00	ATTENDS STRESS MONITORING
	9ON2.00	REFUSES STRESS MONITORING
	E28..00	ACUTE REACTION TO STRESS
	E280.00	ACUTE PANIC STATE DUE TO ACUTE STRESS REACTION
	E281.00	ACUTE FUGUE STATE DUE TO ACUTE STRESS REACTION
	E282.00	ACUTE STUPOR STATE DUE TO ACUTE STRESS REACTION
	E283.00	OTHER ACUTE STRESS REACTIONS
	E283100	ACUTE POSTTRAUMA STRESS STATE
	E283000	ACUTE SITUATIONAL DISTURBANCE
	E283z00	OTHER ACUTE STRESS REACTION NOS
	E284.00	STRESS REACTION CAUSING MIXED DISTURBANCE OF EMOTION/CONDUCT
	E28z.00	ACUTE STRESS REACTION NOS
	E29y100	OTHER POST-TRAUMATIC STRESS DISORDER
	Eu4..00	[X]NEUROTIC, STRESS - RELATED AND SOMOFORM DISORDERS
	Eu43.00	[X]REACTION TO SEVERE STRESS, AND ADJUSTMENT DISORDERS
	Eu43000	[X]ACUTE STRESS REACTION
	Eu43011	[X]ACUTE CRISIS REACTION
	Eu43012	[X]ACUTE REACTION TO STRESS
	Eu43013	[X]COMBAT FATIGUE
	Eu43014	[X]CRISIS STATE
	Eu43015	[X]PSYCHIC SHOCK
	Eu43100	[X]POST - TRAUMATIC STRESS DISORDER
	Eu43111	[X]TRAUMATIC NEUROSIS
	Eu43200	[X]ADJUSTMENT DISORDERS
	Eu43211	[X]CULTURE SHOCK
	Eu43212	[X]GRIEF REACTION
	Eu43213	[X]HOSPITALISM IN CHILDREN
	Eu43y00	[X]OTHER REACTIONS TO SEVERE STRESS
	Eu43z00	[X]REACTION TO SEVERE STRESS, UNSPECIFIED
	Eu43z00	[X]REACTION TO SEVERE STRESS, UNSPECIFIED
	R007z14	[D]WORK STRESS
	R00zW00	[D]STATE OF EMOTIONAL SHOCK AND STRESS, UNSPECIFIED
	Ry15.00	[D]UNDUE CONCERN AND PREOCCUPATION WITH STRESSFUL EVENTS
	Ryu5800	[X]STATE OF EMOTIONAL SHOCK AND STRESS, UNSPECIFIED
	ZVu4E00	[X]OTHER STRESSFUL LIFE EVENTS AFFECTING FAMILY & HOUSEHOLD
Somatisation disorders/fear		
	E207.00	HYPOCHONDRIASIS
	E20y000	SOMATIZATION DISORDER
	E28z.11	EXAMINATION FEAR
	E28z.12	FLYING PHOBIA
	E28z.13	STAGE FRIGHT
	1B1H.11	FEAR

	1Bb..00	SPECIFIC FEAR
	1Bb0.00	FEAR OF FALLING
	1Bb1.00	FEAR OF GETTING CANCER
	9N54.00	ENCOUNTER FOR FEAR
	Eu45.00	[X]SOMATOFORM DISORDERS
	Eu45000	[X]SOMATIZATION DISORDER
	Eu45011	[X]MULTIPLE PSYCHOSOMATIC DISORDER
	Eu45012	[X]BRIQUET'S SYNDROME
	Eu45013	[X]BRIQUET'S DISORDER
	Eu45100	[X]UNDIFFERENTIATED SOMATOFORM DISORDER
	Eu45111	[X]UNDIFFERENTIATED PSYCHOSOMATIC DISORDER
	Eu45200	[X]HYPOCHONDRIACAL DISORDER
	Eu45211	[X]BODY DYSMORPHIC DISORDER
	Eu45212	[X]DYSMORPHOPHOBIA NONDELUSIONAL
	Eu45213	[X]HYPOCHONDRIACAL NEUROSIS
	Eu45214	[X]HYPOCHONDRIASIS
	Eu45215	[X]NOSOPHOBIA
	Eu45300	[X]SOMATOFORM AUTONOMIC DYSFUNCTION
	Eu45311	[X]CARDIAC NEUROSIS
	Eu45312	[X]DA COSTA'S SYNDROME
	Eu45313	[X]GASTRIC NEUROSIS
	Eu45314	[X]NEUROCIRCULATORY ASTHENIA
	Eu45316	[X]PSYCHOGENIC COUGH
	Eu45317	[X]PSYCHOGENIC DIARRHOEA
	Eu45318	[X]PSYCHOGENIC DYSPEPSIA
	Eu45319	[X]PSYCHOGENIC DYSURIA
	Eu45320	[X]PSYCHOGENIC FLATULENCE
	Eu45321	[X]PSYCHOGENIC HICCOUGH
	Eu45322	[X]PSYCHOGENIC HYPERVENTILAT
	Eu45323	[X]PSYCHOGENIC FREQ MICTURIT
	Eu45324	[X]PSYCHOGENIC IBS
	Eu45325	[X]PSYCHOGENIC PYLOROSPASM
	Eu45400	[X]PERSISTENT SOMATOFORM PAIN DISORDER
	Eu45411	[X]PSYCHALGIA
	Eu45412	[X]PSYCHOGENIC BACKACHE
	Eu45413	[X]PSYCHOGENIC HEADACHE
	Eu45414	[X]SOMATOFORM PAIN DISORDER
	Eu45500	[X]GLOBUS PHARYNGEUS
	Eu45y00	[X]OTHER SOMATOFORM DISORDERS
	Eu45y11	[X]PSYCHOGENIC DYSMENORRHOEA
	Eu45y12	[X]GLOBUS HYSTERICUS
	Eu45y13	[X]PSYCHOGENIC PRURITIS
	Eu45y14	[X]PSYCHOGENIC TORTICOLLIS
	Eu45y15	[X]TEETH-GRINDING
	Eu45z00	[X]SOMATOFORM DISORDER, UNSPECIFIED
	Eu45z11	[X]PSYCHOSOMATIC DISORDER NOS
	Eu46.00	[X]OTHER NEUROTIC DISORDERS
	Eu46000	[X]NEURASTHENIA
	Eu46011	[X]FATIGUE SYNDROME
	Eu46100	[X]DEPERSONALIZATION - DEREALIZATION SYNDROME
	Eu46y00	[X]OTHER SPECIFIED NEUROTIC DISORDERS
	Eu46y11	[X]BRIQUET'S DISORDER

