Project:

PATTERN OF USE AND SAFETY PROFILE OF BRANDED VS GENERIC ANTIEPILEPTIC DRUGS

1. Introduction

1.1 Background

Epilepsy is a neurologic disorder that affects around 50 million people world-wide, with a significant higher prevalence in developed countries *[1]*. AEDs are generally considered as non-expensive medications; nevertheless, given their high prevalence of use, they represent a relevant expense item for the National Healthcare System. Concerns on safety, adherence and economic impact of AEDs have driven scientific attention towards the concept of clinical equivalence and the role of generic AEDs.

A systematic review of literature conducted on 68 studies concluded that the switch from branded to generic AEDs may lead to relevant differences of bioavailability, which may lead on turn to therapeutic failure, occurrence of adverse drug reactions, and increase in the frequency of epileptic seizures *[2]*.

1.2. Objectives

The primary objectives of this study are:

- to describe the therapeutic pattern of AEDs treatment, comparing generic vs branded medications.
- to assess the risk profile of generic vs branded AEDs in terms of occurrence of all-cause hospitalizations and/or access to emergency department (ED) (safety outcome 1).

The secondary objectives of this study are:

- to assess the risk profile of generic vs branded AEDs in terms of occurrence of possible AEDs-related adverse drug reactions (ADRs) leading to hospitalizations and/or emergency access to ED (safety outcome 2).
- to describe the most frequent AEDs- related ADRs among users of generic vs branded AEDs (safety outcome 3).

2. Material and methods

2.1. Data source and setting

Italy has a tax-based, universal coverage National Health System organised in three levels: national; regional (21 regions); and local (on average 10 Local Health Authorities per region). Healthcare is

managed for every inhabitant by the Local Health Authority where he/she has her regular address. This study will be based on the analysis of data from the Italian region of Tuscany stored in the Agenzia regionale di sanità (ARS) database. The ARS database contains longitudinal pseudonymized patient-level information on the utilization of healthcare services reimbursed by the National Healthcare Service and dispensed to all subjects who are residents and registered with a general practitioner in Tuscany. For each subject registered in the data base, demographic data can be linked to different registries in which information on healthcare services delivered are recorded.

For the purpose of this study, information will be retrieved from the following databases:

- Database of drug dispensing: this registry collects records of prescription drugs dispensed for outpatient use by either territorial or hospital pharmacies, and includes information on active substance name, ATC code, dose, pharmaceutical formulation and date of dispensing.
- Registry of exemptions from co-payment: this registry collects records of subjects in possession of one or more codes of exemption from co-payment for specific healthcare services, obtained for specific clinical or socio-economic reasons specified by the "Decreto del Presidente del Consiglio dei Ministri sui nuovi Lea del 12 gennaio 2017".
- Hospital Discharge Records: this registry collects records of hospital admittance and discharge, and includes information on primary and secondary diagnosis (coded through the ICD-9-CM codes), date of admittance and discharge, and patient's socio-economic level.
- Access to Emergency Department (ED): this registry collects records of ED visit, and includes information on primary and secondary diagnosis (coded through the ICD-9-CM codes), and date of ED access.

2.2. Study population and design

This is a descriptive, population-based, drug utilization study of first year use of AEDs (objective 1), paired with an observational cohort study (objective 2) to assess the association between branded vs generic AEDs with safety outcome in the first year of use. To handle time-varying exposure [3], we will adopt a mixed strategy, partly per-protocol and partly as-treated, as detailed below in Subsection 2.3.1.

The source population corresponds to all subjects active into the database at January the 1, 2015 and that, at this date, had at least 365 days of look-back period. Within such population, all subjects with ≥1 prescription of any AEDs (ATC: N03*) will be identified.

For each subject, the first AED prescription (ATC: N03*) in the study period will be considered as the index prescription, and its date will be considered as the index date.

Subjects prescribed with AEDs in the 12 months before the index date (look-back period) will be excluded.
In addition, we will exclude all subjects with active neoplasia or with history of neoplasia, identified as presence of prescription records and/or hospitalizations related to neoplasia during the look-back (i.e. use of antineoplastic drug (ATC: L01*), and/or hospital discharge records with a diagnosis of neoplasia (ICD-9-CM codes: 140*-208*; 230*-239*) in primary or secondary diagnosis field).

