Best Practices for the use of the WHO Drug Dictionaries

VERSION 2.0
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This document has been developed together with members of our user community to describe possible solutions to potential challenges when coding by using the WHO Drug Dictionaries. The WHO Drug Dictionaries can be used for coding of concomitant medications as well as Individual Case Safety Reports (ICSRs). We are continuously working on developing new Best Practices, so contact us if you would like to participate in the Best Practices Working Group. Comments are always welcome to the Best Practices described in this document. The goal for this document is to reflect and/or facilitate coding of medicinal products.

Descriptions of drug codes, ATCs and other dictionary characteristics are found in WHO Drug Dictionaries User Guide, available on the User Group portal:

www.usergroup.umc-products.com

For any questions regarding this document and its content, please contact us at drugdictionary@umc-products.com

Version history

<table>
<thead>
<tr>
<th>Version</th>
<th>Release date</th>
<th>Comment</th>
</tr>
</thead>
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<tr>
<td>1.0</td>
<td>May 7th 2012</td>
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<tr>
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I. Non-unique Trade Names

Sometimes a Trade Name in the WHO Drug Dictionaries is available with different active ingredients, making the Trade Name non-unique. Therefore, additional information about the Trade Name may be necessary in order to be able to code to the correct entry. This is one of the reasons the C-format has been introduced, to help the users find the correct entry by choosing the entry that contains the additional information, such as Country, Market Authorisation Holder, Strength and Pharmaceutical Form.

The non-unique Trade Names are represented in different ways in different software interfaces. Systems that are based on the B-format have the name followed by /drug record number+Seq1/.

The Drug Name field is not always sufficient to identify a drug. If more than one entry has the same Trade Name, other data fields need to be investigated. This can happen for the following scenarios:

- 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.

The non-unique Trade Names include different active ingredients or variations of salt forms of active ingredients. But there are often other differences between the non-unique Trade Names: country of origin, pharmaceutical form, therapeutic use, etc.

These differences are called differentiators, shown in Figure 1, and this Best Practice will describe how they, if available to the coder, can be used to select an entry in the WHO Drug Dictionaries in non-unique name situations. Identified differentiators described in this section are:

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

In order to display examples in this document we will use the WHO Drug Dictionary Browser since it can show all differentiators in the B and C format. UMC collaborates with many software providers and it is our intention to encourage them to enable the Best Practices in their systems.
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 ask a series of questions and thereby reduce the number of alternatives and in most cases filter out to one unique entry. The differentiators are not listed in a chronological order; they can be partially or fully carried out according to the internal coding rules and SOPs. The coder can, depending on the coder’s organization policies, contact the reporter for additional information at any stage during the decision process.
1. Finding a differentiator to help decide which entry to choose

a. Is information about ingredients available?

Yes. If information about the ingredients for a reported medication is available, the non-unique Trade Name situation is most often solved – an entry can be selected and coded to.

*Example:* Reported term: ‘Bradosol (Hexylresorcinol)’

![Table showing search results in the WHO Drug Dictionary Browser for 'Bradosol'](image)

Based on the ingredient information given in the verbatim phrase, ‘Bradosol’ with Drug Code 00581401007 can be selected since it has an active ingredient that matches the reported term.

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

b. Can salt variations of the ingredients be used to differentiate?

Yes, for single-ingredient products. In some cases, the only difference between non-unique entries in the WHO Drug Dictionaries is the salt form of the ingredients, as seen in figure 3 below. The reasons for these are often different Route or Pharmaceutical Form, another usable differentiator for these cases.

*Example:* Reported term: ‘Prilosec’

![Table showing search results in the WHO Drug Dictionary Browser for 'Prilosec'](image)

If possible to retrieve more exact information about which salt form was used in the specific case to be coded, this is of course the best alternative.