	Eu46y12	[X]DHAT SYNDROME
	Eu46y13	[X]OCCUPATIONAL NEUROSIS, INCLUDING WRITER'S CRAMP
	Eu46y14	[X]PSYCHASTHENIA
	Eu46y15	[X]PSYCHASTHENIA NEUROSIS
	Eu46y16	[X]PSYCHOGENIC SYNCOPE
	Eu46z00	[X]NEUROTIC DISORDER, UNSPECIFIED
	Eu46z11	[X]NEUROSIS NOS
	Eu63.00	[X]HABIT AND IMPULSE DISORDERS
	Eu63y00	[X]OTHER HABIT AND IMPULSE DISORDERS
	Eu63z00	[X]HABIT AND IMPULSE DISORDER, UNSPECIFIED
	E20y000	SOMATIZATION DISORDER
	E20y011	BRIQUET'S DISORDER
	E20y100	WRITER'S CRAMP NEUROSIS
	E20y200	OTHER OCCUPATIONAL NEUROSIS
	E20y300	PSYCHASTHENIC NEUROSIS
	ZRBo.00	FEAR OF AIDS SCALE
	ZRBo.11	FAIDSS - FEAR OF AIDS SCALE
	ZRBp.00	FEAR SURVEY SCHEDULE
	ZRBp.11	FSS - FEAR SURVEY SCHEDULE

INSOMNIA/SLEEP DISORDERS		
	1B1B.00	CANNOT SLEEP - INSOMNIA
	1B1B.11	C/O - INSOMNIA
	1B1B000	INITIAL INSOMNIA
	1B1B100	MIDDLE INSOMNIA
	1B1B200	LATE INSOMNIA
	1B1Q.00	POOR SLEEP PATTERN
	1BX0.00	DELAYED ONSET OF SLEEP
	1BX1.00	EXCESSIVE SLEEP
	1BX9.00	LIGHT SLEEP
	E274.00	NON-ORGANIC SLEEP DISORDERS
	E274.11	HYPERSOMNIA OF NON-ORGANIC ORIGIN
	E274.12	INSOMNIA DUE TO NONORGANIC SLEEP DISORDER
	E274000	UNSPECIFIED NON-ORGANIC SLEEP DISORDER
	E274100	TRANSIENT INSOMNIA
	E274111	INSOMNIA NOS
	E274200	PERSISTENT INSOMNIA
	E274300	TRANSIENT HYPERSOMNIA
	E274311	HYPERSOMNIA NOS
	E274400	PERSISTENT HYPERSOMNIA
	E274600	SHIFTING SLEEP-WORK SCHEDULE
	E274700	SOMNAMBULISM - SLEEP WALKING
	E274A00	SLEEP DRUNKENNESS
	E274B00	REPEATED RAPID EYE MOVEMENT SLEEP INTERRUPTIONS
	E274C00	OTHER SLEEP STAGE OR AROUSAL DYSFUNCTION
	E274D00	REPETITIVE INTRUSIONS OF SLEEP
	E274D11	RESTLESS SLEEP
	E274E00	SHORT-SLEEPER
	E274F00	INVERSION OF SLEEP RHYTHM
	E274y00	OTHER NON-ORGANIC SLEEP DISORDER

	E274z00	NON-ORGANIC SLEEP DISORDER NOS
	Eu51.00	[X]NONORGANIC SLEEP DISORDERS
	Eu51000	[X]NONORGANIC INSOMNIA
	Eu51100	[X]NONORGANIC HYPERSOMNIA
	Eu51200	[X]NONORGANIC DISORDER OF THE SLEEP-WAKE SCHEDULE
	Eu51213	[X]PSYCHOGENIC INVERSION OF SLEEP RHYTHM
	Eu51300	[X]SLEEPWALKING
	Eu51400	[X]SLEEP TERRORS
	Eu51y00	[X]OTHER NONORGANIC SLEEP DISORDERS
	Eu51z00	[X]NONORGANIC SLEEP DISORDER, UNSPECIFIED
	Eu51z11	[X]EMOTIONAL SLEEP DISORDER NOS
	Fy0..00	SLEEP DISORDERS
	Fy00.00	DISORDERS OF INITIATING AND MAINTAINING SLEEP
	Fy01.00	DISORDERS OF EXCESSIVE SOMNOLENCE
	Fy02.00	DISORDERS OF THE SLEEP-WAKE SCHEDULE
	Fy05.00	NOCTURNAL SLEEP-RELATED EATING DISORDER
	Fyu5800	[X]OTHER SLEEP DISORDERS
	K5A2100	MENOPAUSAL SLEEPLESSNESS
	R000100	[D]SOMNOLENCE
	R005.00	[D]SLEEP DISTURBANCES
	R005.11	[D]INSOMNIA - SYMPTOM
	R005.12	[D]SLEEP RHYTHM PROBLEMS
	R005000	[D]SLEEP DISTURBANCE, UNSPECIFIED
	R005100	[D]INSOMNIA WITH SLEEP APNOEA
	R005200	[D]INSOMNIA NOS
	R005300	[D]HYPERSOMNIA WITH SLEEP APNOEA
	R005311	[D]SLEEP APNOEA SYNDROME
	R005312	[D]SYNDROME SLEEP APNOEA
	R005400	[D]HYPERSOMNIA NOS
	R005500	[D]SLEEP RHYTHM INVERSION
	R005600	[D]SLEEP RHYTHM IRREGULAR
	R005700	[D]SLEEP-WAKE RHYTHM NON-24-HOUR CYCLE
	R005800	[D]SLEEP DYSFUNCTION WITH SLEEP STAGE DISTURBANCE
	R005900	[D]SLEEP DYSFUNCTION WITH AROUSAL DISTURBANCE
	R005z00	[D]SLEEP DYSFUNCTION NOS
	ZV1B100	[V]PERSONAL HISTORY OF UNHEALTHY SLEEP-WAKE SCHEDULE

