12 February 2019
EMA//2019/

Prescribing of codeine for treatment of pain in children: a comparison of results in the transformed THIN OMOP Common Data Model format vs. the THIN source database

1. PASS information

Title	Prescribing of codeine for treatment of pain in children: a comparison of results in the transformed THIN OMOP Common Data Model format vs. the THIN source database
Protocol version identifier	1.0
Date of last version of the protocol	12 February 2019
EU PAS Register No:	Study not registered
Active substance	Codeine ATC codes: R05DA04, N02AA59, N02AA79, N02AG, N02B, N02C and M01
Medicinal product(s):	Multiple
Product reference:	
Procedure number:	
Study initiator	EMA
Research question and objectives	This descriptive study will examine the patterns of prescribing of codeine-containing products for treatment of pain in children in the period 2010-2017 in the UK, and compare results after conversion of data into the OMOP Common Data Model (CDM) format with results from the original THIN source database. The THIN source database and its CDM version are provided by IQVIA. The main objective of the study is to evaluate the implementation of the OMOP CDM in the THIN database and explore any potential loss of information, difference in results and conclusions
Authors	Gianmario Candore & Karin Hedenmalm

Marketing authorisation holder

Marketing authorisation holder(s)	Multiple

Table of contents

List of Abbreviations

ATC: Anatomical Therapeutic Chemical, World Health Organisation classification system for drugs

CDM: Common Data Model

EMA: European Medicines Agency

EHR: Electronic Health Records

EU: European Union

GP: General Practitioner

OMOP: Observational Medical Outcomes Partnership

PRAC: Pharmacovigilance Risk Assessment Committee

SNOMED CT: Systematized Nomenclature Of Medicine, Clinical Terms

THIN: The Health Improvement Network

2. Responsible parties

Project lead: Gianmario Candore

Epidemiologist: Gianmario Candore

Clinical lead: Karin Hedenmalm

Statistical lead: Jim Slattery

Project sign off: Peter Arlett

3. Rationale and background

Between 2012 and 2013 the PRAC undertook a review of the benefit risk balance of codeine for treatment of pain in children.

The following updates to the SmPCs for codeine-containing products indicated for the treatment of pain were agreed in June 2013:

- Codeine is now only indicated in patients ≥12 years of age for the treatment of acute moderate pain that cannot be relieved by other analgesics such as paracetamol or ibuprofen (alone)
- Codeine should be used at the lowest effective dose for the shortest period of time
- Codeine is now contraindicated in all paediatric patients (0 - <18 years of age) who undergo tonsillectomy or adenoidectomy for obstructive-sleep-apnoea syndrome and in patients of any age who are known to be CYP2D6 ultra-rapid metabolisers (up to approximately 10% of Caucasians are CYP2D6 ultra-rapid metabolisers, but prevalence differs according to racial and ethnic group), due to an increased risk of developing serious and life-threatening adverse reactions, and in women who are breastfeeding

4. Research question and objectives

This descriptive study will examine the patterns of prescribing of codeine-containing products for treatment of pain in children in the period 2010-2017 in the UK using the THIN database in two different formats: the source database and the converted database, OMOP CDM version 5.2.

The main objective of the study is to evaluate the implementation of the OMOP CDM in the THIN database by exploring differences in estimates between the THIN source database and the THIN OMOP CDM database, and evaluate whether any such differences result in a change in the interpretation of the results.

Specific aims include estimating in both formats of THIN the following:

- The proportion of children with a prescription for codeine
- The use of codeine in children who have undergone tonsillectomy and/or adenoidectomy
- The distribution of durations in individual codeine prescriptions in children
- The proportion of codeine use in children that follows documented attempts to control pain with other analgesics
- Examine whether a diagnosis of apnoea affects the use of codeine in children with tonsillectomy and/or adenoidectomy

Differences in estimates between the THIN source data and the CDM format of THIN will be investigated to understand the root cause.

5. Research methods

5.1. Study design

A validation study of results from descriptive analyses in an electronic health record (EHR) database for data converted into OMOP CDM vs. original source data.