However, if the company SOPs do not require specific salt information for the ingredients of the products, the entry with Seq1=01 (base form of the ingredient) can be selected. The Drug Code system in the WHO Drug Dictionaries connects all single ingredient products with any salt form of an ingredient by giving them the same DrugRecordNumber (006612 in this example), which means that any of the available alternatives can be chosen if the non-unique entries are single-ingredient and only differentiated by the ingredient salt form.
Yes, for multiple-ingredient products. For multi-ingredient products, the DrugRecordNumber will differ, as seen in figure 4, which makes it important to know how analysis is done on ingredient level before selecting an entry.

Example: Reported term: ‘Aktil’

![Figure 4. Search results in the WHO Drug Dictionary Browser for ‘Aktil’](image)

In this case, there is an entry containing both ingredients as bases (drug code 00852501012), making no assumptions on which salts the reported ‘Aktil’ contained. This entry can be selected if salt-variations are ignored in analysis.

If the company SOP requires coding to the preferred term (seq2=001), this can be done, but still requires thought to which one of the ingredient combinations to choose.

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

c. Is it possible to use indication or ATC to determine the correct entry?
Yes. If the coder has access to information about why the medication has been used, either by ATC code or given indication, this may serve as useful information to be able to select an entry. The WHO Drug Dictionaries give the coder information about the product’s ATC (Anatomical Therapeutic Chemical) class(es).

Please note! 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.

Example: Reported term: ‘Flomax’. In addition, the indication “benign prostatic hypertrophy” has been provided to the coder.

![Figure 5. Search results in the WHO Drug Dictionary Browser for ‘Flomax’](image)
In this case, ‘Flomax’ with Drug Code 01280302013 has an ATC that matches the reported indication, and can therefore be selected.

**No.** If information about indication or ATC is *not* available, or if more than one entry has matching ATC classes, take the possible entries and see if there may be information available for another differentiator that can help in selecting an entry.

d. **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 the WHO Drug Dictionaries the replaced formulations are marked as ‘old form’. This also applies to products no longer marketed.

Entries marked with ‘old form’ should only be selected when coding ‘historic’ data and when the ‘old form’ formulation has been confirmed.

**Example:** Reported term: ‘Ascal.’ This report comes from the Netherlands.

![Figure 6. Search results in the WHO Drug Dictionary Browser for ‘Ascal’](image)

As seen in figure 6, ‘Ascal’ is a non-unique drug name having two different drug codes (different active ingredients) in the Netherlands, whereof one is /old form/. Assuming that the reported drug is the marketed one, code the reported term to the entry without the /old form/ flag (drug code 00800002006).

**No.** If company 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 the WHO Drug Dictionaries as a differentiator, there may be information available for another differentiator that can help in selecting an entry.

e. **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, like in the example below.
**Example:** Reported term: ‘Noval eye drops’.

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Noval</th>
<th>Noval</th>
<th>Noval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name Specifier(s)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug Code</td>
<td>00371202050</td>
<td>00039801020</td>
<td>00020011296</td>
</tr>
<tr>
<td>Active Ingredient(s)</td>
<td>Timolol maleate</td>
<td>Ethynylestradiol</td>
<td>Paracetamol</td>
</tr>
<tr>
<td>Preferred base name</td>
<td>Timolol</td>
<td>Nuvosen</td>
<td>Paracetamol</td>
</tr>
<tr>
<td>Preferred salt name</td>
<td>Timolol maleate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generic Preferred</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATC Code(s)</td>
<td>S01ED Beta blocking agents official</td>
<td>G03FA Progestogens and estrogens, fixed combinations</td>
<td>N02BC Andides official</td>
</tr>
<tr>
<td>Other ATC codes for the active ingredient(s)</td>
<td>S01AA Beta blocking agents, non-selective official</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAH(s)</td>
<td>Demo greece</td>
<td>Yamanouchi seiyaku</td>
<td>United labiorator</td>
</tr>
<tr>
<td>Countries</td>
<td>Greece</td>
<td>Japan</td>
<td>Bangladesh</td>
</tr>
<tr>
<td>Pharmaceutical Form(s)</td>
<td>LIQUIDS, DROPS</td>
<td>TABLETS</td>
<td>LIQUIDS, SYRUPS</td>
</tr>
<tr>
<td>Strength(s)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Figure 7. Search results in the WHO Drug Dictionary Browser for ‘Noval’*