DEPRESSIVE DISORDERS		
	1465.00	H/O: DEPRESSION
	146D.00	H/O: MANIC DEPRESSIVE DISORDER
	1B17.00	DEPRESSED
	1B17.11	C/O - FEELING DEPRESSED
	1B1U.00	SYMPTOMS OF DEPRESSION
	1B1U.11	DEPRESSIVE SYMPTOMS
	1BT..00	DEPRESSED MOOD
	1BT..00	DEPRESSED MOOD
	212S.00	DEPRESSION RESOLVED
	2257.00	O/E - DEPRESSED
	62T1.00	PUERPERAL DEPRESSION
	6G00.00	POSTNATAL DEPRESSION COUNSELLING

	8BK0.00	DEPRESSION MANAGEMENT PROGRAMME
	8CAa.00	PATIENT GIVEN ADVICE ABOUT MANAGEMENT OF DEPRESSION
	8HHq.00	REFERRAL FOR GUIDED SELF-HELP FOR DEPRESSION
	9H90.00	DEPRESSION ANNUAL REVIEW
	9H91.00	DEPRESSION MEDICATION REVIEW
	9H92.00	DEPRESSION INTERIM REVIEW
	9HA0.00	ON DEPRESSION REGISTER
	9HA1.00	REMOVED FROM DEPRESSION REGISTER
	9k4..00	DEPRESSION - ENHANCED SERVICES ADMINISTRATION
	9k40.00	DEPRESSION - ENHANCED SERVICE COMPLETED
	9kQ..00	ON FULL DOSE LONG TERM TREATMENT DEPRESSION - ENH SERV ADMIN
	9kQ..11	ON FULL DOSE LONG TERM TREATMENT FOR DEPRESSION
	E001300	PRESENILE DEMENTIA WITH DEPRESSION
	E002.00	SENILE DEMENTIA WITH DEPRESSIVE OR PARANOID FEATURES
	E002100	SENILE DEMENTIA WITH DEPRESSION
	E002z00	SENILE DEMENTIA WITH DEPRESSIVE OR PARANOID FEATURES NOS
	E004300	ARTERIOSCLEROTIC DEMENTIA WITH DEPRESSION
	E02y300	DRUG-INDUCED DEPRESSIVE STATE
	E11..12	DEPRESSIVE PSYCHOSES
	E112.00	SINGLE MAJOR DEPRESSIVE EPISODE
	E112.11	AGITATED DEPRESSION
	E112.12	ENDOGENOUS DEPRESSION FIRST EPISODE
	E112.13	ENDOGENOUS DEPRESSION FIRST EPISODE
	E112.14	ENDOGENOUS DEPRESSION
	E112000	SINGLE MAJOR DEPRESSIVE EPISODE, UNSPECIFIED
	E112100	SINGLE MAJOR DEPRESSIVE EPISODE, MILD
	E112200	SINGLE MAJOR DEPRESSIVE EPISODE, MODERATE
	E112300	SINGLE MAJOR DEPRESSIVE EPISODE, SEVERE, WITHOUT PSYCHOSIS
	E112400	SINGLE MAJOR DEPRESSIVE EPISODE, SEVERE, WITH PSYCHOSIS
	E112500	SINGLE MAJOR DEPRESSIVE EPISODE, PARTIAL OR UNSPEC REMISSION
	E112600	SINGLE MAJOR DEPRESSIVE EPISODE, IN FULL REMISSION
	E112z00	SINGLE MAJOR DEPRESSIVE EPISODE NOS
	E113.00	RECURRENT MAJOR DEPRESSIVE EPISODE
	E113.11	ENDOGENOUS DEPRESSION - RECURRENT
	E113000	RECURRENT MAJOR DEPRESSIVE EPISODES, UNSPECIFIED
	E113100	RECURRENT MAJOR DEPRESSIVE EPISODES, MILD
	E113200	RECURRENT MAJOR DEPRESSIVE EPISODES, MODERATE
	E113300	RECURRENT MAJOR DEPRESSIVE EPISODES, SEVERE, NO PSYCHOSIS
	E113400	RECURRENT MAJOR DEPRESSIVE EPISODES, SEVERE, WITH PSYCHOSIS
	E113500	RECURRENT MAJOR DEPRESSIVE EPISODES,PARTIAL/UNSPEC REMISSION
	E113600	RECURRENT MAJOR DEPRESSIVE EPISODES, IN FULL