A retrospective cohort of paediatric patients 0-17 years from up-to-standard practices will be identified between 2010 and 2017, and the prescribing of codeine-containing products will be examined in this group.

5.2. Setting and data sources

The THIN database contains electronic primary care medical records extracted from over 500 general practices across the UK covering approximately 6% of the UK population. Data is representative of the UK population in terms of age, deprivation, and geographical distribution and patients are linked via an anonymous patient ID number allowing them to be followed longitudinally over time. Diagnoses, symptoms, procedures, and other relevant health information are recorded using the Read Code clinical classification system, which is a hierarchical classification system for coding of patient data. Drug exposures are recorded using Gemscript codes.

OMOP CDM represents a transformation of data from a source database into a common format with standardised vocabulary[1]. The process includes mapping of terms from the original vocabulary to a standardised vocabulary. OMOP CDM utilises Unified Medical Language System controlled vocabularies. Read codes for conditions and procedures are mapped to Systematized Nomenclature Of Medicine, Clinical Terms (SNOMED CT), and Gemscript codes for drug products are mapped to RxNorm and

[1] Voss EA, Makadia R, Matcho A, Ma Qianli, Knoll C, Schuemie M, DeFalco FJ, Londhe A, Zhu V, Ryan PB. Feasibility and utility of applications of the common data model to multiple, disparate observational health databases. JAMIA 2015; 22 (3): 553-564.

RxNorm Extension. The controlled vocabularies in OMOP CDM are hierarchical. Overarching terms are called 'ascendants'. Terms that are encompassed by an overarching term are called 'descendants'. More information about the identification of products in RxNorm and RxNorm Extension is provided in Annex 1.

The study period will be from 1st January 2000 to 31st December 2016 / 30th June

2018 according to the IMRD-UK version used (1705 or 1809).

5.2.1. Study population

The study population will include children below the age of 18 years. Date of birth will be the first day of the month of birth as available or imputed.

Patients will enter the study at the latest of their current registration date, the date the practice mortality recording rate reached an acceptable level, the Vision date or the 1st January 2010. Follow up will be censored at the date the patient transferred out of the practice, the 18th birthday, the date of last practice data collection, or 31st December 2017, whichever is earliest.

Children one year of age or older are required to have at least one year of follow up, children below the age of one year entered the study at the registration date plus a follow-up period corresponding to the age at the registration date.

5.2.2. Codeine exposure

All products that contain plain codeine, codeine in combination with an analgesic or NSAID, and codeine in combination with an analgesic and an antihistamine will be included in the study and are considered to represent codeine for treatment of pain. Codeine for treatment of pain will then be separated into the following categories:

- Oral solution plain codeine
- Solid oral formulation plain codeine (including dispersible forms)
- Combination with analgesics/NSAIDS
- Combination with an analgesic and an antihistamine

Other plain codeine products, e.g. codeine for injection, are not considered as separate categories, but are included in the study in the overall codeine category. Details about the selection of codeine products in the study are provided in section 5.6.2.1.

Since the study is intended to address only codeine for treatment of pain, the following codeine combinations will be excluded from the study regardless of formulation:

- Codeine in combination with menthol, sympathomimetics, antitussives, expectorants, antihistamines (without analgesic or non-steroidal anti-inflammatory agent), or herbal cough ingredients
- Codeine in combination with antispasmodic agents or antidiarrheals

In counting prescriptions only one prescription within the same category (see above) will be counted on any one day for any patient. Each prescription will be associated to the six month interval or year when the prescription was issued.

5.2.3. Surgery codes

Tonsillectomy/adenoidectomy will be defined by the presence of Read codes and SNOMED-CT codes. Details about the selection of codes are provided in section 5.6.2.2 and selected codes are included in Annex 2. The date of an adenoidectomy or tonsillectomy will be assumed to be the first date on which it is coded by the GP. Exploratory analysis shows that there are patients with a repeat record of adenoidectomy or tonsillectomy more than 3 weeks after the first occurrence. These repeat occurrences are difficult to explain and this study will therefore only consider the first occurrence of either event in the study independently of when another occurrence happens.