In each analysis, all subjects will accumulate person time from the index date until the first date between: i) end of study period (365 days after index date), ii) patient's death, iii) prescription of an AEDs with an ATC code different from the ATC of the index prescription, iv) prescription records and/or hospitalizations related to neoplasia v) outcome or vi) patient's exit from databases.

2.3. Study variables.

2.3.1. Exposure to antiepileptic drugs

2.3.1.1. First AEDs treatment

The index prescriptions will be classified in four mutually exclusive categories: i) available only as branded AEDs; ii) branded AEDs with generic AEDs available (B); iii) generic AEDs (G) (iv) the index prescription is of two or more different ATCs.
Patients prescribed in (i) and (iv) will be excluded from further analysis.

2.3.1.2 Switching between branded and generic drug

When a patient whose index prescription is B (respectively, G) has a record of a prescription of G (respectively, B) of the same ATC, this event will be labelled B-to-G (respectively, G-to-B) and called a *switch*. If a patient who has experienced a switch has a new prescription belonging to the same category (B or G) as the index drug this event will be labelled B-G-B or G-B-G and called *switch back*.
In the cohort analysis, exposure to category B or G drug will be considered as a time-dependent variable. Each subject will be considered exposed to the first medication (B or G) and will accumulate person-time from index date until the occurrence of a first switch B-to-G or G-to-B. Following such switch, subjects will be considered as exposed to the other medication (G or B), and will accumulate person-time from this change to the exit from the study.

2.3.1.3. Change of AEDs molecule

For each patient, prescription of an x with an ATC code different from the ATC of the index prescription will be considered as a censoring event labelled as *class switch.*

2.3.1.4. Length of AEDs treatment coverage

Length of exposure to each B or G AED treatment will be given in days, and calculated based on duration of delivered prescriptions, calculated by dividing the total amount of active substance contained in each prescription by the relevant Defined Daily Dose (DDD).

Three different scenarios may occur: i) therapeutic coverage of the dispensed drug ends exactly at time of the re-fill (or of the prescription of a different drug); ii) therapeutic coverage of the first drug ends before the re-fill (or the prescription of a different drug); iii) therapeutic coverage of the first drug ends after the of the re-fill (or the prescription of a different drug).

In scenario (iii), therapeutic coverage of the first drug will be censored at the time of delivery of the second drug.

In scenario (ii), the subject will be considered as "*not covered by AEDs treatment*" during the period between the end of the therapeutic coverage of the first drug and the re-fill (or the prescription of a different drug).

2.3.2. Outcome variables

2.3.2.1. Occurrence of hospitalizations and/or access to emergency department

For safety outcome 1, all hospitalization and/or access to ED occurring during follow-up will be considered, independently from the main reason for hospital of ED admission, and time-to-occurrence of this event will be calculated from index date.

For Safety Outcome 2, all hospitalization and/or access to ED occurring during follow-up with a diagnosis of possible AEDs-related ADRs in primary or secondary diagnosis field, will be considered. Diagnosis related to the possible ADRs for AEDs are reported in **Table 1** *[43-6]:*

Table 1. ICD-9-CM codes of AEDs-related ADRs [4-6].

ADRs	Less specific ICD-9-CM codes	More specific ICD-9-CM codes
Self-harm and/or Suicide	E950*-E959*	E950*-E959*
Dermatologic Manifestations (including acne, skin rashes, lupus-like syndrome, Stevens-Johnson's syndrome and/or Toxic epidermal necrolysis (TEN)	690*-698*: other inflammatory manifestations of the skin and subcutaneous tissue 708*- urticaria 782*- symptoms involving the skin or the other integumen tissues	691.8*: atopic dermatitis 692.9*: dermatitis with not specified causes 693.0*: drug-related dermatitis 695*: erythematous affections 695.1: multiform and polymorph erythema (including Stevens-Johnson's syndrome and/or Toxic epidermal necrolysis (TEN)) 708.1*: idiopathic urticaria 782.0*: disorders of the cutaneous sensitivity 782.1: rash 782.3: oedema
Neurologic manifestations	320*-389*: Disorders of the nervous system and of the sense organs 780*: general symptoms 781*: Uncontrolled movements and tremors 784*: Symptoms related to the head or neck	307.81, 346.0 – 346.9, 784.0,: Headache 322*: Aseptic Meningitis 323*: Encephalopathy 334*: Cerebellar atrophy- Ataxia 337.0 – 337.1, 356*-357*: Peripheral neuropathy 780.0*: Alterations in consciousness 780.1*: Hallucinations 780.4: Dizziness 780.09, 780.7*: Somnolence 780.93*: Memory loss 781*: Uncontrolled movements and tremors 784.4*, 784.5*, 784.6*: Word-finding difficulties/ Dysarthria
Psychiatric disorders	290*-319*: Mental disorders	290*: Dementia 301*: Disorders of personality 300.0*, 307.42, 313*: Anxiety 296.2*, 296.3*, 296.5*, 300.4*, 309.*, 311*: Depression 314*: Hyperactivity 307.40-43: Insomnia 290* – 299*: Psychosis
Vision disorders	360*-379*: Ocular diseases	361-362*: Retinopathies 368*: Visual alterations 379.5*: Nystagmus
Pancreatitis	577*: Disorders of pancreas	577.0*: Acute pancreatitis
Cardiovascular effects	420-429*: Cardiac disorders 785*: Symptoms related to the cardiovascular system	427.89,427.9*: Alterations in rhythm 427.3*: Atrial flutter 785.1*: Palpitations