		REMISSION
	E113700	RECURRENT DEPRESSION
	E113z00	RECURRENT MAJOR DEPRESSIVE EPISODE NOS
	E114.11	MANIC-DEPRESSIVE - NOW MANIC
	E115.00	BIPOLAR AFFECTIVE DISORDER, CURRENTLY DEPRESSED
	E115.11	MANIC-DEPRESSIVE - NOW DEPRESSED
	E115000	BIPOLAR AFFECTIVE DISORDER, CURRENTLY DEPRESSED, UNSPECIFIED
	E115100	BIPOLAR AFFECTIVE DISORDER, CURRENTLY DEPRESSED, MILD
	E115200	BIPOLAR AFFECTIVE DISORDER, CURRENTLY DEPRESSED, MODERATE
	E115300	BIPOLAR AFFECT DISORD, NOW DEPRESSED, SEVERE, NO PSYCHOSIS
	E115400	BIPOLAR AFFECT DISORD, NOW DEPRESSED, SEVERE WITH PSYCHOSIS
	E115500	BIPOLAR AFFECT DISORD, NOW DEPRESSED, PART/UNSPEC REMISSION
	E115600	BIPOLAR AFFECTIVE DISORDER, NOW DEPRESSED, IN FULL REMISSION
	E115z00	BIPOLAR AFFECTIVE DISORDER, CURRENTLY DEPRESSED, NOS
	E11y.00	OTHER AND UNSPECIFIED MANIC-DEPRESSIVE PSYCHOSES
	E11y000	UNSPECIFIED MANIC-DEPRESSIVE PSYCHOSES
	E11y200	ATYPICAL DEPRESSIVE DISORDER
	E11y300	OTHER MIXED MANIC-DEPRESSIVE PSYCHOSES
	E11yz00	OTHER AND UNSPECIFIED MANIC-DEPRESSIVE PSYCHOSES NOS
	E11z200	MASKED DEPRESSION
	E130.00	REACTIVE DEPRESSIVE PSYCHOSIS
	E130.11	PSYCHOTIC REACTIVE DEPRESSION
	E135.00	AGITATED DEPRESSION
	E200300	ANXIETY WITH DEPRESSION
	E204.00	NEUROTIC DEPRESSION REACTIVE TYPE
	E204.11	POSTNATAL DEPRESSION
	E211200	DEPRESSIVE PERSONALITY DISORDER
	E290.00	BRIEF DEPRESSIVE REACTION
	E290000	GRIEF REACTION
	E291.00	PROLONGED DEPRESSIVE REACTION
	E2B..00	DEPRESSIVE DISORDER NEC
	E2B0.00	POSTVIRAL DEPRESSION
	E2B1.00	CHRONIC DEPRESSION
	Eu02z16	[X] SENILE DEMENTIA, DEPRESSED OR PARANOID TYPE
	Eu20400	[X]POST-SCHIZOPHRENIC DEPRESSION
	Eu25100	[X]SCHIZOAFFECTIVE DISORDER, DEPRESSIVE TYPE
	Eu25111	[X]SCHIZOAFFECTIVE PSYCHOSIS, DEPRESSIVE TYPE
	Eu25112	[X]SCHIZOPHRENIFORM PSYCHOSIS, DEPRESSIVE TYPE
	Eu3y111	[X]RECURRENT BRIEF DEPRESSIVE EPISODES
	Eu31300	[X]BIPOLAR AFFECT DISORDER CUR EPI MILD OR MODERATE DEPRESSN
	Eu31400	[X]BIPOL AFF DISORD, CURR EPIS SEV DEPRESS, NO PSYCHOT SYMP
	Eu31500	[X]BIPOLAR AFFECT DIS CUR EPI SEVERE DEPRES WITH

		PSYC SYMP
	Eu32.00	[X]DEPRESSIVE EPISODE
	Eu32.11	[X]SINGLE EPISODE OF DEPRESSIVE REACTION
	Eu32.12	[X]SINGLE EPISODE OF PSYCHOGENIC DEPRESSION
	Eu32.13	[X]SINGLE EPISODE OF REACTIVE DEPRESSION
	Eu32000	[X]MILD DEPRESSIVE EPISODE
	Eu32100	[X]MODERATE DEPRESSIVE EPISODE
	Eu32200	[X]SEVERE DEPRESSIVE EPISODE WITHOUT PSYCHOTIC SYMPTOMS
	Eu32211	[X]SINGLE EPISODE AGITATED DEPRESSN W'OUT PSYCHOTIC SYMPTOMS
	Eu32212	[X]SINGLE EPISODE MAJOR DEPRESSION W'OUT PSYCHOTIC SYMPTOMS
	Eu32213	[X]SINGLE EPISODE VITAL DEPRESSION W'OUT PSYCHOTIC SYMPTOMS
	Eu32300	[X]SEVERE DEPRESSIVE EPISODE WITH PSYCHOTIC SYMPTOMS
	Eu32311	[X]SINGLE EPISODE OF MAJOR DEPRESSION AND PSYCHOTIC SYMPTOMS
	Eu32312	[X]SINGLE EPISODE OF PSYCHOGENIC DEPRESSIVE PSYCHOSIS
	Eu32313	[X]SINGLE EPISODE OF PSYCHOTIC DEPRESSION
	Eu32314	[X]SINGLE EPISODE OF REACTIVE DEPRESSIVE PSYCHOSIS
	Eu32400	[X]MILD DEPRESSION
	Eu32500	[X]MAJOR DEPRESSION, MILD
	Eu32600	[X]MAJOR DEPRESSION, MODERATELY SEVERE
	Eu32700	[X]MAJOR DEPRESSION, SEVERE WITHOUT PSYCHOTIC SYMPTOMS
	Eu32800	[X]MAJOR DEPRESSION, SEVERE WITH PSYCHOTIC SYMPTOMS
	Eu32y00	[X]OTHER DEPRESSIVE EPISODES
	Eu32y11	[X]ATYPICAL DEPRESSION
	Eu32y12	[X]SINGLE EPISODE OF MASKED DEPRESSION NOS
	Eu32z00	[X]DEPRESSIVE EPISODE, UNSPECIFIED
	Eu32z11	[X]DEPRESSION NOS
	Eu32z12	[X]DEPRESSIVE DISORDER NOS
	Eu32z13	[X]PROLONGED SINGLE EPISODE OF REACTIVE DEPRESSION
	Eu32z14	[X] REACTIVE DEPRESSION NOS
	Eu33.00	[X]RECURRENT DEPRESSIVE DISORDER
	Eu33.11	[X]RECURRENT EPISODES OF DEPRESSIVE REACTION
	Eu33.12	[X]RECURRENT EPISODES OF PSYCHOGENIC DEPRESSION
	Eu33.13	[X]RECURRENT EPISODES OF REACTIVE DEPRESSION
	Eu33.14	[X]SEASONAL DEPRESSIVE DISORDER
	Eu33000	[X]RECURRENT DEPRESSIVE DISORDER, CURRENT EPISODE MILD
	Eu33100	[X]RECURRENT DEPRESSIVE DISORDER, CURRENT EPISODE MODERATE
	Eu33200	[X]RECURR DEPRESS DISORDER CUR EPI SEVERE WITHOUT PSYC SYMPT
	Eu33211	[X]ENDOGENOUS DEPRESSION WITHOUT PSYCHOTIC SYMPTOMS
	Eu33212	[X]MAJOR DEPRESSION, RECURRENT WITHOUT

