



Uppsala
Monitoring
Centre

– Building a global safety culture

Version 6.0

WHODrug Best Practices

Applicable for the B3- and C3-formats

INSPIRE. ENGAGE. TRANSFORM.

WHODrug Best Practices Version 6.0

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1. Introduction

Uppsala Monitoring Centre (UMC) strives towards uniform practices for the coding of drugs across the pharmaceutical industry. This document has been developed with input from coding experts among the WHODrug User Community in order to offer advice on the best ways to handle different coding scenarios. UMC collaborates with many software providers with the intention to encourage them to enable the Best Practices in their systems.

The WHODrug Best Practices are continuously developed, and all WHODrug users are encouraged to influence the Best Practices and suggest new topics for inclusion. For any questions or comments regarding the best practices please contact WHODrug@who-umc.org.

For WHODrug Best Practices covering the B2- and C-formats, please refer to the previous version, version 4.0, of this document.

1.1. Definition of terms

This document contains a section with a definition of terms; further definitions of general terms such as Drug Code, Preferred Name and Non-Unique name can be found in the WHODrug User Guide on the WHODrug User Area at www.who-umc.org.

Dictionary format	WHODrug is distributed to all users in two formats – the B3-format and the C3-format – and the user decides which to use. The B3-format contains information about trade name, ingredients and ATC classification(s). The unique key is the alphanumeric Drug Code. The C3-format contains all the B3-format information (including the Drug Code). In addition, it has information regarding the countries in which the product is marketed, Marketing Authorisation Holders, pharmaceutical forms and strengths. The unique key is the alphanumeric medicinal product ID (MPID).
Drug name	Refers to either a substance name (generic name) or trade name.
Recode	To change the coding for a previously coded verbatim term from one dictionary term to another dictionary term.
Synonym list	A collection of verbatim terms and their assignment to dictionary terms. Often, the synonym list will include the indication and/or route as well.
Trade name	The name under which a medicinal product is marketed (proprietary name).
Unique trade name	A trade name which is used for the same medicinal product when marketed in all countries where the drug is approved (the opposite of Non-Unique trade name).
Upversion	The action of implementing a later version of WHODrug.
Verbatim term	Text in a case report form or an Individual Case Safety Report that describes a medicinal product.
WHODrug record	Drug name and connected information, e.g. Drug Code and ATC assignments.

2. Non-Unique trade names

Sometimes a trade name is available with different active ingredients, and this is reflected in WHODrug, where the trade name is called 'Non-Unique'. In the B3-format, Non-Unique trade names are appended with [INGREDIENT(S)]. If the record has multiple ingredients, they will be written in alphabetical order, separated by semicolons.

The following situations are examples resulting in Non-Unique trade names:

- The same trade name is used in different countries with different sets of ingredients.
- The same trade name is used in different pharmaceutical forms which contain different sets of active ingredients.
- A product has changed its composition without changing its trade name.

In these cases, the trade name alone is not sufficient to identify the reported term, and additional information about the trade name is necessary in order to code it correctly. This is one of the reasons the C3-format is available. The C3-format can help users to find the correct record via additional information about the medicinal product, such as Country, Marketing Authorisation Holder, Strength and Pharmaceutical Form. These attributes are called 'differentiators' as they often differ between the Non-Unique trade names. This chapter will describe how differentiators, if available to the coder, can be used to select a record in WHODrug in Non-Unique name situations. Differentiators described in this section are:

- a. Ingredients
- b. Salt variations of ingredients
- c. Indication or ATC code
- d. Old Form
- e. Route or Pharmaceutical form
- f. Name Specifier
- g. Country

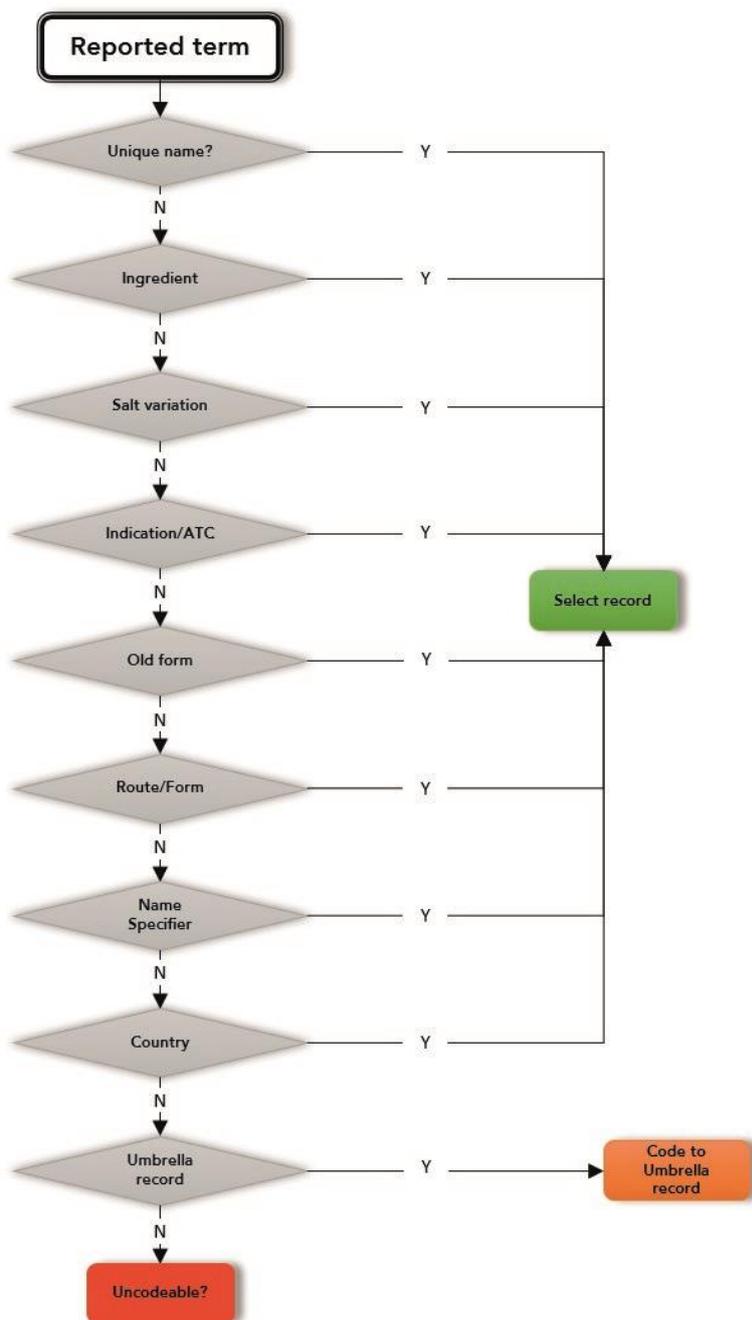


Figure 1. Non-Unique trade name – differentiators (Y= Yes; N = No). In a Non-Unique trade name situation, the coder will start with a list of alternatives. The figure illustrates how the coder can work through a series of questions and thereby reduce the number of alternatives, and in most cases, filter out the unique record. The differentiators are not listed in a chronological order; the steps can be partially or fully carried out according to internal coding rules and SOPs. The coder can, depending on the coding conventions of the organisation, contact the reporter for additional information at any stage during the process.

2.1. Finding a differentiator to help decide which record to choose

2.1.1. Is information about ingredients available?

Yes. If information about the ingredients for a reported medication is available, the Non-Unique trade name situation can usually be solved –a record can be selected and used.

Drug Code	Drug name	Active substance(s)	ATC
00088302055	BRADOSOL [BENZALKONIUM CHLORIDE]	Benzalkonium chloride	A01AB, Antiinfectives and antiseptics for local oral treatment <i>umc-assigned</i> D08AJ, Quaternary ammonium compounds <i>official</i> D09AA, Medicated dressings with antiinfectives <i>official</i> G01AX, Other antiinfectives and antiseptics <i>umc-assigned</i> G02BB, Intravaginal contraceptives <i>umc-assigned</i> R01AX, Other nasal preparations <i>umc-assigned</i> R02AA, Antiseptics <i>official</i> S01XA, Other ophthalmologicals <i>umc-assigned</i>
00093302002	BRADOSOL [DOMIPHEN BROMIDE]	Domiphen bromide	A01AB, Antiinfectives and antiseptics for local oral treatment <i>official</i> R02AA, Antiseptics <i>umc-assigned</i>
00581401007	BRADOSOL [HEXYLRESORCINOL]	Hexylresorcinol	R02AA, Antiseptics <i>official</i>

Example 1. Bradosol in WHODrug. If the reported term is 'Bradosol (Hexylresorcinol)' this information can be used to select the record 'Bradosol' with Drug Code 00581401007 since it has an active ingredient matching the reported term.

No. If the ingredient information is not available, there may be information available for another differentiator that can help in selecting a record.

2.1.2. Can salt variations of the ingredients be used to differentiate the Non-Unique name?

Yes. In some cases, the only difference between Non-Unique names in WHODrug is the salt form of the ingredients. The reasons for these are often different route or pharmaceutical form, which is another usable differentiator for these cases.