Alterations of laboratory parameters	270*: Disorders of the transport of aminoacids 276*: Disorders of liquids and electrolytes 280*-285*: Anaemia 287*: Purpura and haemorrhagic manifestations 288*: Disorders of white cells	288.09: Agranulocytosis 284*: Aplastic anaemia 281.2: Folate deficiency 270.7: Hyperammonemia 276.1: Hyponatremia 287.3*, 287.4*, 287.5*: Thrombocytopenia
Gastrointestinal manifestations Constipation Diarrhoea Nausea and/or vomiting	787*: Symptoms related to the digestive apparatus 564*: Digestive symptoms, not classified elsewhere	564.0*: constipation 787.91: diarrhoea 787.0*: nausea or vomiting
Metabolism and Nutrition Anorexia/Appetite Reduction	783*: Symptoms related to the nutrition, metabolism and growth. 306.4*: Psychogenic vomiting 307.50: Not specified nutrition disorders	783.0*: anorexia 307.1*: nervous anorexia
General symptoms	780*: General symptoms	780.6*: fever 780.7*: fatigue
Falls and fractures	733.1*: Pathologic fractures (excluding traumatic and stress fractures) 733.93-733.95: Stress fractures 850*-854*: Intracranial traumatism (excluding cranial fractures) 830*-848*: Dislocations 860-869*: Thoracic and abdominal traumatism 905*-908*: Aftereffects of trauma 920*-924.9*: Contusions	800*-829*: Traumatic fractures E880*-E888*:Accidental falls
Car or (motor)bike accidents	E826*-E829*: Accident of road vehicles	E826*-E829*: Accident of road vehicles

2.3.2.2. Classification of AEDs-related ADRs

For safety outcome 3, AEDs- related ADRs identified as reported in section 2.3.2.1, will be classified in non-mutually exclusive classes (Table 1): i) Self-harm and/or Suicide; ii) Dermatologic Manifestations; iii) Neurologic manifestations; iv) Psychiatric disorders; v) Vision disorders; vi) Pancreatitis; vii) Cardiovascular effects; viii) Alterations of laboratory parameters; ix)

Gastrointestinal manifestations; x) Metabolism and Nutrition, xi) General symptoms; xii) Falls and fractures; xiii) Car or (motor)bike accidents.

2.3.3. Variables

2.3.3.1. Demographic and socio-economic characteristics

Demographic characteristics (sex, age at index date) will considered.

Socio-economic level will be estimated based on hospital discharge records occurring during the look-back period, considering the educational level recorded in such database. For subjects that changed their educational level during two or more subsequent hospitalisations occurred in the look-back period, only the highest educational level will be considered.

Educational level will be adjusted by subject's age and stratified in: low educational level (for subjects born before year 1952: no education or primary school certificate; for subjects born after year 1952: no education or primary school certificate or intermediate school certificate), intermediate (for subjects born before year 1952: intermediate school certificate; for subjects born after year 1952: high school certificate) or high level (for subjects born before year 1952: high school certificate or university degree; for subjects born after year 1952: university degree).