As seen in figure 7, there are three entries in the WHO Drug Dictionaries with the name ‘Noval’. However, the ‘Noval’ with Drug Code 00371202050 has an ATC code (S01ED) as well as the pharmaceutical form ‘Liquid, Drops’ which matches the reported term ‘eye drops’. This gives the coder an entry to select based on the information given in the reported term.

**No.** If more than one alternative is possible, or if the information reported does not match any one specific entry in the WHO Drug Dictionaries, there may be information available for another differentiator that can help in selecting an entry.

**f. Can Name Specifier be used as a differentiator?**

**Yes.** Name Specifier is a part of a drug 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 entry.

*Example:* Reported term: ‘Espaven pediatrico’.

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Espaven</th>
<th>Espaven</th>
<th>Espaven</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name Specifier(s)</td>
<td></td>
<td>Pediatrico</td>
<td></td>
</tr>
<tr>
<td>Drug Code</td>
<td>01477501003</td>
<td>0055080228</td>
<td>00150501050</td>
</tr>
<tr>
<td>Active Ingredient(s)</td>
<td>Calcium pantothenate</td>
<td>Ranitidine hydrochloride</td>
<td>Dimeticon</td>
</tr>
<tr>
<td>Preferred base name</td>
<td>Spl-mat-ean</td>
<td>Ranitidine</td>
<td>Dimeticon</td>
</tr>
<tr>
<td>Preferred salt name</td>
<td>Spl-mat-ean</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generic Preferred</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Figure 8. Search results in the WHO Drug Dictionary Browser for ‘Espaven’*

There is no entry with the complete reported term in the product name field, but for one on the ‘Espaven’ products, pediatrico is available in the Name Specifier field, and can therefore be coded to.

**No.** If Name Specifier information is not a possible differentiator, there may be information available for another differentiator that can help in selecting an entry.
g. Is information about country provided?

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


<table>
<thead>
<tr>
<th>Product Name</th>
<th>Aerius</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name Specifier(s)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug Code</th>
<th>Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>01009701022</td>
<td>Pakistan</td>
</tr>
<tr>
<td>01398501005</td>
<td>Sweden</td>
</tr>
</tbody>
</table>

There are two ‘Aerius’ entries, 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, ‘Aerius’ with Drug Code 01398501005 can be chosen.

**No.** If country cannot be used to differentiate one non-unique entry from another there may be information available for another differentiator that can help in selecting an entry.
2. No differentiator is possible to use

a. Possibility to code to an umbrella entry?

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

Example: After eliminating all possible entries for a non-unique name, the remaining alternatives all have the same ATC class (on 4th or higher level). All ATC terms from the 4th level exist as umbrella entries in the WHO Drug Dictionaries, and can be chosen to code a non-unique name to.

Example: Are all alternatives in the same substance class, e.g. vitamins, the coder can select the umbrella entry ‘Vitamins,’ for example.

If no other options exist, one of the two umbrella entries in figure 10 can be chosen.

![Umbrella entries available when no other options exist.](image)

Keep in mind that drug names coded to any of these two entries will not be included in most kind of analysis or presentations/tabulations.

No. If no umbrella entries exist to code the reported term to, the reported term may be uncodable.

b. Uncodeable?

If a term is uncodable it may be possible to add another entry in the WHO Drug Dictionaries to be able to distinguish a non-unique name. That process is described in the section 0. II Missing Drug
II Missing Drug

A WHO Drug Dictionary Enhanced subscriber can at any time submit a request for a new drug entry. This can be done through the Browser or by contacting drugdictionary@umc-products.com.