Drug Code	Drug name	Active substance(s)	ATC
00661201005	PRILOSEC [OMEPRAZOLE]	Omeprazole	A02BC, Proton pump inhibitors <i>official</i>
00661203010	PRILOSEC [OMEPRAZOLE MAGNESIUM]	Omeprazole magnesium	A02BC, Proton pump inhibitors <i>official</i>

Example 2. Prilosec in WHODrug. If the reported term is 'Prilosec', salt variation can be used as differentiator to select the right record.

If it is possible to retrieve more exact information about which salt form was used in the specific case, this is clearly the best alternative. However, if the organisation SOPs do not require specific salt information for the ingredients of the products, the record with Sequence 1=01 (base form of the ingredient(s)) can be selected. The Drug Code system in WHODrug connects all WHODrug records with any salt form of an ingredient by giving them the same DrugRecordNumber, 006612 in Example 2.

No. If the coder cannot select an alternative, or if the organisation SOPs require the exact salt variation of the ingredients, there may be information available for another differentiator that can help in selecting a record.

2.1.3. Is it possible to use indication or ATC to decide which record to code to?

Yes. If the coder has access to information about why the medication has been used, either by ATC (Anatomical Therapeutic Chemical) code or a given indication, this may serve as useful information to enable selection of a record. WHODrug gives the coder information about the product's ATC class(es).

It should be noted that the ATC system does not give the coder a complete list of possible indications (or off-label use) of a drug. An indication may be reported that does not match existing ATC codes.

Drug Code	Drug name	Active substance(s)	ATC
00889901003	FLOMAX [MORNIFLUMATE]	Morniflumate	M01AX, other anti-inflammatory and rheumatic agents, non-steroids <i>official</i>
01280302013	FLOMAX [TAMSULOSIN HYDROCHLORIDE]	Tamsulosin hydrochloride	G04CA, Alpha-adrenoreceptor antagonists <i>official</i>

Example 3. Flomax in WHODrug. If the reported term 'Flomax' is provided to the coder with the additional information "benign prostatic hypertrophy" as indication, it is in this case possible to select 'Flomax' with Drug Code 01280302013, because that record has an ATC code that matches the reported indication.

No. If information about an indication or ATC is not available, or if more than one record has matching ATC classes, users should take the possible records and see if there is information available for another differentiator that can help in selecting a record. If the organisation SOPs do not allow coding to an Umbrella Record that contains no active ingredients, then the term may have to be left uncoded.

2.1.4. Can the designation 'Old Form' be used as a differentiator?

Yes. For many reasons, formulations of drugs may change and be replaced on the market in one or more countries. In WHODrug the replaced formulations are marked as 'Old Form'. This also applies to products no longer marketed.

Records marked with 'Old Form' should only be selected when coding 'historic' data and when the 'old from' formulation has been confirmed.

Drug Code	Drug name	Name Specifier	Active substance(s)	Country of sales
00002702002	ASCAL [ACETYLSALICYLATE CALCIUM]	/old form/	Acetylsalicylate calcium	Netherlands
00800002006	ASCAL [CARBASALATE CALCIUM]	100 • 300 • 38 • Tablet • 600	Carbasalate calcium	Morocco • Netherlands • Spain

Example 4. Ascal in WHODrug. If the reported term is 'Ascal' and the report comes from the Netherlands, the Old Form flag can be used as a differentiator to help decide which record to choose. Assuming that the reported drug is the marketed one, the coder can select the record without the /Old Form/ flag, Drug Code 00800002006.

No. If the organisation SOPs state that one cannot assume that the reported drug is the one currently marketed, and when it is therefore not possible to use the 'Old Form' information in WHODrug as a differentiator, there may be information available for another differentiator that can help in selecting a record.

2.1.5. Is information about route or pharmaceutical form provided?

Yes. In some Non-Unique name situations, the route or pharmaceutical form separates the products from each other, as in the example below.

Drug Code	Drug name	Active substance(s)	ATC	Pharmaceutical form
00020001796	NOVAL [PARACETAMOL]	Paracetamol	N02BE, Anilides <i>official</i>	Liquids, syrups
00371202050	NOVAL [TIMOLOL MALEATE]	Timolol maleate	C07AA, Beta blocking agents, non-selective <i>official</i> S01ED, Beta blocking agents <i>official</i>	Liquids, drops
10510703010	NOVAL [ESTRADIOL; NOMEGESTROL ACETATE]	Estradiol, Nomegestrol acetate	G03AA, Progestogens and estrogens, fixed combinations <i>official</i> G03FB, Progestogens and estrogens, sequential preparations <i>umc-assigned</i>	Coated tablets, film
11213502008	NOVAL [ETHINYL-ESTRADIOL; MEGESTROL ACETATE]	Ethinylestradiol, Megestrol acetate	G03AA, Progestogens and estrogens, fixed combinations <i>official</i> G03AB, Progestogens and estrogens, sequential preparations <i>official</i> G03FA, Progestogens and estrogens, fixed combinations <i>umc-assigned</i> G03FB, Progestogens and estrogens, sequential preparations <i>umc-assigned</i>	Tablets

Example 5. Noval in WHODrug. If the reported term is 'Noval eye drops' the coder can select the record with Drug Code 00371202050 because that record has an ATC code (S01ED) and a pharmaceutical form (liquids, drops) that matches the reported term 'eye drops'.

No. If more than one alternative is possible, or if the information reported does not match any specific record in WHODrug, there may be information available for another differentiator that can help in selecting a record.

2.1.6. Can Name Specifier be used as a differentiator?

Yes. Name Specifier is a part of a trade name that is sometimes used to specify a special form, or strength, etc. Examples are: 'Forte', 'For Children', 'Sustained Release' etc.

If Name Specifier information is available to the coder, it may be used to select a Non-Unique name.

Drug Code	Drug name	Name Specifier	Active substance(s)	ATC
00159501050	ESPAVEN [DIMETICONE]	Pediatrico	Dimeticone	A01AD, Other agents for local oral treatment <i>umc-assigned</i> A03AX, Other drugs for functional gastrointestinal disorders <i>umc-assigned</i> D02AA, Silicone products <i>umc-assigned</i> D10, ANTI-ACNE PREPARATIONS <i>umc-assigned</i> P03AX, Other ectoparasiticides, incl. scabicides <i>official</i> S01K, SURGICAL AIDS <i>umc-assigned</i> S01X, OTHER OPHTHALMOLOGICALS <i>umc-assigned</i>
00550802328	ESPAVEN [RANITIDINE HYDROCHLORIDE]		Ranitidine hydrochloride	A02BA, H2-receptor antagonists <i>official</i>
10902002004	ESPAVEN [CALCIUM PANTOTHENATE; DIMETICONE]		Calcium pantothenate, Dimeticone	A03AX, Other drugs for functional gastrointestinal disorders <i>umc-assigned</i>

Example 6. Espaven in WHODrug. Reported term 'Espaven pediatrico'. There is no record with the complete reported term in the drug name field, but for one of the records, 'pediatrico' is available in the Name Specifier field. Because of the information in the Name Specifier field, the record with Drug Code 00159501050 can be selected to code to.

No. If Name Specifier information is not a possible differentiator, there may be information available for another differentiator that can help in selecting a record.

2.1.7. Is information about country provided?

Yes. If the coder has access to information about the country where the subject/patient is located or other information that can give the coder a suggestion as to where the drug has been obtained, this can be used to select an alternative. Remember that drugs sometimes are bought over the internet and that they could be bought in a neighbouring country, etc.

Drug Code	Drug name	Active substance(s)	Country of sales
01009701022	AERIUS [EBASTINE]	Ebastine	Pakistan
01398501005	AERIUS [DESLORATADINE]	Desloratadine	Argentina • Austria • Belarus • Belgium • Bulgaria • Canada • Chile • China • Colombia • Croatia • Czech Republic • Dominican Republic • Egypt • Estonia • Finland • France • Germany • Greece • Hong Kong • Hungary • Indonesia • Israel • Italy • Jordan • Korea, Republic of • Kuwait • Latvia • Lebanon • Lithuania • Luxembourg • Malaysia • Morocco • Netherlands • Norway • Peru • Philippines • Poland • Portugal • Romania • Russian Federation • Saudi Arabia • Singapore • Slovakia • Slovenia • South Africa • Spain • Sweden • Switzerland • Thailand • Tunisia • Turkey • Ukraine • United Arab Emirates • Uruguay • Venezuela, Bolivarian Republic of

Example 7. Aerius in WHODrug. Reported term 'Aerius', reporter country Sweden. There are two records named 'Aerius' in WHODrug, one available in over 50 countries, the other only available in Pakistan. If it can be assumed that the drug was obtained in the reporter country, or assumed that it was not obtained in Pakistan, the record with Drug Code 01398501005 can be selected.

No. If country cannot be used to differentiate one Non-Unique name from another there may be information available for another differentiator that can help in selecting a record.

2.2. No differentiator is appropriate to use in a particular situation

2.2.1. Is it possible to code to an Umbrella Record?

Yes. If no information from any available differentiator can be used, the coder can choose an Umbrella Record to use for coding. Umbrella Records do not contain any ingredients, but do have ATC codes and can therefore still be used in analysis done on ATC codes. Umbrella Records can also be identified as having a Drug Code starting with 9.