		PSYCHOTIC SYMPTOMS
	Eu33213	[X]MANIC-DEPRESS PSYCHOSIS,DEPRESSD,NO PSYCHOTIC SYMPTOMS
	Eu33214	[X]VITAL DEPRESSION, RECURRENT WITHOUT PSYCHOTIC SYMPTOMS
	Eu33300	[X]RECURRENT DEPRESS DISORDER CUR EPI SEVERE WITH PSYC SYMP
	Eu33311	[X]ENDOGENOUS DEPRESSION WITH PSYCHOTIC SYMPTOMS
	Eu33312	[X]MANIC-DEPRESS PSYCHOSIS,DEPRESSED TYPE+PSYCHOTIC SYMPTOMS
	Eu33313	[X]RECURR SEVERE EPISODES/MAJOR DEPRESSION+PSYCHOTIC SYMPTOM
	Eu33314	[X]RECURR SEVERE EPISODES/PSYCHOGENIC DEPRESSIVE PSYCHOSIS
	Eu33315	[X]RECURRENT SEVERE EPISODES OF PSYCHOTIC DEPRESSION
	Eu33316	[X]RECURRENT SEVERE EPISODES/REACTIVE DEPRESSIVE PSYCHOSIS
	Eu33400	[X]RECURRENT DEPRESSIVE DISORDER, CURRENTLY IN REMISSION
	Eu33y00	[X]OTHER RECURRENT DEPRESSIVE DISORDERS
	Eu33z00	[X]RECURRENT DEPRESSIVE DISORDER, UNSPECIFIED
	Eu33z11	[X]MONOPOLAR DEPRESSION NOS
	Eu34111	[X]DEPRESSIVE NEUROSIS
	Eu34112	[X]DEPRESSIVE PERSONALITY DISORDER
	Eu34113	[X]NEUROTIC DEPRESSION
	Eu34114	[X]PERSISTANT ANXIETY DEPRESSION
	Eu3y111	[X]RECURRENT BRIEF DEPRESSIVE EPISODES
	Eu41200	[X]MIXED ANXIETY AND DEPRESSIVE DISORDER
	Eu41211	[X]MILD ANXIETY DEPRESSION
	Eu43212	[X]GRIEF REACTION
	Eu53011	[X]POSTNATAL DEPRESSION NOS
	Eu53012	[X]POSTPARTUM DEPRESSION NOS
	Eu92000	[X]DEPRESSIVE CONDUCT DISORDER
	R007z13	[D]POSTOPERATIVE DEPRESSION
	ZRLfH00	HEALTH OF THE NATION OUTCOME SCALE ITEM 7 - DEPRESSED MOOD
	ZRLfI00	HEALTH OF THE NATION OUTCOME SCALE ITEM 7 - DEPRESSED MOOD
OTHERS		
Alcohol withdrawal		
	E01..00	ALCOHOLIC PSYCHOSES
	E010.00	ALCOHOL WITHDRAWAL DELIRIUM
	E010.11	DTS - DELIRIUM TREMENS
	E010.12	DELIRIUM TREMENS
	E011.00	ALCOHOL AMNESTIC SYNDROME
	E011000	KORSAKOV'S ALCOHOLIC PSYCHOSIS
	E011100	KORSAKOV'S ALCOHOLIC PSYCHOSIS WITH PERIPHERAL NEURITIS
	E011200	WERNICKE-KORSAKOV SYNDROME
	E011z00	ALCOHOL AMNESTIC SYNDROME NOS
	E012.00	OTHER ALCOHOLIC DEMENTIA
	E012.11	ALCOHOLIC DEMENTIA NOS
	E012000	CHRONIC ALCOHOLIC BRAIN SYNDROME

	E013.00	ALCOHOL WITHDRAWAL HALLUCINOSIS
	E014.00	PATHOLOGICAL ALCOHOL INTOXICATION
	E014.11	DRUNKENNESS - PATHOLOGICAL
	E015.00	ALCOHOLIC PARANOIA
	E01y.00	OTHER ALCOHOLIC PSYCHOSIS
	E01y000	ALCOHOL WITHDRAWAL SYNDROME
	E01yz00	OTHER ALCOHOLIC PSYCHOSIS NOS
	E01z.00	ALCOHOLIC PSYCHOSIS NOS
	Eu10.00	[X]MENTAL AND BEHAVIOURAL DISORDERS DUE TO USE OF ALCOHOL
	Eu10000	[X]MENTAL & BEHAV DIS DUE TO USE ALCOHOL: ACUTE INTOXICATION
	Eu10011	[X]ACUTE ALCOHOLIC DRUNKENNESS
	Eu10100	[X]MENTAL AND BEHAV DIS DUE TO USE OF ALCOHOL: HARMFUL USE
	Eu10200	[X]MENTAL AND BEHAV DIS DUE TO USE ALCOHOL: DEPENDENCE SYNDR
	Eu10211	[X]ALCOHOL ADDICTION
	Eu10212	[X]CHRONIC ALCOHOLISM
	Eu10300	[X]MENTAL AND BEHAV DIS DUE TO USE ALCOHOL: WITHDRAWAL STATE
	Eu10400	[X]MEN & BEHAV DIS DUE ALCOHL: WITHDRAWL STATE WITH DELIRIUM
	Eu10411	[X]DELIRIUM TREMENS, ALCOHOL INDUCED
	Eu10500	[X]MENTAL & BEHAV DIS DUE TO USE ALCOHOL: PSYCHOTIC DISORDER
	Eu10511	[X]ALCOHOLIC HALLUCINOSIS
	Eu10512	[X]ALCOHOLIC JEALOUSY
	Eu10513	[X]ALCOHOLIC PARANOIA
	Eu10514	[X]ALCOHOLIC PSYCHOSIS NOS
	Eu10600	[X]MENTAL AND BEHAV DIS DUE TO USE ALCOHOL: AMNESIC SYNDROME
	Eu10611	[X]KORSAKOV'S PSYCHOSIS, ALCOHOL INDUCED
	Eu10700	[X]MEN & BEHAV DIS DUE ALCOH: RESID & LATE-ONSET PSYCHOT DIS
	Eu10711	[X]ALCOHOLIC DEMENTIA NOS
	Eu10712	[X]CHRONIC ALCOHOLIC BRAIN SYNDROME
	Eu10800	[X]ALCOHOL WITHDRAWAL-INDUCED SEIZURE
	Eu10y00	[X]MEN & BEHAV DIS DUE TO USE ALCOHOL: OTH MEN & BEHAV DIS
	Eu10z00	[X]MENT & BEHAV DIS DUE USE ALCOHOL: UNSP MENT & BEHAV DIS
	E23..00	ALCOHOL DEPENDENCE SYNDROME
	E23..11	ALCOHOLISM
	E23..12	ALCOHOL PROBLEM DRINKING
	E230.00	ACUTE ALCOHOLIC INTOXICATION IN ALCOHOLISM
	E230.11	ALCOHOL DEPENDENCE WITH ACUTE ALCOHOLIC INTOXICATION
	E230000	ACUTE ALCOHOLIC INTOXICATION, UNSPECIFIED, IN ALCOHOLISM
	E230100	CONTINUOUS ACUTE ALCOHOLIC INTOXICATION IN ALCOHOLISM
	E230200	EPISODIC ACUTE ALCOHOLIC INTOXICATION IN ALCOHOLISM