For subjects with no hospital discharge record during the look-back period, or with no information on educational level recorded in such database, socio-economic level will be estimated based on the deprivation index of their district of residence, obtained from the 2011 census of the national institute of statistics.

2.3.3.2. Clinical characteristics

The following comorbidities will be measured during the look-back period, based on drug dispensing, diagnosis recorded at hospital discharge, and possession of exemptions from co-payment (**Table 2**).

Table 2. ATC codes , ICD-9-CM codes and codes of exemptions from co-payment, related to the considered comorbidities.

Comorbidity	**ATC codes**	**ICD-9-CM codes**	**Codes of exemptions from co-payment**
Disorders of the Central Nervous System			
Anxiety	N05B*	300.0*	
Depression	N06A*	296*, 300.4*, 309*, 311*	
ADHD syndrome	N06B*	314.0*	
Dementia	N06D*	290*	011 (Dementia) or 029

			(Alzheimer's disease)
Parkinson	N04*	332*	038
Diabetes	A10*	250*	013
Hypertension	C02*-C03*	401*-405*	A31 or D31
Cardiac comorbidities	between C07* and C10*	393*-398*, 410*-417*, 423*-429*, 430*-441*	A02 or B02 or 021 (heart failure)
Renal failure	-	584*-585*	023 (chronic renal failure)
Alcohol or drug abuse and/or alcohol-related disease	-	303*, 304*, 305.0, 357.5, 425.5, 353*, 571.0 – 571.3, 790.3, V11.3	014*

In addition, for each patient, the sum of the number of hospital admissions and of emergency department visits occurred in the look-back period will be calculated, as a proxy of the complexity of the clinical condition.

2.3.3.3. Therapeutic indication for use of antiepileptic drugs

Indication for use of AED is not available directly in the database and must therefore be approximated using existing information.

Subjects prescribed with AEDs with ATC code N03AD01, N03AF03, N03AF04, N03AX15, N03AX17, N03AX18, N03AX21, N03AX22 or N05BA09 will be considered as treated for epilepsy (EPI), given that these medications are only prescribed for this indication.

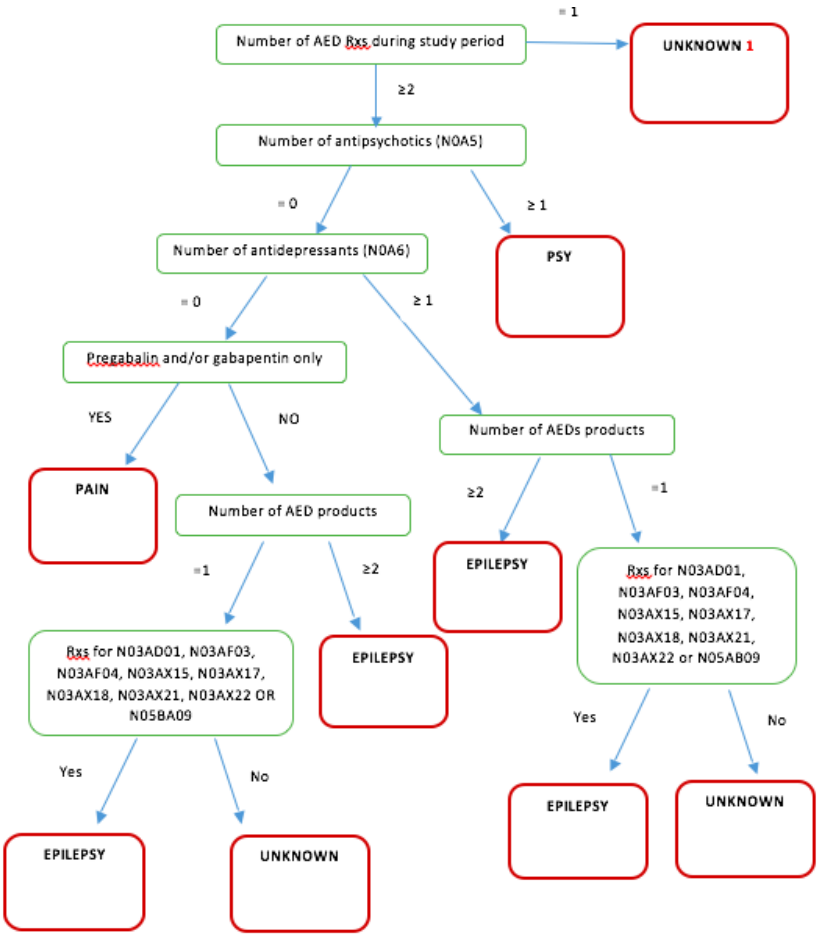
For subjects prescribed with AEDs with ATC code different for the above mentioned ones, indication for AEDs use will be estimated based on diagnosis of hospital discharge records occurred in the 365 days of look-back: subjects with a diagnosis of EPI (ICD-9-CM codes 345* or V172*) in primary or secondary diagnosis field will be considered as taking AEDs for the treatment of EPI; subjects with a diagnosis related to psychiatric condition (PSY) (ICD-9-CM codes 295* or 296* or 297* or 298* or 299*) in primary or secondary diagnosis field will be considered as taking AEDs for the treatment of PSY. Subjects with both a diagnosis of EPI and PSY will be considered as taking AEDs for the treatment of EPI.