Children with a prescription for codeine within ±30 and ±90 days of the surgery date will be identified.

5.2.4. Sleep apnoea

Details about the selection of codes for sleep apnoea are provided in section 5.6.2.3 and identified sleep apnoea codes are listed in Annex 3. These codes will be searched ever before and up until the surgery date, and analyses will be split by whether such a code is found.

5.2.5. Other analgesics

Use of other analgesics, defined as ATC codes M01A (NSAIDs; Non-steroidal Anti-Inflammatory Drugs), M01B (Antiinflammatory/antirheumatic agents in combination), N02A (Opioids) or N02B (Other analgesics and antipyretics), excluding codeine, and in keeping with the exclusion criteria for codeine exposure in section 5.2.2 of the protocol (i.e. excluding analgesics in combination with menthol, sympathomimetics, antitussives, expectorants, herbal cough ingredients, antispasmodic agents or antidiarrheals), within 90 days preceding the codeine prescription will be identified

Details about the selection of codes for other analgesics are provided in section 5.6.2.4.

5.3. Variables

In tabulations the following variables and classifications will be used:

1. Time: from January 2010 to December 2017 in six month (Jan-Jun and Jul-Dec) and yearly intervals. Persons will only count once for each time interval

2. Gender: male or female

3. Age: 0 to <12 years and 12 to <18 years.

4. Recent surgery: within 30 and 90 days of the surgery.

5. Apnoea: a code indicative of apnoea within one year prior to surgery. Any code of apnoea recorded within a year of surgery will be counted as with apnoea, regardless of any record of apnoea for the same patient more than one year prior to surgery.

6. Product type: oral solution plain codeine products (Liquid), solid oral plain codeine products (Solid), combination products containing codeine in combination with analgesics or NSAIDs (Combanalges1) and combination products containing codeine in combination with an analgesic and an antihistamine (Combanalges2).

7. Previous analgesic: recorded prescription for a non-codeine containing analgesic within the 90 days preceding a codeine prescription.

5.4. Study size

This study is a descriptive analysis of EHR data. No sample size or statistical precision calculation is performed.

5.5. Data management

Data extraction and management will be performed in SAS Enterprise Guide 7.13.

5.6. Data analysis

This analysis is descriptive in nature.

5.6.1. Data tabulations

The following tabulations will be presented from the THIN source database and from THIN OMOP CDM for each six-monthly and yearly time interval:

- The number of children in the study population by gender and by age
- The prevalence as the number of children with a prescription for one of the codeine products in the study divided by the number of children belonging to the study population stratified by product type, gender, and age
- The number of prescriptions of any codeine product in the study stratified by product type, gender, and age
- The prevalence for total use of codeine for pain for children that have a record of a tonsillectomy, adenoidectomy or combined tonsillectomy/adenoidectomy. The prevalence estimations will use as denominator those children that have undergone the respective procedures during the time interval ± 30 and 90 days. The prevalence of use of codeine will be stratified by gender, and by age
- The prevalence as above but only for children with a diagnosis of sleep apnoea (see also section 5.2.4)
- The duration of use of codeine: mean (standard deviation), median (25th to 75th percentiles) and range, stratified by product type, gender, and age
- The proportion of all children with a codeine prescription that had another analgesic prescribed within 90 days before the codeine prescription stratified by gender, and by age

5.6.2. Codes for THIN source database and THIN OMOP CDM

5.6.2.1. Codes for codeine exposure

In the THIN source database, Gemscript codes for codeine products will be identified by searching generic names for text strings ('codeine' and trade names for combination products; 'tercolix', 'solpadeine', 'migraleve', 'co-codaprin', 'co-codamol', 'codagesic', 'propain', 'ultramol' paradein'), by searching for the bnf codes 4.7.1 (Non-opioid analgesics and compound preparations) and 4.7.2 (Opioid analgesics), and by searching for the ATC code for plain codeine (R05D A04).