Example 8. Code to an Umbrella record.

- After eliminating all possible records for a Non-Unique name, the remaining alternatives may all have the same ATC class (on 4th or higher level). All ATC terms from the 4th level exist as umbrella records in WHODrug, and can be chosen for coding a Non-Unique name.
- If all alternatives are in the same substance class, e.g. vitamins, the coder can select the Umbrella record 'Vitamins', for example.
- Available Umbrella Records in WHODrug when no other option exists; 'All other non-therapeutic products' (Drug Code: 90047501001), 'All other therapeutic products' (Drug Code: 90042501001). Bear in mind that drug names coded to any of these two records will not be excluded from most analyses or presentations/tabulations.

No. If no Umbrella Records exist to code the reported term, it may not be possible to code it.

2.2.2. Can the term be coded or is it uncodeable?

If it is impossible to code a term it may be possible to add another record in WHODrug to be able to distinguish a Non-Unique name. That process is described in the Missing drug section.

3. Missing drug

A WHODrug user can at any time submit a request for a new drug. This can be done in the WHODrug Change Request. This chapter describes the Best Practices for when a coder cannot find an appropriate drug name.

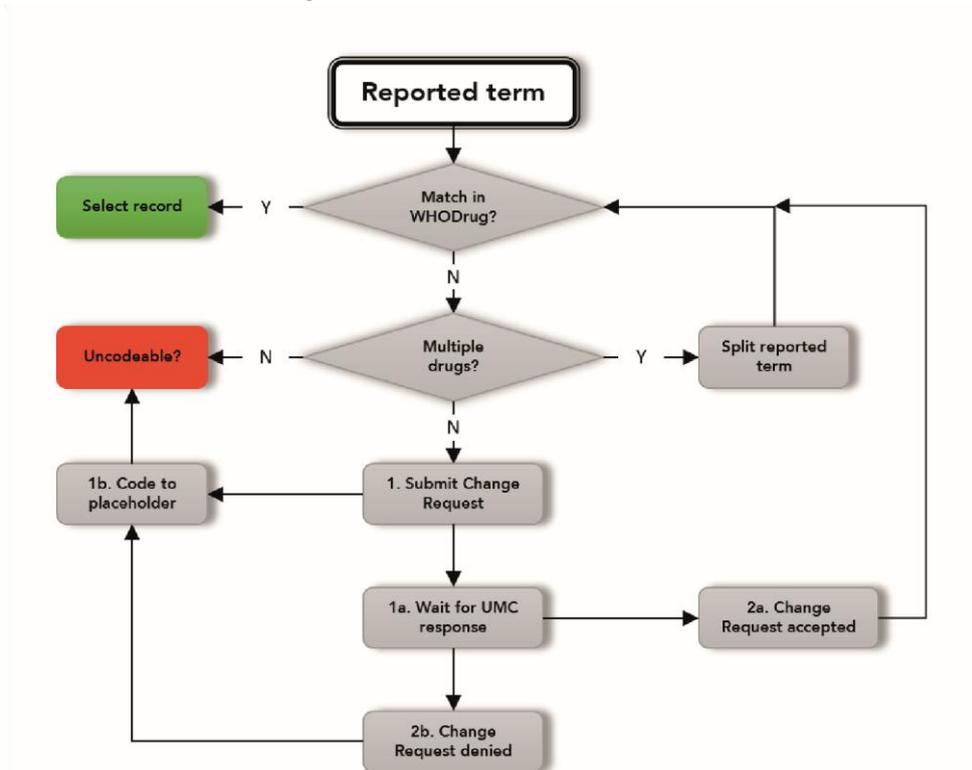


Figure 2. Schematic explanation of how to handle a coding situation where a drug is missing in WHODrug (Y= Yes; N = No).

3.1. Submitting a Change Request

Before submitting a Change Request, please check that the drug name does not already exist in WHODrug or in the upcoming version by searching for the record in WHODrug Insight Upcoming Data.

Sometimes a reported term contains multiple substances or product names for other reasons than reporting a multi ingredient drug.

Example 9. Reported term 'Omeprazol/Lanzoprazole'. There are currently no records in WHODrug that contain the two reported substances in one drug. It is likely that the reporter meant that the patient sometimes takes omeprazole and sometimes lanzoprazole. In these cases, the verbatim should be split and coded to the two individual ingredients.

It might be that a combination of drugs actually does exist and that the coder does not want the reported term to be split. In other cases, it might be a single-ingredient product name that simply cannot be found in the version of WHODrug being assessed.

The coder can then submit a Change Request, and in the meantime either leave the reported term uncoded until the approval response has been received (3.2) or code to a 'placeholder' (3.3).

3.2. Wait for response of Change Request

If it is possible to wait for the approval of the Change Request and in the meantime, leave the reported term uncoded until the next dictionary version is released, this is preferred. The

decision of how to code the reported term is thereby postponed until the approval response is received.

3.3. Code to ‘place holder’

If the reported term must be coded, i.e. the coding cannot wait until the response to the Change Request has been received, the coder can code to a ‘place holder.’ In this document, a ‘place holder’ is the drug name requested in the Change Request or an existing record in WHODrug.

Using the requested drug name as a ‘place holder’ requires that organisation SOPs allow for recoding of a coded term since the requested drug name may be declined and another option has to be chosen as the selected record for coding. This option also requires that a reported term can be coded to a non-existing term in the current version of WHODrug until the study is upversioned.

Using an existing record in WHODrug as a ‘place holder’ may be another option. If the user cannot wait for the Change Request response, or if the user’s organisation or process is not set up to manually update the coding system with the newly approved record from UMC, the user should find an alternative place holder.

This requires that the organisation guidelines allow changes to coded data, at least in the timespan until the new dictionary version is released, and bearing in mind that the Change request may be declined. If the Change Request is rejected, the placeholder may be decided as an approved, existing, term to code to.

3.3.1. Generic name

Even if the reported trade name does not exist in WHODrug, it is likely that a generic name for the substance(s) does. This can easily be found by using the browsing tool WHODrug Insight, shown in Figure 3.

If the organisation’s coding principles allow, the base (without salt information), or combination of base-substances for reported substances with salts can be chosen.

The screenshot shows the WHODrug search interface. At the top, it says 'Drug search'. Below this, there are several input fields and filter options. On the left, there is a 'Product name' field with a placeholder 'Enter product name'. Below it is an 'Extended search' section with two radio buttons: 'Active ingredients' (selected) and 'UNII code'. Underneath these is a dropdown menu labeled 'Select active ingredient'. Below the dropdown are three radio buttons: 'Contains only' (selected), 'Contains at least', and 'Include base and salts'. On the right side, there is an 'ATC code/name' field with a placeholder 'Enter ATC code or ATC name'. Below this is a 'Product filter' section with four checkboxes: 'Exact match on product name' (unchecked), 'Preferred and/or generic' (checked), 'Old form' (unchecked), and 'Umbrella records' (unchecked). Below the filters is a 'Country' dropdown menu with the placeholder 'Select a country'. At the bottom right, there is a 'Drug code' field with a placeholder 'Enter drug code', a 'Search' button, and a 'Clear' button.

Figure 3. Example of searching for all records containing the substance(s) to be coded. Choosing the box ‘Preferred and/or generic’ will give the coder generic records. In WHODrug, the Preferred Name is always generic.

3.3.2. Preferred Name

For all WHODrug records, the Preferred Name is always generic.

The Preferred Name will have a Drug Record Number that corresponds to the active ingredients of the drug name in the Change Request. The Preferred Name has all ATC codes for all products with the same Drug Record Number.

If there is no Preferred Name that exactly corresponds to the ingredient of your requested drug name (and you have requested a salt or a combination of salts and bases), there may still exist a Preferred Name for the corresponding base ingredient(s). If so, an option could be to code to this Preferred Name.

3.3.3. Umbrella Record

If neither a suitable generic name nor a suitable Preferred Name is found, an alternative 'place holder' could be an Umbrella Record. If the active ingredient can be identified, one may be able to find the pharmacological class it belongs to.

3.4. Change Request process

3.4.1. Change Request approved

If the Change Request is approved, the requested drug name will appear in the next dictionary release. The approval response provides a link to WHODrug Upcoming Data in Insight where information about the new record, its corresponding Preferred Name, assigned ATC classes, etc. is presented. This enables you to create a temporary record in your dictionary to be used until the next version is released.

3.4.2. Change Request rejected

If the Change Request is rejected, users should either code to the place holder chosen in 3.3 (Code to 'place holder') or the reported term will have to be labelled as not being possible to code. If coding is required, the Umbrella Records in Example 8 may represent alternative coding options.

4. Medication classification (ATC coding)

Within the pharmaceutical industry there are several approaches used to classify the medications included in a study or on safety reports. Always verify the current regulations of your authorities. Here are the Best Practices and description of four methods for classification of medications when using WHODrug.