This chapter describes the Best Practices for when a coder is missing a drug name to code to.

![Diagram of handling a coding situation where a drug is missing in the WHO Drug Dictionaries](Diagram)

**Figure 11.** Schematic explanation of how to handle a coding situation where a drug is missing in the WHO Drug Dictionaries ((Y=Yes; N=No)).

1. Submitting a New Drug Request

Before submitting a New Drug Request, please check that the drug name does not exist in a more current version of the WHO Drug Dictionaries.

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

*Example:* Reported term: ‘Omeprazole/Lanzoprazole’

There are currently no products in the WHO Drug Dictionaries that contain the two reported substances in one drug. Most likely, 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.
However, it might be that the 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 subscribed version of the WHO Drug Dictionaries.

The coder can then submit a New Drug Request, and in the mean time either (1a) leave reported term uncoded until the approval response has been received or (1b) code to a ‘place holder.’

**a. Wait for response of New Drug Request**

If possible to wait for the approval of the New Drug Request and in the meantime leave the reported term uncoded until the next dictionary version is released, this option is preferred. The decision of how to code the reported term is thereby postponed until the approval response is received.

**b. Code to ‘place holder’**

If the reported term has to be coded, i.e. the coding cannot wait until the response of the New Drug 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 New Drug Request
- An existing entry from the WHO Drug Dictionaries

**Using the requested drug name** as a ‘place holder’ requires that company SOPs allow for recoding of a coded term since the requested drug name may be denied and another option has to be chosen as the selected entry to code to. This option also requires that a reported term can be coded to a non-existing term in the current version of the WHO Drug Dictionaries until the next version of the dictionaries is released.

**Using an existing entry in the WHO Drug Dictionaries** as a ‘place holder’ may be another option. If the user cannot wait for the New Drug Request response, or if the user’s organization or process is not set up to manually update the coding system with the newly approved term from UMC, the user should find an alternative place holder.

This requires that company guidelines allow changes to coded data, at least in the time-span until the new dictionary version is released, and with consideration to that the New Drug request may be denied. If the New Drug Request is denied, the placeholder may be decided as an approved, existing, term to code to.

**Generic Name entry**

Even though the reported trade name does not exist in the WHO Drug Dictionaries, it is very likely that a generic entry for the substance(s) exists. This can easily be found by using the WHO DD Browser, shown in figure 12. The file Ingredient_LongText is another tool where all drug codes with their substance combinations in long text format can be found.

If company coding principles allow, the base (without salt information), or combination of base-substances for reported substances with salts can be chosen.
**Preferred Name entry**

For single ingredients, the preferred and generic name will always be the same. For multi-ingredients, the generic name is not always the preferred drug name, meaning that if there is no generic entry for a multi-ingredient, an option can be to code to the preferred entry instead.

The Preferred name entries will have a Drug Record Number that corresponds with the active ingredients of your New Drug Request. The Preferred entries have all ATC codes for all products with the same Drug Record Number.

If there is no preferred entry with the correct salt forms, an option can be to code to the preferred name with the base substance(s).

**Umbrella entry**

If neither a suitable generic entry nor a suitable preferred entry is found, an alternative ‘place holder’ can be an umbrella entry. If the active ingredient can be identified, one may be able to find the pharmacological class it belongs to.

**2. New Drug Request Process**

**a. New Drug Request approved**

If the new drug request is approved, the requested drug name will appear in the next dictionary release. You will, in the approval response, also get information about the corresponding Preferred Name, the assigned ATC classes etc. This enables you to enter a temporary entry in the dictionary until the next version is released.

**b. New Drug Request denied**

If the new drug request is denied, either code to the place holder chosen in (II.1) Code to ‘place holder,’ or the reported term will have to be labelled as ‘uncodable’. If ‘uncodable’ is not an option, the umbrella entries in figure 10 may be an option.
III Medication classification (ATC coding)

Within the pharmaceutical industry there are several approaches used in order to classify the medications included in a study or on safety reports. Here are the best practices and description of four methods for classification of medications when using the WHO Drug Dictionaries.