In the THIN OMOP CDM, 'descendants' to codeine will be identified by searching for the Ingredient 'codeine'. Subsequently, all Clinical Drug Formulations and Branded Drug Component will be reviewed and classified. If the same 'descendant' is classified as 'plain codeine unknown formulation' on the basis of the Branded Drug Component and as 'plain codeine oral solution' or as 'plain codeine solid oral formulation' on the basis of the Clinical Drug Formulation, the Clinical Drug Formulation will determine

how the ‘descendant’ is classified. If the same descendant has more than one Clinical Drug Formulation, the most inclusive category will be selected, e.g. ‘codeine in combination with an analgesic and an antihistamine’ will be preferred over ‘codeine in combination with analgesics or NSAIDs’. The selected Clinical Drug Formulations and Branded Drug Components and all of their ‘descendants’ will be included.

5.6.2.2. Codes for tonsillectomy and adenoidectomy

In the THIN source database, Read codes for tonsillectomy and adenoidectomy will be identified by searching for the text strings ‘tons’ and ‘adenoi’.

In the THIN OMOP CDM, SNOMED CT codes for procedures and conditions related to tonsillectomy and adenoidectomy will also be identified by searching for the text strings ‘tons’ and ‘adenoi’. The most overarching terms that encompass all relevant ‘descendants’ will be selected. The selected SNOMED CT codes and all ‘descendants’ will be included.

5.6.2.3. Codes for sleep apnoea

In the THIN source database, Read codes for sleep apnoea will be identified by searching for the text strings ‘apno’ or ‘apne’.

In the THIN OMOP CDM, SNOMED CT codes for procedures and conditions related to sleep apnoea will be identified by searching for codes with the text string ‘apne’. The most overarching terms that encompass all relevant ‘descendants’ will be selected. The selected SNOMED CT codes and all ‘descendants’ will be included.

5.6.2.4. Codes for other analgesics

All active substance names in ATC codes M01A, M01B, N02A and N02B, excluding codeine as well as papaveretum and opium, which contain spasmolytics, have been considered. The WHO ATC code system will be used for classification of products except in case of systemic administration of plain acetylsalicylic acid, which will be considered to be for pain for the purpose of this study, even if acetylsalicylic acid is contraindicated for pain in younger children due to a risk of Reye’s syndrome and low dose acetylsalicylic acid may be used for antithrombotic treatment. Any use of plain acetylsalicylic acid is expected to be low.

Text strings to target active substances in ATC codes M01A, M01B, N02A and N02B in the THIN source database, searching generic names for Gemscript codes, include the following:'enylbuta', 'mofebuta', 'oxyphenbuta', 'oxyfenbuta', 'clofezon', 'kebuzon', 'indomet', 'sulindac', 'tolmetin', 'zomepir', 'diclofenac', 'alclofenac', 'bumadi', 'etodolac', 'lonazolac', 'entiazac', 'acemeta', 'enpiramid', 'oxameta', 'proglumeta', 'ketorolac', 'aceclofenac', 'bufexamac', 'mefenam', 'tolfenam', 'flufenam', 'meclofenam', 'celecoxib', 'rofecoxib', 'valdecoxib', 'parecoxib', 'etoricoxib', 'lumiracoxib', 'polmacoxib', 'tenidap', 'oxaceprol', 'chondroitin', 'soyabean oil', 'feprazon', 'piroxicam', 'tenoxicam', 'droxicam', 'lornoxicam', 'meloxicam', 'ibuprofen', 'naproxen', 'ketoprofen', 'enoprofen', 'enbufen', 'benoxaprofen', 'suprofen', 'pirprofen', 'flurbiprofen', 'indoprofen', 'tiaprofen', 'oxaprozin', 'ibuproxam', 'dexibuprofen', 'flunoxaprofen', 'alminoprofen', 'dexketoprofen', 'naproxcinod', 'nabumeton', 'niflumic', 'azapropazon', 'glucosamin', 'benzydamin', 'sulfated glycosaminoglycan', 'proquazon', 'orgotein', 'nimesulid', 'feprazon', 'diacerein', 'morniflumat', 'dipyrocetyl', 'acetylsalic', 'aspirin', 'morphin', 'morfin', 'hydrom', 'nicomor', 'oxycodon', 'dihydrocod', 'ketobemidon', 'pethidin', 'fentanyl', 'dextromoramid', 'piritramid', 'dextropropox', 'buprenorphin', 'bezitramid', 'methadon', 'pentazocin', 'enazocin', 'butorphanol', 'nalbuphin', 'tramadol', 'tilidin', 'dezocin', 'meptazinol', 'tapentadol', 'aloxiprin', 'choline salicyl', 'sodium salicyl', 'salsalat', 'ethenzamid', 'morpholine salicyl', 'dipyrocetyl', 'benorilat', 'diflunisal', 'potassium