4.1. Introduction

4.1.1. ATC classification system

The Anatomical Therapeutic Chemical (ATC) and the Herbal ATC (HATC) classifications are integrated parts of WHODrug. The ATC classification system is maintained by WHO Collaboration Centre for Drug Statistics Methodology, and UMC integrates this classification into WHODrug. The HATC classification is maintained by UMC and integrated in WHODrug. A brief overview of the ATC system follows, for more details please read the WHODrug User Guide at the WHODrug User Area.

4.1.2. The difference between ATC and indication

The intended use for the ATC classification system is drug utilisation research. The ATC system is therefore designed to classify the combination of main indication, mechanism of action and/or chemical properties of medicinal substances. The ATC classification system is not purely a therapeutic or pharmacological classification system, and consequently it does not reflect all indications of a medication. It is important to remember that the mechanism of action of a drug is often included in the determination of ATC classification.

One example to illustrate the difference between ATC and indication is duloxetine, a drug used for treatment of depressive disorder, but also indicated for treatment of stress urinary incontinence. Duloxetine has the mechanism of action as an antidepressant drug and is therefore classified in the 'other antidepressants' group, even though there is an ATC class for 'drugs for urinary frequency and incontinence'. Thus, if ATC classification is used in a clinical study, it may not necessarily identify all patients who have taken drugs for urinary incontinence. A classification system based on indication only would be more likely to identify those patients.

It is essential to have a thorough knowledge of the ATC classification system in order to use it for the classification of medications.

The WHODrug user should preferably have a basic knowledge about the ATC structure, limitations and how criteria for ATC assignment are set up. More information and education opportunities can be found at www.whocc.no.

4.1.3. ATC classification within WHODrug

The classification of medicinal products in WHODrug is primarily based on the guidelines for ATC classification, found at www.whocc.no. The ATC classifications that follow the guidelines are flagged as official. Some medicinal products are classified in WHODrug with additional ATC codes to reflect the main use of the product. An example is sildenafil: it has an official ATC classification in 'drugs used for erectile dysfunction' and is therefore assigned this classification within WHODrug. The substance is also used to treat pulmonary arterial hypertension, so the product is also classified within WHODrug in 'Antihypertensives for pulmonary arterial hypertension'. This is a UMC assigned classification and is therefore not flagged as official.

4.1.4. ATC assignment in the B₃- and C₃-format

In the B₃-format of WHODrug medicinal products are linked to the same ATC codes as the associated Preferred Name (preferred bases and preferred salts).

However, in the C₃-format each individual medicinal product is generally assigned one ATC code only. The assigned ATC code reflects the intended use of the product. The generic and Preferred Names in the C₃-format are assigned ATC codes in the same manner as in the B₃-format, i.e. the generic records are assigned all ATC codes for the linked products (see Table 1 and Table 2).

Table 1. Illustration of the difference in ATC assignment for the ingredient acetylsalicylic acid in B₃- and C₃-format.

Drug name (ingredient)	ATC in B ₃ format	ATC in C ₃ format
Acetylsalicylic acid (acetylsalicylic acid)	A ₀₁ AD	A ₀₁ AD
	B ₀₁ AC	B ₀₁ AC
	M ₀₂ AC	M ₀₂ AC
	N ₀₂ BA	N ₀₂ BA
Alidor (acetylsalicylic acid)	A ₀₁ AD	N ₀₂ BA
	B ₀₁ AC	
	M ₀₂ AC	
	N ₀₂ BA	
Casprin (acetylsalicylic acid)	A ₀₁ AD	B ₀₁ AC
	B ₀₁ AC	
	M ₀₂ AC	
	N ₀₂ BA	

Table 2. Illustration of the difference in ATC assignment for the ingredient erythromycin in B₃- and C₃- format.

Drug name (ingredient)	ATC in B ₃ format	ATC in C ₃ format
Erythromycin (erythromycin)	D ₀₆ AX	D ₀₆ AX
	D ₁₀ AF	D ₁₀ AF
	J ₀₁ FA	J ₀₁ FA
	S ₀₁ AA	S ₀₁ AA
Emina (erythromycin)	D ₀₆ AX	D ₁₀ AF
	D ₁₀ AF	
	J ₀₁ FA	
	S ₀₁ AA	
Eritrovit (erythromycin)	D ₀₆ AX	J ₀₁ FA
	D ₁₀ AF	
	J ₀₁ FA	
	S ₀₁ AA	

In both formats, the Preferred Name is linked to all ATC classifications assigned to the Trade Names with the same active ingredient(s). There is a possibility to make use of the C₃-format assignments in the B₃-format by using the 'DDA Exclusive' text file. DDA is the file where ATC

code assignments are found and DDA Exclusive is an additional file to further specify ATC assignments.

4.1.5. DDA exclusive

An additional features text file is available, named 'DDA Exclusive'. This file is designed to increase the efficiency of ATC coding in the B₃-format by implementing C₃-format specific ATC assignments. The 'DDA Exclusive' file is exchangeable with the ordinary 'DDA' text file. When exchanging DDA with DDA Exclusive, the proportion of Drug Codes linked to more than one ATC code decreases from 30% to 7%. The DDA Exclusive file is found in the 'additional features' folder in the download package. When using DDA Exclusive it is important to know that fewer ATC codes can be used to reflect the indication, especially for off-label use of the product. However, the Preferred Name is always linked to all available ATC codes. Using the DDA Exclusive file is optional; it is described here for information only.

It should be noted that while the DDA Exclusive file is exchangeable with the DDA file, all trials within a program should be coded with the same file type to avoid inconsistent summary output for pooled data.

4.2. Classification methods

When planning a study, there are several options for how to handle medication classification. The method of classification should be chosen by the study team with regard to the chosen analysis method. The analysis method should be determined before coding starts, to ensure manual efforts are spent wisely. Firstly, it is decided whether classification of medication is to be done or not. If it should be done, there are three methods recommended by the Uppsala Monitoring Centre.

This section will give method definitions, advantages/disadvantages, and best practices for each recommended method.

4.3. Methods description

Table 3 lists the recommended methods: three classification methods and the 'No classification' option, and the respective definition and description of each method.

Table 3. Definition and description of the recommended classification methods.

Method	Definition and description
All possible ATC pathways	Defined as selecting all available ATC codes for a specific Drug Code. It can be done manually or the system can be set up to automatically choose all ATC codes available.
Single ATC selection	Defined as actively and manually selecting only one ATC code for each reported medication, when there are several ATC codes to choose from. The selection is based on information available in the CRF such as indication, route or strength. Note that this is not the same as programming the system to automatically select one ATC code. Manual review is always required to ensure the most appropriate ATC is selected.

Method	Definition and description
Classification using a system other than ATC	Defined as using another system than ATC in order to better capture the reason for the patient taking the medication (indication). There are several systems for classifying medications based solely on their indications. Two such systems are MedDRA and ICD. These can be used if the main intention for analysis is to aggregate data on the indication of the medications. If this method is used it is important to understand that classification according to ingredient properties and mechanism of action is not available.
No classification of medication	Not a method, but rather an active and informed choice not to classify medications in the ordinary medication coding process. Not performing any medication classification could result in difficulties in subgroup analysis, analysis of prohibited medications, etc. However, if this approach is chosen, there is always the possibility to go back and classify medications if needed later in the study.

4.3.1. Advantages and disadvantages

None of the presented methods will fulfil all possible needs within all types of studies. Table 4 displays advantages and disadvantages of each classification method.

Table 4. Advantages and disadvantages for the classification methods (the No classification method is not included in this table).

Method	Advantages	Disadvantages
All possible ATC pathways	<p>Coding to all possible ATC selections saves time and resources, thus saving money on the study budget.</p> <p>Changes of ATC classification in WHODrug can be automatically updated without manual revision since no specific ATC has been chosen.</p> <p>Coding to all possible ATC pathways means that there is a reduced risk of missing a signal and signals can be more easily recognised.</p> <p>No need to store ATC codes in the database. The ATC classification can be derived directly from WHODrug.</p>	<p>Requires a more experienced analysis team to interpret the data correctly.</p> <p>Coding to all possible ATC pathways selections will entail more complicated calculations during the statistical analysis. The same medication can show up more than once, which can be an issue if the statisticians are not aware of the multi-axiality of ATC. Often this can lead to literal translation of figures and misleading interpretations of the data.</p>
Single ATC selection	<p>Allows data to be grouped in a more medically relevant manner and categories of interest to be reviewed in more detail.</p> <p>Facilitates and promotes consistency in specific drug classification based on the reported indication.</p> <p>Supports the medication coding process such as in checking the consistency between the Drug Code and the reported indication, route and dosage.</p> <p>Groups medications according to their ATC codes with no double counting/ reporting.</p>	<p>Means that changes in ATC classification need to be reviewed manually during upversioning.</p> <p>Is often time-consuming, putting a strain on tight study budgets.</p> <p>Could often exclude medications from a specific analysis if the medication affects the body in many ways (e.g. aspirin taken orally for pain and coded to No2BA (Salicylic Acid and Derivatives) would not be included in an analysis that is looking for Antithrombotic agents).</p> <p>Could generate more queries when a substance is used 'off-label', or if the indication is missing, especially for a Non-Unique drug name.</p>

Classification using a system other than ATC	Straightforward to find appropriate match to indication on CRF. Since indications are not included in WHODrug and not connected to a specific medication (as with ATC codes), the whole system can be used to find an appropriate match. Better overview of indication, rather than the mechanism of action.	Not current industry practice. Probably not supported in available software systems. Will not group medications with same mechanism of action, which will make some analyses difficult, for example interactions analysis. In some analyses, it is beneficial to aggregate medications with the same mechanism of action to get more medications in the same group and thus stronger signals. Time-consuming in the same manner as for single ATC selection. Can be inconsistent due to the different ways the same indication could be reported. Example: indication for the use of an antibiotic drug could be reported as Anti-infective, Antibiotic therapy, Infection, etc. Retrieval of protocol violations and prohibited medications could be limited if ATC categories are retrieved for these purposes.
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4.3.2. Choice of classification method

This section provides a short checklist, to aid in the process of choosing a classification method.