Introduction

**ATC classification system**
The Anatomical Therapeutic Chemical (ATC) and the Herbal ATC (HATC) classifications are an integrated part of the WHO Drug Dictionaries. The ATC classification system is maintained by WHO Collaboration Centre for Drug Statistics Methodology, and Uppsala Monitoring Centre (UMC) integrates this classification into the WHO Drug Dictionaries. The HATC classification is maintained by UMC and integrated in the WHO Herbal Dictionary. A brief overview of the ATC system follows, for more details please visit the User Guide at the User Group portal.

**The difference between ATC and indication**
The intended use for the ATC classification system is drug utilization research. The ATC system is therefore designed to classify the combination of indication, mechanism of action and chemical properties of medicinal substances. The ATC classification system is not primarily a therapeutic indication classification system and consequently the ATC classification does not reflect all indications of a medication. It is important to remember that the mechanism of action of a drug is included in the determination of classification ATC classification.

One example to illustrate the difference between ATC and indication is bupropion, a common treatment of nicotine dependence. Bupropion has the mechanism of action as an antidepressant drug and therefore is classified in the ‘other antidepressants’ group, even though there is an ATC class for ‘drugs used in nicotine dependence’. Thus, if ATC classification is used in a clinical study, it may not necessarily identify all patients who have taken drugs to quit smoking. 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 classification of medications.

The WHO Drug Dictionaries user should know 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](http://www.whocc.no).

**ATC classification within the WHO Drug Dictionaries**
The classification of medicinal products in the WHO Drug Dictionaries is primarily based on the guidelines for ATC classification. The ATC classifications that follow the guidelines are flagged as official. If the ATC guidelines do not explicitly state how to classify a substance, some medicinal products can be classified in the WHO Drug Dictionaries with additional ATC codes to reflect the main use of the particular product. An example is duloxetine: duloxetine has an official ATC classification in ‘other antidepressants’ and is therefore assigned this classification within WHO Drug Dictionaries. The substance is also used to treat urinary incontinence, so the product is also classified within the WHO Drug Dictionaries in ‘other urologicals’. This classification is not flagged as official.
**ATC assignment in the B- and C-format**

In the B-format of the WHO Drug Dictionaries medicinal products are linked to the same ATC codes as the associated preferred record (preferred bases and preferred salts).

In the C-format on the other hand, each individual medicinal product is generally assigned one ATC code only. The assigned ATC code reflects the intended use of the particular product. The generic records in the C-format are assigned an ATC code in the same manner as in the B-format, i.e. the generic records are assigned all ATC codes for the linked products (see table I and II).

Table I. Illustration of the difference of ATC assignment for the ingredient acetylsalicylic acid in B- and C-format.

<table>
<thead>
<tr>
<th>Trade name (ingredient)</th>
<th>ATC in B-format</th>
<th>ATC in C-format</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylsalicylic acid</td>
<td>A01AD, B01AC, M02AC, N02BA</td>
<td>A01AD, B01AC, M02AC, N02BA</td>
</tr>
<tr>
<td>Albyl (acetylsalicylic acid)</td>
<td>A01AD, B01AC, M02AC, N02BA</td>
<td>N02BA</td>
</tr>
<tr>
<td>Casprin (acetylsalicylic acid)</td>
<td>A01AD, B01AC, M02AC, N02BA</td>
<td>B01AC</td>
</tr>
</tbody>
</table>

Table II. Illustration of the difference of ATC assignment for the ingredient erythromycin in B- and C-format.