salicyl', 'guacetisal', 'carbasalat', 'imidazole salicyl', 'salicylamid', 'enazon', 'metamizol', 'paracetamol', 'acetaminophen', 'enacetin', 'bucetin', 'propacetamol', 'rimazolium', 'glafenin', 'floctafenin', 'viminol', 'nefopam', 'flupirtin', 'ziconotid', 'methoxyfluran', 'cannab', 'co-dydramol', and 'codydramol'.

The same text strings will be used for THIN OMOP CDM to search among Ingredients in RxNorm/RxNorm Extension, except that 'sulfated glycosaminoglycan' will be used instead of 'glycosaminoglycan'. In addition, the text strings: 'diacetylrhein', 'apazone', 'meperidin', 'piritramide', 'propoxyphene', 'aminopyrin', 'choline', 'salicylic acid', 'imidazole-2-hydroxybenz', 'pirinitramid', 'dipyron' and 'antipyrin' will also be used for RxNorm/RxNorm Extension ingredient names. All 'descendants' to selected Ingredients will be identified.

In OMOP CDM all children treated with codeine in the study will first be identified. All other prescriptions besides codeine in these children during the study period will then be linked to the identified 'descendants' to other analgesics, and the linked 'descendants' will be classified.

5.6.3. Calculation of duration in codeine prescriptions

The duration will be determined from the variable prscdays, and if this is missing, it will be calculated from the variables prscqty and dosgval. Prscqty values ≤1 will be excluded

5.7. Strengths and limitations of the research methods

- THIN collects anonymised observational data from a sample of GPs in the UK, linked to demographic and socioeconomic data. In the UK, GPs act as gatekeepers, and patients need to be registered with a GP for their health care. The population of THIN is considered representative of the general population in terms of gender and age distribution, and patients are followed longitudinally. Estimates of prevalence of use are therefore considered valid
- A potential limitation of this study is that tonsillectomies and adenoidectomies are carried out in secondary care, and it is possible that not all procedures are recorded in the database
- Another potential limitation is that data on dose and duration may be incomplete
- The use of other analgesics will be studied as the proportion of children with a codeine prescription that have received a prescription for an analgesic medicine. Analgesic medicines may, however, also be prescribed for other purposes than pain, and no attempt will be made to determine to what extent they were prescribed for pain
- Any differences between the THIN source database and in the THIN CDM database will be investigated.

6. Plans for communicating study results

The study including the protocol will be registered in the ENCePP E-Register of Studies http://www.encepp.eu/encepp/studiesDatabase.jsp which currently serves as the EU PAS register referred in the Module VIII of the good pharmacovigilance practices (GVP) on post-authorisation studies.

Annex 1

Common Data Model: Identification of Gemscript products in RxNorm and RxNorm Extension

Gemscript codes for drug products in The Health Improvement Network (THIN) database are mapped to the vocabularies RxNorm and RxNorm Extension. RxNorm is a Unified Medical Language System controlled vocabulary with a hierarchical structure.

In RxNorm and RxNorm Extension, available (clinical) information on the composition of a drug product (active ingredients, strength and formulation) is extracted. This information can then be utilised in order to identify relevant products.

The first hierarchical level of interest for this study is the Ingredient, which consists of a single active substance. Please see Figure on next page for the hierarchical relationships. Ingredients generally use the United States Adopted Name (USAN). A multi-ingredient product is linked to more than one Ingredient.

One level below the Ingredient the hierarchy defines the:

1) Clinical Drug Component, which consists of a single active substance and the strength of the substance, and the

2) Clinical Drug Formulation, which includes all active substances in the product and the formulation of the product.