	E230300	ACUTE ALCOHOLIC INTOXICATION IN REMISSION, IN ALCOHOLISM
	E230z00	ACUTE ALCOHOLIC INTOXICATION IN ALCOHOLISM NOS
	E231.00	CHRONIC ALCOHOLISM
	E231.11	DIPSOMANIA
	E231000	UNSPECIFIED CHRONIC ALCOHOLISM
	E231100	CONTINUOUS CHRONIC ALCOHOLISM
	E231200	EPISODIC CHRONIC ALCOHOLISM
	E231300	CHRONIC ALCOHOLISM IN REMISSION
	E231z00	CHRONIC ALCOHOLISM NOS
	E23z.00	ALCOHOL DEPENDENCE SYNDROME NOS
Muscle relaxation		
	N138.00	CERVICALGIA
	N142.00	PAIN IN LUMBAR SPINE
	N142.11	LOW BACK PAIN
	N142.12	LUMBALGIA
	N142.13	ACUTE BACK PAIN - LUMBAR
	N142.14	LUMBAGO
	N142000	LUMBAGO WITH SCIATICA
	N143.00	SCIATICA
	N143.11	ACUTE BACK PAIN WITH SCIATICA
	N144.00	THORACIC AND LUMBOSACRAL NEURITIS
	N144000	THORACIC NEURITIS, UNSPECIFIED
	N144011	THORACIC NERVE ROOT PAIN
	N144100	LUMBOSACRAL NEURITIS, UNSPECIFIED
	N144z00	THORACIC AND LUMBOSACRAL NEURITIS NOS
	N145.00	BACKACHE, UNSPECIFIED
	N145.11	ACUTE BACK PAIN - UNSPECIFIED
	N145.12	BACK PAIN, UNSPECIFIED
	N238.00	MUSCLE CONTRACTURE
	N238000	CONTRACTURE OF PECTORALIS MAJOR
	N238100	CONTRACTURE OF TRICEPS
	N238200	CONTRACTURE OF BICEPS
	N238300	CONTRACTURE OF WRIST FLEXOR(S)
	N238400	CONTRACTURE OF WRIST EXTENSOR(S)
	N238500	CONTRACTURE OF FLEXOR POLLICIS LONGUS
	N238600	CONTRACTURE OF THUMB EXTENSOR(S)
	N238700	CONTRACTURE OF FLEXOR DIGITORUM SUPERFICIALIS
	N238800	CONTRACTURE OF FLEXOR DIGITORUM PROFUNDUS
	N238900	CONTRACTURE OF ADDUCTOR POLLICIS
	N238A00	CONTRACTURE OF OTHER INTRINSIC MUSCLE(S) OF HAND
	N238B00	CONTRACTURE OF ILIOPSOAS
	N238C00	CONTRACTURE OF RECTUS FEMORIS
	N238D00	CONTRACTURE OF ADDUCTOR MUSCLE(S) OF HIP
	N238E00	CONTRACTURE OF ABDUCTOR MUSCLE(S) OF HIP
	N238F00	CONTRACTURE OF HAMSTRING(S)
	N238G00	CONTRACTURE OF QUADRICEPS
	N238H00	CONTRACTURE OF TENDO ACHILLES
	N238J00	CONTRACTURE OF TIBIALIS ANTERIOR
	N238K00	CONTRACTURE OF TIBIALIS POSTERIOR
	N238L00	CONTRACTURE OF LONG TOE FLEXOR(S)