<table>
<thead>
<tr>
<th>Trade name (ingredient)</th>
<th>ATC in B-format</th>
<th>ATC in C-format</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythromycin (erythromycin)</td>
<td>D06AX, D10AF, J01FA, S01AA</td>
<td>D06AX, D10AF, J01FA, S01AA</td>
</tr>
<tr>
<td>Erycette (erythromycin)</td>
<td>D06AX, D10AF, J01FA, S01AA</td>
<td>D10AF</td>
</tr>
<tr>
<td>Eritrovit (erythromycin)</td>
<td>D06AX, D10AF, J01FA, S01AA</td>
<td>J01FA</td>
</tr>
</tbody>
</table>

In both formats, the preferred record 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 C-format assignments in the B-format by using the ‘DDA exclusive’ text file.

**DDA exclusive**

An additional text file is available, named ‘DDA Exclusive’. This file has the advantages of the C-format, designed to increase the efficiency of ATC coding for the B-format users. The ‘DDA Exclusive’ file is fully 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. Read more about DDA Exclusive in the WHO Drug Dictionaries user guide (found on the User Group portal under user guide heading, section 4.4). When using DDA exclusive it is important to know that less ATC codes can be used to reflect the indication, especially for off-label use of the particular product. However, the preferred record is always linked to all available ATC codes.

Note: It is optional to use the DDA exclusive file; it is described in here for information purposes.

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1 The WHO Drug Dictionary Browser displays the ATC assignments in ‘DDA Exclusive’ mode.
**Classification methods**

When planning a study there are several options for how to handle medication classification. First to be decided is whether classification of medication is to be done or not. If it is, there are several methods to choose from of which three are recommended by the Uppsala Monitoring Centre. These three methods as well as the non-classification option are described herein.

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.

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

**Method descriptions**

Table III lists the four recommended methods and the respective definition and description of each method.

<table>
<thead>
<tr>
<th>Method</th>
<th>Definition and description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. All possible ATC pathways</td>
<td>All possible ATC pathways is here 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.</td>
</tr>
<tr>
<td>2. Single ATC selection</td>
<td>Single ATC selection is here 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: this is not the same as setting up a system to programmatically select one ATC code. Manual review is always required to ensure the most appropriate ATC is selected.</td>
</tr>
<tr>
<td>3. Classification using system other than ATC</td>
<td>Classification using system other than ATC is here defined as using another system than ATC in order to better capture the reason for the patient taking the medication (indication). There are several classification systems for classifying medications based solely on their indication. Two such systems are MedDRA and ICD. These systems 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 know that classification according to ingredient properties and mechanism of action is not available.</td>
</tr>
<tr>
<td>4. No classification of medication</td>
<td>No classification of medication is not a method, 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 a possibility to go back and classify medications if needed later on in the study.</td>
</tr>
</tbody>
</table>
Advantages and Disadvantages

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

Table IV. Advantages and disadvantages for the classification methods (the no classification method is excluded in the table)

<table>
<thead>
<tr>
<th>Advantages</th>
<th>2. Single ATC selection</th>
<th>3. Classification using system other than ATC</th>
</tr>
</thead>
<tbody>
<tr>
<td>➢ Coding to all possible ATC selections saves time and resources thus saving money on the budget.</td>
<td>➢ Coding to a single ATC allows data to be grouped in a more medically relevant manner and categories of interest can be reviewed in more detail.</td>
<td>➢ Straightforward to find appropriate match to indication on CRF. Since indications are not included in the WHO Drug Dictionaries and not connected to a specific medication (like ATC codes are), the whole system can be used to find an appropriate match.</td>
</tr>
<tr>
<td>➢ Changes of ATC classification in the WHO Drug Dictionaries can be automatically updated without manual revision since no specific ATC has been chosen.</td>
<td>➢ Facilitates and promotes consistency in specific drug classification based on the reported indication.</td>
<td>➢ Better overview of indication rather than the mechanism of action.</td>
</tr>
<tr>
<td>➢ Coding to all possible ATC selections means that there is a reduced risk of missing a signal and signals can be more easily recognized.</td>
<td>➢ Supports the medication coding process such as to check the consistency between the drug code and the reported indication, route and dosage.</td>
<td></td>
</tr>
<tr>
<td>➢ No need to store ATC codes in the database. The ATC classification can be derived directly from WHO DDs.</td>
<td>➢ Grouping medications according to their ATC codes with no double counting/reporting.</td>
<td></td>
</tr>
</tbody>
</table>