A multi-ingredient product is linked to more than one Clinical Drug Component.

Two levels below the Ingredient the hierarchy defines the:

1) Clinical Drug, which contains all active substances in the product, their strengths, and the formulation of the product, and the

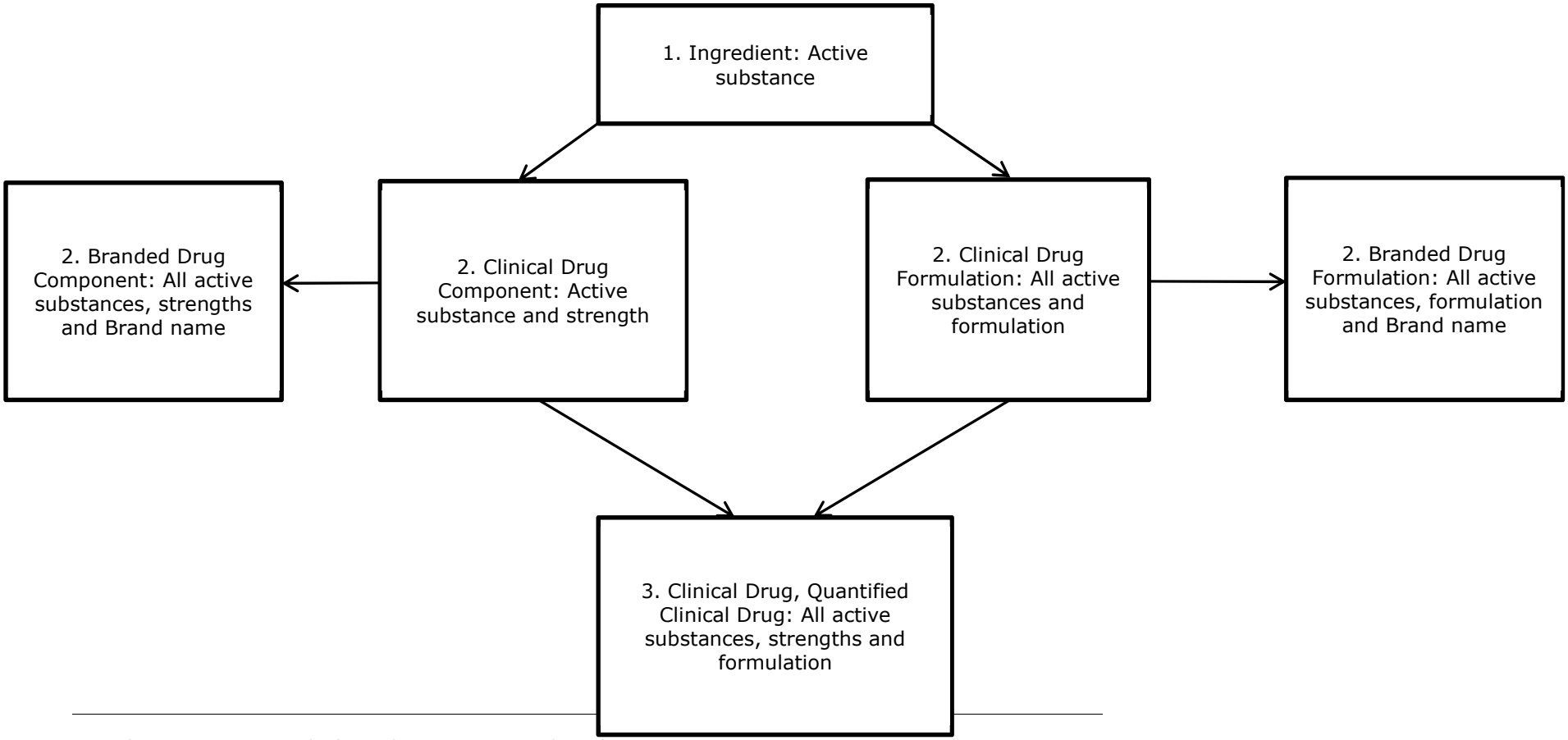
2) Quantified Clinical Drug, which contains the same information as the Clinical Drug, and the size (such as volume of a liquid product).