4.3.2.1. Choose all possible ATC pathways if:

- Your priority is to detect all signals, and thereby accept an increased risk of false positives.
- You want to detect medications affecting the body in several ways.
- Your statistical team is familiar with and understands the multi-axiality of ATC.
- You want to classify the medication but do not have the budget to choose the Single ATC selection method.
- You want to prepare data for protocol violation, prohibited medications or subgroup analysis.
- You are aware that the data may be used more than once. Re-used data may have different requirements which can be easier to deal with the multi-axial representation.

4.3.2.2. Choose Single ATC selection if:

- You are not constrained by time limitations.
- You do not have the possibility to use an indication classification system but you wish to capture as much about indication as possible.
- You want to double check the consistency of reported indication and drug coding.
- You may have difficulties handling the multi-axiality of the ATC system (your software system does not support other methods; your statistical team requires only one ATC code etc.)
- You do not want to risk interpretation of a false positive signal.
- Your statistical team prefers to have specific classification handled at the coding level.

4.3.2.3. Choose Classification using system other than ATC if:

- You want to aggregate and/or analyse the data according to indication rather than mechanism of action.
- You wish to follow up conditions or diseases in a study population.

4.3.2.4. Choose No classification of medication if:

- You are not planning any of the analyses described above.

- You are not going to aggregate on ATC level in your study report.
- You have the possibility to do ad hoc classifications later on, if needed.

4.4. Best practice procedures for each classification method

Below are the best practice procedures for each individual classification method described. The best practice procedures are summarised in a flow chart in Figure 4. Drug classification methods (Y=Yes, N=No). The figure illustrates alternatives and best practice for each classification alternative. The list is not in chronological order: the steps can be partially or fully carried out according to the internal coding rules and SOPs. The coder can, depending on policies of the coder's organisation, contact the reporter for additional information at any stage during the decision process.

4.4.1. All possible ATC pathways

This method has only one best practice step to consider:

4.4.1.1. Choose all ATC codes available.

If you have chosen this method for classification you do not make a judgement regarding which ATC code to use. Either you set your system to automatically choose all listed ATC codes (preferred option to save time) or you manually always choose all ATC codes.

4.4.2. Single ATC selection

The following are the recommended best practice steps for choosing an ATC code. Not all software systems give the possibility to follow all the steps, but the best practice should be followed as far as the software system allows.

The steps are not in chronological order: the steps can be partially or fully carried out according to the internal coding rules and SOPs. If information for several of the listed steps is available, all information needs to be taken into consideration when selecting ATC code. (Please note that examples may vary between versions of WHODrug.)

4.4.2.1. Is there only one ATC assigned for the medication?

If the medication has only one ATC code, it is recommended to choose the assigned ATC code.

4.4.2.2. Is indication available?

If indication is given, choose the most appropriate ATC code according to the information given.

Drug Code	Drug name	Active substance(s)	ATC
00002701001	ACETYSALICYLIC ACID	Acetylsalicylic acid	A01AD, Other agents for local oral treatment <i>official</i> B01AC, Platelet aggregation inhibitors excl. heparin <i>official</i> M02AC, Preparations with salicylic acid derivatives <i>umc-assigned</i> N02BA, Salicylic acid and derivatives <i>official</i>

Example 10. Acetylsalicylic acid is linked to four different ATC codes in WHODrug. Choose the most appropriate ATC code according to the reported information.

4.4.2.3. Off-label use?

If the medication is taken for an off-label indication, choose the appropriate code according to route of administration or dosage. Since classification using a system other than ATC method was not chosen, off-label indications should be ignored and an appropriate ATC should be selected according to the other criteria given in this best practice.

Drug Code	Drug name	Active substance(s)	ATC
00082701001	Metformin	Metformin	A10BA, Biguanides <i>official</i>

Example 11. Metformin in WHODrug. Metformin is an antidiabetic drug assigned ATC code A10BA, but can be used to treat Polycystic Ovarian Syndrome (PCOS). In this case, select ATC code A10BA according to section 4.4.2.1.

4.4.2.4. Is route of administration available?

If route of administration is given, choose an ATC code corresponding to this. Route can be indicated by words such as systemic, otic, parenteral, oral, injection, eye drops etc. Note that pharmaceutical formulation is available in WHODrug, which can be used as indicator of route of administration.

Drug Code	Drug name	Active substance(s)	ATC
00587301001	Aciclovir	Aciclovir	D06BB, Antivirals <i>official</i> J05AB, Nucleosides and nucleotides excl. reverse transcriptase inhibitors <i>official</i> S01AD, Antivirals <i>official</i>

Example 12. Aciclovir in WHODrug is assigned three ATC codes; D06BB-transdermal, J05AB-systemic, S01AD-ophthalmic. If information about route of administration is available, choose the most appropriate ATC according to that.

4.4.2.5. Is dosage available?

Some ATC assignments differ only in dosage. If dosage is available, choose the appropriate ATC code according to ATC guidelines.

Drug Code	Drug name	Active substance(s)	ATC
01130001001	FINASTERIDE	Finasteride	D11AX, Other dermatologicals <i>official</i> G04CB, Testosterone-5-alpha reductase inhibitors <i>official</i>

Example 13. Finasteride in WHODrug. Finasteride is classified with different ATC codes depending on dosage. D11AX is used for 1mg/day and G04CB is used for 5mg/day, choose the most appropriate ATC code according to the reported information.

4.4.2.6. The given indication has no corresponding ATC code

There may be circumstances where an additional ATC code can be added to the WHODrug record. First, go to the case to look for more information. If there are no apparent errors, contact the reporter to ensure the information given was correct. If everything seems correct, and you think there is a need for an additional ATC code, submit a WHODrug Change Request.

Drug Code	Drug name	Active substance(s)	ATC
00068901001	METHADONE	Methadone	N02AC, Diphenylpropylamine derivatives <i>umc-assigned</i> N07BC, Drugs used in opioid dependence <i>official</i>

Example 14. Methadone in WHODrug. N02AC (umc-assigned) was assigned upon requests from WHODrug users.

4.4.2.7. All above unknown?

If none of the above alternatives are applicable or not possible to do in the coding system, the organisation's conventions should be developed to provide guidance for the coder. A few common examples of conventions are:

- Choose the most systemic ATC code
- Choose the ATC code most commonly used
- Manually create preferred ATC lists; for the most common drugs some organisations set up listings for which ATC is the preferred if no other information is available.
- Systemic or umbrella codes on a higher ATC level (than level four) can be chosen.
- If your system and/or coding conventions allow, all available ATC codes can be chosen.

4.4.2.8. Take advantage of previous selections

To facilitate the ATC selection (if your system allows), you can set up an algorithm remembering your previous ATC choices, which then can be used to autoencode ATC codes by the three following steps:

1. If there is only one ATC code, select the one code.
2. Set up the system to remember which ATC code was chosen for the combination of a drug name + indication, drug name + route or drug name + strength, etc. The system can then automatically select the same ATC code when the same combination occurs.
3. In this algorithm, a preferred ATC could be added if no information is available to make a proper choice of ATC.

4.4.3. Classification using a system other than ATC

The UMC does not provide best practice for this option since the medications in WHODrug are not classified according any other such system.