Disadvantages

| ➢ Requires a more educated analysis team in order to interpret the data correctly. | ➢ Changes in ATC classification need to be reviewed manually during upversioning. | ➢ Not industry practice today |
| ➢ Coding to all possible ATC pathways selections will make for 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 multiaxiality of ATC. Often times this can lead to literal translation of figures and misleading perceptions of the data. | ➢ Coding to a single ATC is often time-consuming putting a strain on tight study budgets. | ➢ Probably not supported in available software systems. |
| ➢ Coding to all possible ATC pathways selections will make for 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 multiaxiality of ATC. Often times this can lead to literal translation of figures and misleading perceptions of the data. | ➢ Coding to a single ATC 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 N02BA (Salicylic Acid and Derivatives) would not be included in an analysis that is looking for Antithrombotic agents) | ➢ Will not group medications with same mechanism of action which will make some analysis difficult, for example interactions analysis. In some analysis it is beneficial to aggregate medications with the same mechanism of action to get more medications in the same group and thus stronger signals. |
| ➢ Coding to all possible ATC could generate more queries when a substance is “off-label use”, or indication is missing, especially for a non-unique drug name. | ➢ Coding to a single ATC could generate more queries when a substance is “off-label use”, or indication is missing, especially for a non-unique drug name. | ➢ 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 antibiotic drug could be reported as Anti-infective, Antibiotic therapy, Infection, etc. | | ➢ Can be inconsistent due to the different ways the same indication could be reported. Example: Indication for the use of antibiotic drug could be reported as Anti-infective, Antibiotic therapy, Infection, etc. |
Choice of method
This section provides a short checklist, which is intended to aid in the process of choosing a method.

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 multiaxiality of ATC.
• You want to classify the medication but do not have the budget to choose the Specific 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 handle with the multiaxial representation.

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 of indication as possible.
• You want to double check the consistency of reported indication and drug coding.
• You may have difficulties handling the multiaxiality 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 signal where the signal is false positive.
• Your statistical team prefers to have specific classification handled at the coding level.

Choose Classification using system other than ATC if:
• You want to aggregate and/or analyze the data according to indication rather than mechanism of action.
• You wish to follow up conditions or diseases in a study population.

Choose No classification of medication if:
• You are not planning any of the analysis 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.
Best practice procedures for each classification method

Below are the best practice procedures for each individual classification method described. The best practice procedures are summarized in a flow chart in figure 17.

1. **All possible ATC pathways**

This method has only one best practice step to consider:

   a. Choose all ATC codes available

If you have chosen this method for classification you do not make a judgment 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.

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 much 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 the WHO Drug Dictionaries.

   a. **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.

   b. **Is indication available?**

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

*Example:* Acetylsalicylic acid is linked to four different ATC codes depending on indication.

<table>
<thead>
<tr>
<th>Product Name:</th>
<th>Acetylsalicylic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicinal Product ID:</td>
<td>1066</td>
</tr>
<tr>
<td>Drug Code:</td>
<td>00002701001</td>
</tr>
<tr>
<td>ATC code(s):</td>
<td>B01AD Other agents for local oral treatment official; B01AC Platelet aggregation inhibitors excl. heparin official; N02AC Preparations with salicylic acid derivatives; N02BA Salicylic acid and derivatives official</td>
</tr>
</tbody>
</table>

*Figure 13. Search results in the WHO Drug Dictionary Browser for ‘Acetylsalicylic acid’.*
c. 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 neglected and appropriate ATC should be selected according to the other criteria given in this best practice.