Each Clinical Drug Component is associated with one or more corresponding Branded Drug Components, which contain the brand name, all active substances in the product and the strength of each active substance. Similarly, each Clinical Drug Formulation is associated with one or more corresponding Branded Drug Formulations, which contain the brand name, all active substances in the product, and the formulation.

If an Ingredient is selected along with all its descendants, then all products (including branded products) that contain the ingredient will be included. Similarly, if a Clinical Drug Formulation is selected along with all its descendants, then all products (including branded products) that contain the same active ingredients and formulation will be included.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Figure of hierarchy in RxNorm and RxNorm Extension



7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8613
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Annex 2

List of selected Read codes for tonsillectomy and adenoidectomy in the THIN Source database

Read Code	Read Code Description
7530.11	Tonsillectomy
7530600	Tonsillectomy and adenoidectomy
7421000	Adenoidectomy
7530500	Excision of lingual tonsil
7421200	Curettage of adenoid
7530400	Excision of remnant of tonsil
7530000	Dissection tonsillectomy
7530200	Bilateral laser tonsillectomy
7530.00	Excision of tonsil
7530z00	Excision of tonsil NOS
7530A00	Bilateral dissection tonsillectomy
7530B00	Bilateral guillotine tonsillectomy
7530800	Dissection tonsillectomy and adenoidectomy
7530900	Guillotine tonsillectomy and adenoidectomy
7530300	Other bilateral tonsillectomy
7530y00	Other specified excision of tonsil
7530100	Guillotine tonsillectomy
7530700	Other unilateral tonsillectomy
7421.11	Excision of adenoid
7530C00	Coblation tonsillectomy
7530D00	Bilateral coblation tonsillectomy
7421400	Suction diathermy adenoidectomy
SP21300	Primary post tonsillectomy haemorrhage
SP21400	Secondary post tonsillectomy haemorrhage

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8613
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

List of selected SNOMED codes for tonsillectomy and adenoidectomy in the THIN CDM database

Concept_Id	Concept_Class_Id	Concept_Name
36713169	Clinical Finding	Bleeding following tonsillectomy
4152061	Clinical Finding	Primary post tonsillectomy hemorrhage
4152062	Clinical Finding	Secondary post tonsillectomy hemorrhage
4003875	Procedure	Adenoid excision
4033022	Procedure	Control of hemorrhage after tonsillectomy and adenoidectomy
4068352	Procedure	Curettage of adenoids
46270863	Procedure	Excision of lesion of tonsil and adenoid
4139473	Procedure	Sluder operation of tonsillectomy
4070719	Procedure	Tonsillectomy

Annex 3

List of selected Read codes for sleep apnoea in the THIN Source database

Read Code	Read Code Description
Fy03.00	Sleep apnoea
Fy03.11	Obstructive sleep apnoea
H5B..00	Sleep apnoea
H5B0.00	Obstructive sleep apnoea
Q318.00	Primary sleep apnoea of newborn
R005100	[D]Insomnia with sleep apnoea
R005300	[D]Hypersomnia with sleep apnoea
R005311	[D]Sleep apnoea syndrome
R005312	[D]Syndrome sleep apnoea

List of selected SNOMED codes for sleep apnoea in the THIN CDM database

Concept_Id	Concept_Class_Id	Concept_Name
46269690	Clinical Finding	Acute hypercapnic respiratory failure due to obstructive sleep apnea
4044240	Clinical Finding	Alveolar sleep apnea
439794	Clinical Finding	Central sleep apnea syndrome
439150	Clinical Finding	Hypersomnia with sleep apnea
434172	Clinical Finding	Insomnia with sleep apnea
313459	Clinical Finding	Sleep apnea
4122478	Procedure	Insertion of appliance for sleep apnea
4048339	Procedure	Pharyngeal operation for obstructive sleep apnea and snoring
4013067	Procedure	Sleep apnea recording
4121953	Procedure	Take impression for sleep apnea appliance