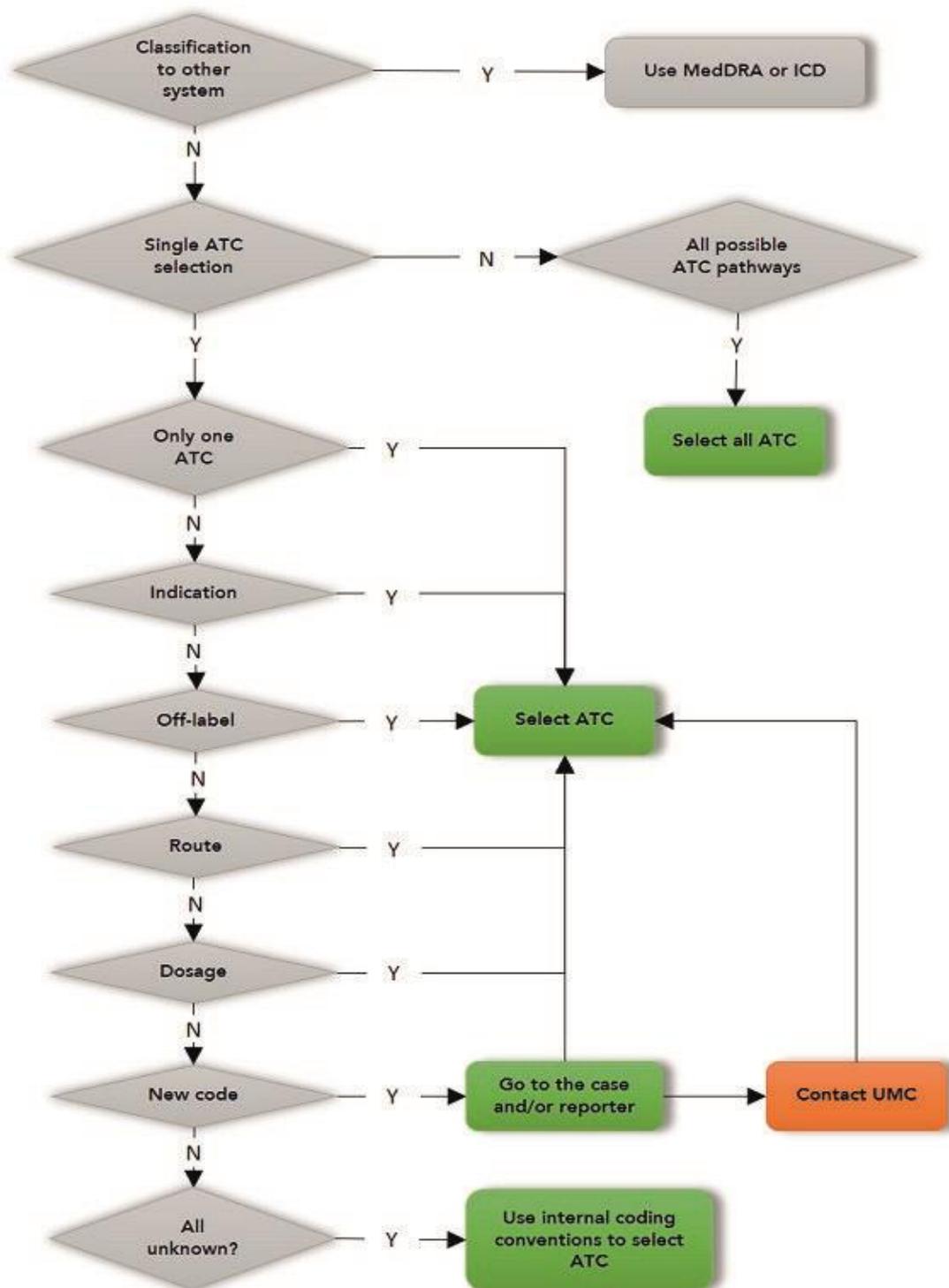


Figure 4. Drug classification methods (Y=Yes, N=No). The figure illustrates alternatives and best practice for each classification alternative. The list is not in chronological order: the steps can be partially or fully carried out according to the internal coding rules and SOPs. The coder can, depending on policies of the coder's organisation, contact the reporter for additional information at any stage during the decision process.

4.5. Other considerations

4.5.1. CDISC compliance

The Clinical Data Interchange Standards Consortium ([CDISC](#)) provides guidelines for data submission standards in clinical trials. By following the recommendations made in this Best Practice, you will be compliant with the CDISC guidelines. The CDISC Study Data Tabulation Model (SDTM) gives advice to anyone who is submitting clinical data to national authorities on how to classify the concomitant medications into a medication class such as an ATC class.

4.5.2. Standardised Drug Groupings

There is another classification system available for WHODrug users: Standardised Drug Groupings (SDGs). The SDGs can be used for some analysis where ATC codes were used previously, for example in prohibited medications analysis. Please check the SDG User Guide for more information.

5. Upversioning

5.1. Background

Over the years, the registration, coding and analysis of concomitant medications have become increasingly important. In the past, it was a practice in the industry to utilise the same WHODrug version throughout an entire program or for a long time period. While not required in most countries, updating to a recent version may however provide more specific coding selections, which in turn may facilitate analysis of the coded data.

Drugs are continuously released onto the market, and soon after may be recorded as concomitant medications in clinical or observational studies or as post-marketing cases. WHODrug is therefore updated quarterly with new drug names and ATC code assignments. Major changes to the contents of the dictionaries, such as hierarchies and those due to ATC system changes, take place in the March 1 release every year while minor updates are made in all releases. When implementing a new dictionary version, these changes need to be assessed and adjusted for. This document describes different strategies that can be applied and the best practice procedure for how to implement a new version and handle changes in the upversioning process.

5.2. Rationale for upversioning

- Moving to an updated version ensures the most up to date coding. This is especially important in clinical and observational trials in areas where many new drugs are used as concomitant medication (e.g. oncology trials) and in safety coding, since post-marketing cases often concern drugs that are new to the market.
- Using an updated version ensures all data in a pooled analysis is in the same dictionary version, facilitating better summarising, presentation and analysis.
- Using current ATC codes results in more accurate coding and thereby aids in summarising of data.
- Some authorities expect coded data to be presented in concordance with the version used by the authority. Clarify your country's requirements for which version should be used.
- Upversioning allows users to take advantage of the most up-to-date Standardised Drug Groupings in order to assist with analysis and reporting medications.

5.3. Upversioning strategies

Different organisations use different strategies to handle the releases of updated versions of WHODrug in relation to the coding conducted in earlier versions. Some strategies involve continuous upversioning of coded data as the updated versions are released and implemented, while other strategies employ less frequent upversioning or do not include upversioning of coded data at all. The same organisation may use one strategy for post-marketing data and another for data in clinical trials.

UMC acknowledges that it is up to every organisation to determine their strategy and frequency for upversioning, but we would emphasise the benefits of having all trials within a program or the entire safety database coded to the same – and preferably most recent – version. By implementing such a strategy, one can achieve the most accurate and up to date coding. Furthermore, the risk of having a regulatory authority reject data due to their requirements regarding which version to use is avoided if the data is reported with the most recent version.

5.3.1. Clinical trial data

One strategy is to have all trials within a program coded with the version that was the most recent at the time of the first trial start. This strategy does not require any changes in the version for already coded data, and all data in a pooled analysis will be in the same version. However, the coding selections may not always be the most specific possible.

An alternative is to code each trial within the program with the version that is most recent at the time of trial start. At the time of project closure, the coding may be kept as it is for each trial. This option does not require any upversioning of the coded data, but the results from a pooled analysis may not be optimal since the data will be in different versions.

A third strategy is to start each trial with the most recent version at the time, and then continuously update the coded data as updated versions are released throughout the course of the program. Alternatively, one larger upversioning effort to the most recent version can be made at the end of the program. This strategy ensures both that the coding selections are the most specific possible and that all data in a pooled analysis will be in the same version.

If the strategy chosen includes continuous upversioning, then the frequency needs to be considered as well. Upversioning can be conducted for all versions included in the subscription or less frequently.

5.3.2. Post-marketing data

A common strategy for post-marketing data is to not require recoding of verbatim terms coded to dictionary terms in the previous version when a new version is implemented in the post-marketing data base. This makes the upversioning process fast and straightforward. However, as mentioned previously, there are many benefits of having all data coded in the same version.

5.4. Best practice procedure for upversioning

The procedure described in this document can be applied regardless of the chosen strategy and frequency. However, it is ultimately the organisation itself that sets the framework for the upversioning and therefore not all steps in the procedure apply in each specific case. For example, consistency checks and QA reviews may be handled in a separate review process rather than in the upversioning process. Also, the order of the different steps may vary since organisations use different systems and hence have differing processes.

Upversioning is performed between two versions of the same dictionary type and the same dictionary format (B₃ or C₃).

5.4.1. Utilise UMC resources

UMC provides several resources that can provide an understanding of how upversioning impacts on coded data.

- *WHODrug Change Analysis Tool (CAT)*

WHODrug CAT is a UMC application, available for all users of WHODrug, that analyses changes between any two versions of WHODrug from 2006 onwards. The output shows in detail all modifications, deletions and insertions between the versions, and a summary helps the user predict both the impact of the upversioning as well as the workload involved. Users can upload their coded data and CAT will match the full set of changes with the uploaded data. Uploaded verbatim terms, indications and routes will be displayed together with any matching modifications or deletions, making it easier to decide how to handle each separate change.

- *What's New*

In connection with each March 1 release, UMC publishes a 'What's new' document that outlines the most important new developments, improvements and changes since the last March 1 release – why they have been made and how they will affect the users.

The What's New document is found on the WHODrug User Area and may provide valuable input when preparing for upversioning.

- *WHODrug Newsletter*

The WHODrug Newsletter is a shorter and more compact description of major news concerning WHODrug than the What's new document. The WHODrug Newsletter is published in connection to each quarterly release.

5.4.2. Load new version

As part of the upversioning, the WHODrug text files for the new version need to be loaded into the organisation's coding system.