For subjects with no hospital discharge record related to EPI or PSY during the look-back period, indication for AEDs use will be estimated based on codes of exemptions from co-payment: subjects in possession of the code of exemptions from co-payment 017 will be considered as affected by EPI, whereas subjects possessing the code of exemptions 044 (psychosis) will be considered as treated for PSY. Subjects with both exemptions from co-payment related EPI and PSY will be considered as taking AEDs for the treatment of EPI.

For subjects with no hospital discharge record related to EPI or PSY during the look-back period and not in possession of exemptions from co-payment related to EPI or PSY, indication for AEDs use

will be estimated according to the algorithm proposed by Naldi et al and represented in **Figure 1** [7]. This algorithm will be applied in the first 365 days following index date.

Figure 1. Prescription-based classification tree to distinguish subjects with epilepsy (EPI) or psychiatric disorders (PSY) [Naldi et al, 2016].



2.4. Analysis plan

2.4.1 Descriptive analysis

To fulfil objective 1, we will describe the most frequently prescribed index drugs, in terms of both active principle (ATC level V) and exposure classes defined in section 2.3.1.1.

The proportions of subjects experiencing *switches* or *switches back* will be calculated and compared among subjects initially treated with generic vs branded AEDs, using the Chi-square test.

In addition, the median number of changes (either *switches* or *switches back*) and related interquartile range (IQR) will be calculated and compared among subjects initially treated with generic vs branded AEDs, using the U-Mann-Whitney test.

Most frequent *class switches* (from which molecule to which molecule) will be reported, and median time to *class switches* and IQR will be calculated.

The most frequent AEDs- related ADRs experienced among subjects treated with generic vs branded AEDs will be evaluated (safety outcome 3). The proportion of subjects within each AEDs- related ADR class reported in section 2.3.2.2 will be compared among subjects exposed to generic vs branded AEDs, using the Chi-square test.
Statistical significance will be considered for p-values <0.05.

2.4.2. Calculation of the propensity score

Since it is likely that there is imbalance in the baseline characteristics between subjects treated with branded or generic AEDs, we will use propensity score matching to balance the baseline characteristics between these two groups reported in sections 2.3.3.1 and 2.3.3.2 *[8]*. We will use multivariate logistic regression to estimate each patient's propensity score, which is the conditional probability of them being exposed to branded or generic AEDs given their baseline characteristics *[9]*. The a propri decided covariates included in the regression will be: sex, age, socio-economic level, comorbidities (including: disorders of the central nervous system, diabetes, hypertension, cardiac comorbidities, renal failure, alcohol or drug abuse), and therapeutic indication for use of AEDs as known before index date *[10-13]*. We will then form pairs of subjects treated with branded vs generic AEDs by using the Stata routine PSmatch2 to perform nearest number matching with a caliper of 0.2. of the SD of propensity score *[14-16]*.
Standardised differences between subjects with branded vs generic AEDs will be computed for each covariate. A standardised difference of ≤0.1 will be considered to denote negligible imbalance between the two groups, to select an optimal propensity score matching model *[17]*.

2.4.3. Statistical analysis

Continuous variables will be reported as mean values and standard deviation or as median values and interquartile range, and will be compared using the t-Student or the Mann-Whitney test, according to data distribution. Categorical variables will be reported as absolute frequencies and percentages, and will be compared using the Chi-square test.
Incident users of AEDs, stratified in mutually exclusive categories according indication for AEDs use, will be described in terms of sex and age at index prescription.
Statistical significance will be considered for p-values <0.05.