	N238M00	CONTRACTURE OF LONG TOE EXTENSOR(S)
	N238N00	CONTRACTURE OF INTRINSIC MUSCLE(S) OF FOOT
	296..00	O/E - MUSCLE CONTRACTURE
	2962.00	O/E - MUSCLE CONTRACTION
	296Z.00	O/E - MUSCLE CONTRACTURE NOS
	Nyu9300	[X]OTHER CONTRACTURE OF TENDON (SHEATH)
	N084.00	CONTRACTURE OF JOINT
	N084000	JOINT CONTRACTURE OF UNSPECIFIED SITE
	N084100	JOINT CONTRACTURE OF THE SHOULDER REGION
	N084200	JOINT CONTRACTURE OF THE UPPER ARM
	N084211	ELBOW JOINT CONTRACTURE
	N084300	JOINT CONTRACTURE OF THE FOREARM
	N084311	WRIST JOINT CONTRACTURE
	N084400	JOINT CONTRACTURE OF THE HAND
	N084500	JOINT CONTRACTURE OF THE PELVIC REGION AND THIGH
	N084511	HIP JOINT CONTRACTURE
	N084600	JOINT CONTRACTURE OF THE LOWER LEG
	N084611	KNEE JOINT CONTRACTURE
	N084700	JOINT CONTRACTURE OF THE ANKLE AND FOOT
	N084711	ANKLE JOINT CONTRACTURE
	N084800	JOINT CONTRACTURE OF OTHER SPECIFIED SITE
	N084900	CONTRACTURE OF MULTIPLE JOINTS
	N084A00	FLEXION CONTRACTURE-SHOULDER
	N084B00	EXTENSION CONTRACTURE-SHOULDER
	N084C00	ABDUCTION CONTRACTURE-SHOULDER
	N084D00	ADDUCTION CONTRACTURE-SHOULDER
	N084E00	INTERNAL ROTATION CONTRACTURE-SHOULDER
	N084F00	EXTERNAL ROTATION CONTRACTURE-SHOULDER
	N084G00	FLEXION CONTRACTURE - ELBOW
	N084H00	EXTENSION CONTRACTURE - ELBOW
	N084J00	PRONATION CONTRACTURE - FOREARM
	N084K00	SUPINATION CONTRACTURE - FOREARM
	N084L00	FLEXION CONTRACTURE - WRIST
	N084M00	EXTENSION CONTRACTURE OF THE WRIST
	N084N00	ULNAR DEVIATION CONTRACTURE OF THE WRIST
	N084P00	RADIAL DEVIATION CONTRACTURE OF THE WRIST
	N084Q00	FLEXION CONTRACTURE OF MCP JOINT
	N084R00	EXTENSION CONTRACTURE OF MCP JOINT
	N084S00	FLEXION CONTRACTURE OF PIP JOINT
	N084T00	FLEXION CONTRACTURE OF DIP JOINT
	N084U00	FLEXION CONTRACTURE OF HIP
	N084V00	EXTENSION CONTRACTURE OF HIP
	N084W00	ABDUCTION CONTRACTURE OF HIP
	N084X00	ADDUCTION CONTRACTURE OF HIP
	N084Y00	INTERNAL ROTATION CONTRACTURE OF HIP
	N084Z00	EXTERNAL ROTATION CONTRACTURE OF HIP
	N084a00	FLEXION CONTRACTURE OF THE KNEE
	N084b00	EQUINUS CONTRACTURE OF THE ANKLE
	N084c00	CALCANEUS CONTRACTURE OF THE ANKLE
	N084d00	FLEXION CONTRACTURE OF MTP JOINT
	N084e00	EXTENSION CONTRACTURE OF MTP JOINT

	N084f00	FLEXION CONTRACTURE OF TOE IP JOINT
	N084g00	EXTENSION CONTRACTURE OF TOE IP JOINT
	N084z00	CONTRACTURE OF JOINT NOS
	N135.00	TORTICOLLIS UNSPECIFIED
	N135.11	CONTRACTURE OF NECK
	N135000	INTERMITTENT TORTICOLLIS
	N135100	RHEUMATIC TORTICOLLIS
	N135z00	TORTICOLLIS NOS
	N135z11	STIFF NECK NOS
	N135z12	WRY NECK
Convulsions/epilepsy		
	1B1W.00	TRANSIENT EPILEPTIC AMNESIA
	1B63.00	HAD A FIT
	1B63.11	FIT - HAD ONE, SYMPTOM
	1B64.00	HAD A CONVULSION
	1B64.11	CONVULSION - SYMPTOM
	1O30.00	EPILEPSY CONFIRMED
	282..00	O/E - FIT/CONVULSION
	282..11	O/E - A CONVULSION
	282..12	O/E - A FIT
	282..13	O/E - A SEIZURE
	2822.00	O/E - GRAND MAL FIT
	2823.00	O/E - PETIT MAL FIT
	2824.00	O/E - FOCAL (JACKSONIAN) FIT
	2824.11	O/E - JACKSONIAN FIT
	2824.12	O/E - FOCAL FIT
	2825.00	O/E - PSYCHOMOTOR FIT
	2828.00	ABSENCE SEIZURE
	282Z.00	O/E - FIT/CONVULSION NOS
	667..00	EPILEPSY MONITORING
	6675.00	FIT FREQUENCY
	6676.00	LAST FIT
	6678.00	EPILEPSY TREATMENT CHANGED
	6679.00	EPILEPSY TREATMENT STARTED
	667B.00	NOCTURNAL EPILEPSY
	667C.00	EPILEPSY CONTROL GOOD
	667D.00	EPILEPSY CONTROL POOR
	667E.00	EPILEPSY CARE ARRANGEMENT
	667G.00	EPILEPSY RESTRICTS EMPLOYMENT
	667H.00	EPILEPSY PREVENTS EMPLOYMENT
	667J.00	EPILEPSY IMPAIRS EDUCATION
	667K.00	EPILEPSY LIMITS ACTIVITIES
	667L.00	EPILEPSY DOES NOT LIMIT ACTIVITIES
	667M.00	EPILEPSY MANAGEMENT PLAN GIVEN
	667N.00	EPILEPSY SEVERITY
	667Q.00	1 TO 12 SEIZURES A YEAR
	667R.00	2 TO 4 SEIZURES A MONTH
	667S.00	1 TO 7 SEIZURES A WEEK
	667T.00	DAILY SEIZURES
	667V.00	MANY SEIZURES A DAY
	667W.00	EMERGENCY EPILEPSY TREATMENT SINCE LAST APPOINTMENT