5.4.3. Review impact on coding

This section describes the impact of the different types of changes and how to approach them on a high level. Different organisations have their own coding conventions, and will therefore handle changes and recoding differently during the upversioning. This section of the Best Practice procedure sets out a number of general and, a few specific scenarios.

5.4.3.1. Review modified dictionary terms

Verbatim terms coded to dictionary terms that have been modified between the two versions need to be reviewed in order to decide whether the coding is still accurate or not. CAT enables users to easily review modifications.

There are several reasons why a term is modified. For example, misspelled trade names can be corrected or the Preferred Name for a record may be modified. Specific to the B3-format is that trade names may have [INGREDIENTS(S)] appended (if they become Non-Unique) or removed (if they used to be Non-Unique but become unique). A Non-Unique trade name is a trade name that is used for two or more medicinal products with different ingredients. If a trade name that used to be unique becomes Non-Unique in the new version (Table 5), then previous coding decisions directed to this term need to be reviewed. In ongoing trials, it is recommended to treat such terms as if they were new and follow the best practices for how to handle Non-Unique trade names. For legacy data, leaving the previous coding as it was may be the most reasonable choice.

Table 5. Agaril l used to be a unique trade name, but became Non-Unique in the 'New' version of WHODrug. Please note that the table below is an example using mock data.

	'Previous' version of WHODrug	'New' version of WHODrug	
Trade name	Ache and pain	Ache and pain [Codeine phosphate;Paracetamol]	Ache and pain [Paracetamol]
Drug Code	01277202035	01277202035	00345401123
Ingredients	Codeine phosphate Paracetamol	Codeine phosphate Paracetamol	Paracetamol

ATC codes can be removed from a dictionary WHODrug record, or new ATC codes can be added to the already existing ones (table 6). The impact of such changes needs to be considered regardless of which medication classification method is used. If single ATC selection is applied then the previous ATC code selection may even need to be re-evaluated.

In the C3 format, incorrect name specifiers, Marketing Authorisation Holders and strengths can be adjusted. The Old Form status may also change.

Table 6. In the ‘New’ version of WHODrug, P01CX was added to Milteli in addition to L01XX. Please note that the table below is an example using mock data.

	‘Previous’ version of WHODrug	‘New’ version of WHODrug
Trade name	Milteli	Milteli
Drug Code	05067401001	05067401001
ATC code(s)	L01XX – Other antineoplastic agents	L01XX – Other antineoplastic agents P01CX - Other agents against leishmaniasis and trypanosomiasis

5.4.3.2. Recode deleted WHODrug records

Verbatim terms coded to WHODrug records that are no longer present in the new version need to be recoded. The most common reason why a term is deleted is that its ingredients are found to be incorrect. A deleted term is always referenced to an active replacement term which describes the same, but corrected, information (Table 7). This replacement term may or may not be the appropriate term to recode to.

Table 7. In the ‘New’ version of WHODrug, Hepbv with Drug Code 09697501134 was, due to incorrect information regarding ingredients, deleted and replaced by 05504501022. Please note that the table below is an example using mock data.

	‘Previous’ version of WHODrug	‘New’ version of WHODrug
Trade name	Hepbv	Hepbv
Drug Code	09697501134	05504501022
Ingredient(s)	Hepatitis B vaccine	Diphtheria vaccine Hepatitis B vaccine Pertussis vaccine

5.4.3.3. Look for new direct or better matches

In one year alone, an average of 35, 000 new drug names are added to WHODrug, which means that verbatim terms coded to non-identical drug names or Umbrella Records in the earlier version may have direct or better matches in the new version.

Recoding non-identical matches is a time-consuming task and reviewing the entire data set may therefore be more suitable during a periodic consistency review rather than during upversioning. However, selective recoding of data of special interest is often performed. For

example, one may wish to check for direct or better matches for verbatim terms coded to Umbrella Records in the earlier version, or recode a predefined list of verbatim terms impacted by trade names that have been explicitly requested to be added in the new version. Another scenario is applicable for organisations coding to salt. It may not always be possible to find the correct salt in WHODrug and in those instances most users choose to code to the corresponding base instead. Some coding conventions then require the coder to check whether the salt has appeared in the new version and adapt the previous coding according to what they find (Table 8).

Table 8. Comtq is an example of a salt change between two WHODrug versions. *Please note that the table below is an example using mock data.*

	'Previous' version of WHODrug	'New' version of WHODrug
Trade name	Comtq	Comtq
Drug Code	037498101002	037498102002
Ingredient(s)	Cabozantinib	Cabozantinib s-malate

Organisations coding to base may experience a similar situation but the other way around, and may want to actively look to see if certain drug name have become available as the base in the new version. It should however be noted that the coding conventions allow the previous coding to be left as it is, even if a certain salt or base should appear.

5.4.4. Perform consistency checks and QC review of recoded terms

Recoding of study data or synonym lists is usually followed by a QC review. The extent of the reviewing can vary widely between organisations. Some perform partial reviews of selected data while others perform complete reviews of all the recoded data or entire synonym lists to ensure consistency. Yet others postpone it to the regular review process, outside of the upversioning process. Each organisation should have a review policy that supports that organisation's specific needs and abilities.

Organisations using synonym lists should note that when upversioning is complete, some manually coded verbatim terms may have become direct matches to dictionary terms available in the new version. Any manually coded term in the synonym list that is now a direct match in the new version should ideally be recoded to that direct matching record. Some organisations remove terms with direct matches in the dictionaries from the synonym lists, while others keep them.

As part of the QC process, organisations may want to use the CAT output to QC the upversioned data. For example, if CAT identified new exact matches based on imported verbatim terms, the user should expect these medications to autoencode. Likewise, checks based on deleted or modified terms could be performed.

5.4.5. Review coding conventions

Finally, ensure coding conventions are up to date with observed version differences and information in the What's New and Best Practices documents. Focus on the need to update any examples that may have been used in the coding conventions.

6. Essential Information for WHODrug Coding Review

If your organisation is performing medical coding review, it is strongly recommended that you circulate this chapter of the WHODrug Best Practices document to those staff who will undertake the review.

6.1. Background

In many organisations a review of coded drugs forms part of several processes during a clinical trial. In some instances the reviewer is not a coder and may not have in-depth knowledge of the different features of WHODrug. For this reason, this document has been prepared to provide some important insights to achieve a more efficient review. If having read it you have additional questions, please consult with the coding professionals available to you.

6.2. Purpose of drug coding review

It is up to each organisation to decide on the roles, responsibilities and expectations for drug coding review. Ensure you understand your organisation's purpose for reviewing the coded drug data before starting the review.

6.3. Coding conventions

Each organisation should have their own coding conventions. Ensure that you as a reviewer are familiar with these.

6.4. Auto-encoded data

The vast majority of coding applications offer the functionality to automatically code drug terms that have an identical match in WHODrug. In addition, a synonym file or thesaurus created within your organisation may be in use to increase the auto-encoding rate. The policies on auto-encoded data should be decided before you commence the review.

6.5. Identifying drugs of interest, for example prohibited drugs

Exclusively using an ATC code to identify a class of drugs may not always be appropriate. UMC has specifically developed the Standardised Drug Groupings (SDGs) as a tool for such searches. Your organisation may also have developed its own internal custom drug groupings to assist in identifying specific drugs or classes of drugs that are outside of the existing UMC SDGs. Please consult with the coding professionals available to you, or with UMC, for questions or more information.

(continues overleaf)

6.6. Production of review listing

Organisations themselves determine what information to include in review listings. The following is an example of what may be included:

- Verbatim
- Indication
- Route
- Trade name
- Preferred Name
- Ingredient(s)
- ATC
- WHODrug version and format

Verbatim	Indication	Route	Trade name	Ingredient(s)	Preferred Name	ATC Code	ATC Text 4	ATC Text 3	ATC Text 2	ATC Text 1	Version
Advil (ibuprofen)	Intermittent headaches	Oral	ADVIL [IBUPROFEN]	Ibuprofen	IBUPROFEN	M01AE	PROPION-IC ACID DERIVATIVES	ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STEROIDS	ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	MUSCULO-SKELETAL SYSTEM	WHO DDE B3 March 1, 2017
Robitussin nighttime cough dm	Cough	Oral	ROBITUSSIN NIGHTTIME COUGH DM	Dextromethorphan hydrobromide, Doxylamine succinate	DEXTRO-METHORPHAN HYDROBROMIDE; DOXYLAMINE SUCCINATE	R05DA	OPIUM ALKALOIDS AND DERIVATIVES	COUGH SUPPRESSANTS, EXCL. COMBINATIONS WITH EXPECTORANTS	COUGH AND COLD PREPARATIONS	RESPIRATORY SYSTEM	WHO DDE B3 March 1, 2017
Antibiotics Ear Drops Unknown*	Ear Infection	Otic	ANTIINFECTIVES, OTOLOGICAL		ANTIINFECTIVES, OTOLOGICAL	S02A		ANTIINFECTIVES	OTOLOGICALS	SENSORY ORGANS	WHO DDE B3 March 1, 2017
Acetaminophen	Ankle Pain	Oral	ACETAMINOPHEN	Paracetamol	PARACETAMOL	N02BE	ANILIDES	OTHER ANALGESICS AND ANTIPYRETICS	ANALGESICS	NERVOUS SYSTEM	WHO DDE B3 March 1, 2017

Figure 5. Example of drug coding review listing.