Example: Carbamazepine is an antiepileptic drug assigned ATC code N03AF – Carboxamide derivatives but can be used to treat bipolar disorders. In this case, choose the N03AF ATC code according to step a.

d. Is route of administration available?
If route of administration is given, choose ATC code according 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 the WHO Drug Dictionaries, which can be used as indicator of route of administration.

Example: Aciclovir has three ATC codes: D06BB – transdermal, J05AB – systemic, S01AD – ophthalmic.

<table>
<thead>
<tr>
<th>Product Name:</th>
<th>Aciclovir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicinal Product ID:</td>
<td>32485</td>
</tr>
<tr>
<td>Drug Code:</td>
<td>00587301001</td>
</tr>
<tr>
<td>ATC code(s):</td>
<td>D06BB Antivirals official, J05AB Nucleosides and nucleotides excl, reverse transcriptase inhibitors official, S01AD Antivirals official</td>
</tr>
</tbody>
</table>

Figure 14. Search results in the WHO Drug Dictionary Browser for ‘Aciclovir’.

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

Example: Finasteride is classified in different ATC classes depending on dosage, D11AX – Other dermatologicals, is used for 1 mg/day and G04CB – Testosterone-5-alpha reductase inhibitors, is used for 5mg/day.

<table>
<thead>
<tr>
<th>Product Name:</th>
<th>Finasteride</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicinal Product ID:</td>
<td>43876</td>
</tr>
<tr>
<td>Drug Code:</td>
<td>01130001001</td>
</tr>
<tr>
<td>ATC code(s):</td>
<td>D11AX Other dermatologicals official, G04CB Testosterone-5-alpha reductase inhibitors official</td>
</tr>
</tbody>
</table>

Figure 15. Search results in the WHO Drug Dictionary Browser for ‘Finasteride’.

f. The given indication has no corresponding ATC code
There might be circumstances where an additional ATC code can be added to the medication. First, go to the case to find out more information. If there are no apparent errors, contact the reporter to ensure the information given was correct. If everything seems correct, contact UMC if you think there is a need for an additional ATC code, either via e-mail: drugdictionary@umc-products.com, or use the ‘request tab’ in the WHO Drug Dictionary Browser.
Example: Oxygen is officially classified in V03AN – Medical gases. However, on request from WHO Drug Dictionary users the ATC R07A – Other respiratory system drugs, is also assigned.

<table>
<thead>
<tr>
<th>Product Name:</th>
<th>Oxygen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicinal Product ID:</td>
<td>17032</td>
</tr>
<tr>
<td>Drug Code:</td>
<td>00150301001</td>
</tr>
</tbody>
</table>
| ATC code(s):   | A01AD Other agents for local oral treatment
                | R07A OTHER RESPIRATORY SYSTEM PRODUCTS
                | V03AN Medical gases official |

Figure 16. Search results in the WHO Drug Dictionary Browser for ‘oxygen’.

- **g. All of above unknown?**
  If none of the above alternatives is available within the coding tool, company 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
  - Manual creation of preferred ATC lists; for the most common drugs some companies 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.

**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 two 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.

**3. Classification using system other than ATC**
The UMC does not provide best practice for this option since the medications in the WHO Drug Dictionaries are not classified according to such a system.
Figure 17. 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 the coder’s organisation polices, contact the reporter for additional information at any stage during the decision process.
Other considerations

**CDISC compliance**
Clinical Data Interchange Standards Consortium (CDISC) provides guidelines for submission data standards in clinical trials. By following the recommendations made here, you will be compliant with the CDISC guidelines. The CDISC Study Tabulation Model ([SDTM](#)) gives advice to anyone who is submitting clinical data to national authorities for how to classify the concomitant medications into a medication class such as an ATC class (1).

**Standardised Drug Groupings**
Please note there is also another classification system available for the WHO Drug Dictionaries: 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 find the SDG guidelines for more information (section 8 in the user guide on the User Group portal).

**References**
1. Study Data Tabulation Model Implementation Guide: Human Clinical Trials. Version 3.1.2. CDISC.