The risk of hospitalization and/or access to ED for any cause (safety outcome 1) will be estimated for patients exposed to generic vs branded AEDs, separately according to indication for AEDs use.

A mixture of as-treated and per-protocol analysis will be adopted: exposure to branded or generic drug will be defined as a time-dependent variable, and estimated as reported in section 2.3.1.
Subjects exposed to a generic drug as first treatment will be matched by propensity score and first ATC code prescribed, to subjects exposed to branded drug as a first treatment, using a 1:5 ratio. Cox regression models adjusted by indication for AEDs use and conditioned by propensity score will be applied to estimate Hazard Ratios, with 95% confidence intervals, of acute events in patients exposed to generic versus branded AEDs.
Type of AEDs active principle will be considered as an effect modifier of the association between branded/generic and outcomes. Sub-group analysis will be conducted within strata of different ATC codes.

The risk of hospitalization and/or access to ED for possible AEDs- related ADRs (safety outcome 2) will be estimated for patients exposed to generic vs branded AEDs, separately according to indication for AEDs use. For this analysis, only the first hospitalization and/or access to ED will be included and only the date of this first AEDs-related event will be considered, i.e. subsequent additional hospitalizations and/or access to ED for possible AEDs- related ADRs will not be considered.

As for outcome 1, a per-protocol analysis will be adopted: exposure to branded or generic drug will be defined as a time-dependent variable, and estimated as reported in section 2.3.1.
Subjects exposed to a generic drug as first treatment will be matched by propensity score and first ATC code prescribed, to subjects exposed to branded drug as a first treatment, using a 1:5 ratio. Subjects treated with AEDs from whom only branded drug was available, will be excluded.

Adjusted Cox regression models will be applied to estimate Hazard Ratios, with 95% confidence intervals, of acute events in patients exposed to generic versus branded AEDs.
Type of AEDs active principle will be considered as an effect modifier of the association between branded/generic and outcomes. Sub-group analysis will be conducted within strata of different ATC codes.

2.4.4. Stratified analysis

Risk of all cause hospitalizations and/or access to EDs, and risk of AEDs-related events (safety outcome 1 and 2) will be further evaluated among strata of different AEDs active principles (effect modifiers).

Occurrence of the different AEDs- related ADRs (safety outcome 3) will be stratified according to AEDs active principle.

2.4.5. Sensitivity analysis

Two sensitivity analysis will be conducted, to verify whether results are influenced by the methodology used to estimate therapeutic coverage (section 2.3.1.4).
In the first sensitivity analysis, in scenario (ii) described in section 2.3.1.4, subject will be considered as still exposed to the previous drug during all the period between the end of the therapeutic coverage of the first drug estimated using DDD, and the re-fill (or the prescription of a different drug).
In the second sensitivity analysis, in scenario (iii) described in section 2.3.1.4, subject will be considered as still exposed to the previous drug until the end of the therapeutic coverage of the first drug estimated using DDD, with exposure to the second drug starting at the end of the therapeutic coverage of the first drug. In case of re-fill of the same drug, exposure as defined in the main analysis will remain unaltered in this sensitivity analysis. On the contrary, in case of switch from B to G (respectively, from G to B), the subjects will be considered as still exposed to B (respectively, to G) until the end of the therapeutic coverage estimated using DDD, with exposure to G (respectively, to B) starting at the end of the therapeutic coverage of the first drug.

2.4.6. Validation analysis

A validation analysis will be conducted, to verify whether or not the algorithm proposed in section 2.3.3.3. is a valid tool for the identification of the treatment indication.
To this aim, only subjects with hospital discharge records related to EPI or PSY in the 365 days of look-back and/or in possession of the code of exemptions from co-payment for EPI or PSY, will be considered.
For these subjects, indication for AEDs use will be estimated by applying the above mentioned algorithm.
Indications for AEDs treated estimated using the algorithm will be compared with the indications captured from hospital discharge records and/or exemptions from co-payment. The sensitivity and specificity of the algorithm in distinguish EPI and PSY will be estimated.

Given that this algorithm is derived from a study from Naldi et al. [7], that validated it in a setting of young women, this sensitivity analysis will be conducted separately for women in fertile age and for all other subjects in the cohort.

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