* The WHODrug record for this verbatim does not have ingredients or all ATC levels.

WHODrug properties to understand

Why is [INGREDIENT(S)] appended to the trade name?

The [INGREDIENT(S)] differentiates 'Non-Unique trade names', in WHODrug, i.e. products with the same trade name but different ingredients. This is fixed within the dictionary structure for correct code identification. It cannot be removed by the coder.

ATC-hierarchy

The coder cannot change the ATC hierarchy. When a specific ATC code is selected the entire hierarchy is automatically populated.

Why does the ATC code not reflect the reported indication?

The ATC classification system is not simply based on the indication and consequently it may not reflect all possible indications for each drug. If ATC coding is being performed, the coder would select the most appropriate ATC code available and cannot add ATC codes that are not listed for the selected drug, as the ATC hierarchy is fixed within the dictionary structure.

Why do I not see fifth level ATC codes?

The standard WHODrug coding files do not include fifth level ATCs since not all active substances have an officially assigned fifth level code. Therefore, ATC codes are available up to level four. If necessary, ATC level 5 is available as an add-on product from the UMC, called Cross Reference ATC 5.

Why do some records have blank ATC levels?

Some records in WHODrug have fewer than four ATC levels due to lack of specific code for the active ingredient. Instead they may only have first, second or third level ATC codes. This will lead to blank ATC levels in the review listing.

Why do some records lack ingredients?

Records lacking ingredients are Umbrella Records, i.e. records that represent a drug category rather than a specific drug name. This allows WHODrug to accommodate verbatim terms where the drug class is known, but the specific agent is not (e.g., Antibiotic - unknown, Steroid - unknown, Antihistamine - unknown).

7. Coding of imprecise verbatim (Umbrella coding)

7.1. Introduction

Umbrella records are available as a defined category of records in WHODrug. They represent a drug category or common concept related to drug administration, rather than a specific drug name. Since they do not refer to a specified medication they are not linked to any ingredients, however, they do have one or several ATC codes assigned to them. An Umbrella record has a corresponding Drug Code which begins with '9'.

Not Otherwise Specified (NOS) Records represent defined groups of substances and are generally included to be used as non-specific ingredients for records in WHODrug when specific ingredients are unverifiable. NOS Records also have one or several ATC codes assigned to them, but cannot be identified by specific Drug Code attributes.

Umbrella and NOS Records are included in WHODrug to facilitate coding by enabling each reported verbatim term to be coded to a standard term. As with any coding practice, organisation-specific conventions on when and how to select Umbrella or NOS Records should be defined, so that coding consistency may be ensured, and thus analysis enhanced.

Table 9. Differences and similarities between Umbrella and NOS records.

	Are there ingredients?	Have ATC code(s) been assigned?	Is there a WHODrug Drug Code starting with '9'?
Umbrella	×	✓	✓
NOS	✓	✓	×

7.2. When should Umbrella and NOS Records be used?

Coding to an Umbrella or NOS Record should usually be considered as the last resort, i.e. when a search returns no appropriate records from WHODrug or when the verbatim term cannot be identified as a specific medication or be queried.

Umbrella and NOS Records are mainly used in two situations: 1) coding imprecise verbatim terms that cannot be coded to specific drug names or 2) as a placeholder until the correct medication record is added to WHODrug. The latter situation is common when substances, trade names or investigational drugs are too new to have been entered in the dictionary. When the medication record is available in the dictionary, organisations may prefer to recode verbatim terms that contain those medications.

The following scenarios are typical cases for use of Umbrella or NOS Records:

- Verbatim mentions a drug category or therapeutic use, but no specific drug name (see Table 10).
- Verbatim mentions a drug name or the active ingredient(s) of the drug that is not available in WHODrug.
- Verbatim mentions a list of drugs which cannot be coded in combination in WHODrug, or cannot be split, e.g. for legacy data that cannot be updated.

Table 10. Examples of Umbrella Records in use. Coding conventions may differ within the industry and the examples should therefore not necessarily be interpreted as coding advice.

Verbatim term	Drug Code	Drug Name	Active Ingredient
Cough and cold tablets	90039801001	Cough and cold preparations	
Birth control pills	90113401001	Contraceptives	
Eye drops for dry eyes	90056201001	Other ophthalmologicals	
Drug / Placebo	90150901001	Blinded therapy	
Pronilide or paracetamol	90062101001	Anilides	

7.3. How should Umbrella and NOS Records be selected?

There are several approaches to the selection of Umbrella and NOS Records, and this best practice document describes the most commonly used. However, each organisation should determine the best approach for their needs and this should be documented in the organisation's coding conventions.

1. The Umbrella or NOS Record can be selected based on its associated ATC(s), using the ATC guidelines provided by the WHO Collaborating Centre for Drug Statistics Methodology, available at www.whocc.no. Note that the official ATC classifications and guidelines are revised and updated in January each year which in turn leads to ATC changes in the following March release of WHODrug.
2. The selection of an Umbrella or NOS Record can also be based on the reported verbatim without considering the ATC assignments. For this approach, consider how the associated ATC codes will be used in aggregate tables and listings. This approach is not recommended if the organisation includes ATC codes in aggregated tables and listings.

Table 11. Examples of nuances to consider when choosing an Umbrella Record.

Umbrella	Route	Indication	ATC code	Consequence
Corticosteroids, plain	Intra-articular	Rheumatoid arthritis	So1BA, Corticosteroids, plain Do7A, Corticosteroids, plain	If the verbatim corticosteroid with intra-articular route is coded to 'corticosteroids, plain', the selection of ATC codes will not include the systemic ATC since this Umbrella is connected to the ophthalmological and dermal routes only.
Corticosteroids	Intra-articular	Rheumatoid arthritis	Co5AA, Corticosteroids Do7A, Corticosteroids, plain Ho2, Corticosteroids for systemic use Ro1AD, Corticosteroids So1BA, Corticosteroids, plain So2B, Corticosteroids So2BA, Corticosteroids So3B, Corticosteroids So3BA, Corticosteroids	If the verbatim corticosteroid with intra-articular route is coded to 'corticosteroids', the selection of ATC codes will include the systemic ATC since this Umbrella is connected to several routes and indications.
Antiandrogens	Oral	Prostate cancer	Go3H, Antiandrogens	If the verbatim antiandrogen is coded to 'Antiandrogens', the ATC for antineoplastic endocrine therapy will not be included, since this Umbrella is only connected to the ATC for sex hormones and modulators.
Anti-androgens	Oral	Prostate cancer	Lo2BB, Anti-androgens	If the verbatim antiandrogen is coded to 'Anti-androgens', the ATC code for antineoplastic endocrine therapy will be included.
Anticholinergics	Oral	Parkinson's disease	Ro3BB, Anticholinergics So1FA, Anticholinergics	If the verbatim oral anticholinergic is coded to 'Anticholinergics', the selection of ATC codes will not include the ATC for Parkinson's disease since this Umbrella is connected to the inhalation and ophthalmological routes only.
Anticholinergic agent	Oral	Parkinson's disease	No4A, Anticholinergic agents	If the verbatim oral anticholinergic is coded to 'Anticholinergic agent', the systemic ATC code for Parkinson's disease is included.

A full list of Umbrella Records can be found in the WHODrug file package (additional features file) or when searching in WHODrug Insight with the Umbrella Record Product filter. All Umbrella Records can be identified by having a Drug Code starting with '9' (as seen in Table 10).

7.4. Choosing between Umbrella or NOS Records

Some Umbrella Records and NOS Records are very similar. For these scenarios, a common approach among organisations is to select the NOS Record, since this selection will lead to a populated ingredients field and may provide a more specific ATC code.

Table 12. Example of an Umbrella Record and a NOS Record with similar names.

Verbatim Term	Drug Code	Drug Name	Active ingredients	ATC code	Version
Probiotic therapy	90114801001	Probiotics [Umbrella Record]		A07 • A16	March 1, 2018
Probiotic therapy	07501101001	Probiotics nos	Probiotics nos	A07FA • A16AX	March 1, 2018

Coding to Umbrella Records in a safety database can cause problems when submitting cases via E2B to certain regulatory authorities. In these cases, coding to NOS Records is preferable, if possible. However, if no NOS Record is available, some organisations choose not to code that specific verbatim term. Instead, a note can be made in the notes field explaining the reason and asking the case processors to mention it in the narrative.

7.5. Impact of Upversioning to Terms Coded to Umbrella Records

When implementing a new WHODrug version, check for direct or better matches for verbatim terms coded to Umbrella Records in the earlier version. This can be done, for example by utilising the pre-upversion coding reports with Drug Codes and filtering for all medications having Drug Codes starting with '9'.

Newer versions of WHODrug covers more entries for Trade Names, Active Ingredients, and Ingredient Combinations, however the lack of specificity and/or otherwise poor quality of verbatim terms will always require coding to an Umbrella Record.

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