	667Z.00	EPILEPSY MONITORING NOS
	8BIF.00	EPILEPSY MEDICATION REVIEW
	9Of3.00	EPILEPSY MONITORING VERBAL INVITE
	9Of4.00	EPILEPSY MONITORING TELEPHONE INVITE
	9Of5.00	EPILEPSY MONITORING CALL FIRST LETTER
	9Of6.00	EPILEPSY MONITORING CALL SECOND LETTER
	9Of7.00	EPILEPSY MONITORING CALL THIRD LETTER
	Eu05212	[X]SCHIZOPHRENIA-LIKE PSYCHOSIS IN EPILEPSY
	Eu06013	[X]LIMBIC EPILEPSY PERSONALITY
	Eu10800	[X]ALCOHOL WITHDRAWAL-INDUCED SEIZURE
	Eu80300	[X]ACQUIRED APHASIA WITH EPILEPSY [LANDAU - KLEFFNER]
	F132100	PROGRESSIVE MYOCLONIC EPILEPSY
	F132z12	MYOCLONIC SEIZURE
	F25..00	EPILEPSY
	F250.00	GENERALISED NONCONVULSIVE EPILEPSY
	F250000	PETIT MAL (MINOR) EPILEPSY
	F250011	EPILEPTIC ABSENCES
	F250100	PYKNO-EPILEPSY
	F250200	EPILEPTIC SEIZURES - ATONIC
	F250300	EPILEPTIC SEIZURES - AKINETIC
	F250400	JUVENILE ABSENCE EPILEPSY
	F250500	LENNOX-GASTAUT SYNDROME
	F250y00	OTHER SPECIFIED GENERALISED NONCONVULSIVE EPILEPSY
	F250z00	GENERALISED NONCONVULSIVE EPILEPSY NOS
	F251.00	GENERALISED CONVULSIVE EPILEPSY
	F251000	GRAND MAL (MAJOR) EPILEPSY
	F251011	TONIC-CLONIC EPILEPSY
	F251111	OTOHARA SYNDROME
	F251200	EPILEPTIC SEIZURES - CLONIC
	F251300	EPILEPTIC SEIZURES - MYOCLONIC
	F251400	EPILEPTIC SEIZURES - TONIC
	F251500	TONIC-CLONIC EPILEPSY
	F251600	GRAND MAL SEIZURE
	F251y00	OTHER SPECIFIED GENERALISED CONVULSIVE EPILEPSY
	F251z00	GENERALISED CONVULSIVE EPILEPSY NOS
	F252.00	PETIT MAL STATUS
	F253.00	GRAND MAL STATUS
	F253.11	STATUS EPILEPTICUS
	F254.00	PARTIAL EPILEPSY WITH IMPAIRMENT OF CONSCIOUSNESS
	F254000	TEMPORAL LOBE EPILEPSY
	F254100	PSYCHOMOTOR EPILEPSY
	F254200	PSYCHOSENSORY EPILEPSY
	F254300	LIMBIC SYSTEM EPILEPSY
	F254400	EPILEPTIC AUTOMATISM
	F254500	COMPLEX PARTIAL EPILEPTIC SEIZURE
	F254z00	PARTIAL EPILEPSY WITH IMPAIRMENT OF CONSCIOUSNESS NOS
	F255.00	PARTIAL EPILEPSY WITHOUT IMPAIRMENT OF CONSCIOUSNESS
	F255000	JACKSONIAN, FOCAL OR MOTOR EPILEPSY

	F255011	FOCAL EPILEPSY
	F255012	MOTOR EPILEPSY
	F255100	SENSORY INDUCED EPILEPSY
	F255200	SOMATOSENSORY EPILEPSY
	F255300	VISCERAL REFLEX EPILEPSY
	F255311	PARTIAL EPILEPSY WITH AUTONOMIC SYMPTOMS
	F255400	VISUAL REFLEX EPILEPSY
	F255500	UNILATERAL EPILEPSY
	F255600	SIMPLE PARTIAL EPILEPTIC SEIZURE
	F255y00	PARTIAL EPILEPSY WITHOUT IMPAIRMENT OF CONSCIOUSNESS OS
	F255z00	PARTIAL EPILEPSY WITHOUT IMPAIRMENT OF CONSCIOUSNESS NOS
	F256.12	WEST SYNDROME
	F257.00	KOJEVNIKOV'S EPILEPSY
	F258.00	POST-ICTAL STATE
	F259.11	OHTAHARA SYNDROME
	F25A.00	JUVENILE MYOCLONIC EPILEPSY
	F25D.00	MENSTRUAL EPILEPSY
	F25E.00	STRESS-INDUCED EPILEPSY
	F25F.00	PHOTOSENSITIVE EPILEPSY
	F25X.00	STATUS EPILEPTICUS, UNSPECIFIED
	F25y.00	OTHER FORMS OF EPILEPSY
	F25y000	CURSIVE (RUNNING) EPILEPSY
	F25y100	GELASTIC EPILEPSY
	F25y200	LOCL-RLT(FOC)(PART)IDIOP EPILEP&EPILPTIC SYN SEIZ LOCL ONSET
	F25y300	COMPLEX PARTIAL STATUS EPILEPTICUS
	F25y400	BENIGN ROLANDIC EPILEPSY
	F25y500	PANAYIOTOPOULOS SYNDROME
	F25yz00	OTHER FORMS OF EPILEPSY NOS
	F25z.00	EPILEPSY NOS
	F25z.11	FIT (IN KNOWN EPILEPTIC) NOS
	Fyu5000	[X]OTHER GENERALIZED EPILEPSY AND EPILEPTIC SYNDROMES
	Fyu5100	[X]OTHER EPILEPSY
	Fyu5200	[X]OTHER STATUS EPILEPTICUS
	Fyu5900	[X]STATUS EPILEPTICUS, UNSPECIFIED
	R003.00	[D]CONVULSIONS
	R003200	[D] FIT
	R003211	[D]FIT (IN NON EPILEPTIC) NOS
	R003y00	[D]OTHER SPECIFIED CONVULSION
	R003z00	[D]CONVULSION NOS
	R003z11	[D]SEIZURE NOS
	Ryu7100	[X]OTHER AND UNSPECIFIED CONVULSIONS
	ZS82.00	ACQUIRED EPILEPTIC APHASIA