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1. Introduction

Uppsala Monitoring Centre 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. The 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.

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.umc-products.com.

| Dictionary format | WHODrug is distributed to all users in two formats – the B2-format and the C-format – and the user decides which to use. The B2-format contains information about trade name, ingredients and ATC classification(s). The unique key is the alphanumeric Drug Code. The C format contains all the B2-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. |
| 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). |
| Upgrade | The addition to a current subscription of a new dictionary or feature in the WHODrug portfolio. WHODrug Enhanced can for example be upgraded to WHODrug Enhanced an WHODrug Herbal. |
| 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 B2-format, non-unique trade names are appended with /Drug Record Number Sequence 1/.

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 C-format has been introduced. The C-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 Best Practice 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

Examples in this document use WHODrug Insight since it can show all differentiators in the B2- and C-formats. 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 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.

Example: Reported term: ‘Bradosol (Hexylresorcinol)’

<table>
<thead>
<tr>
<th>Product name</th>
<th>Drug code</th>
<th>Active Ingredient(s)</th>
<th>ATC</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRADOSOL 00088302/</td>
<td>000683 02 055</td>
<td>Benzalkonium chloride</td>
<td>A01AB, Antimicrobials and antiseptics for local oral treatment umc-assigned</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>D08AJ, Quaternary ammonium compounds official •</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>D09AA, Medicated dressings with antimicrobials official •</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>G01AX, Other antimicrobials and antiseptics umc-assigned •</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>G02BB, Intravenous contraceptives umc-assigned •</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>R01AX, Other nasal preparations umc-assigned •</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>R02AA, Antiseptics official •</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>S01XA, Other ophthalmologicals umc-assigned •</td>
</tr>
<tr>
<td>BRADOSOL 00093302/</td>
<td>000933 02 002</td>
<td>Domiphen bromide</td>
<td>A01AB, Antimicrobials and antiseptics for local oral treatment official •</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>R02AA, Antiseptics umc-assigned •</td>
</tr>
<tr>
<td>BRADOSOL 000581401/</td>
<td>005814 01 007</td>
<td>Hexylresorcinol</td>
<td>R02AA, Antiseptics official •</td>
</tr>
</tbody>
</table>

*Figure 2. Search results in WHODrug Insight for ‘Bradosol’."

Based on the ingredient information given in the report, ‘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 a record.

2.1.2. Can salt variations of the ingredients be used to differentiate the non-unique name?

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

Example: Reported term: ‘Prilosec’

<table>
<thead>
<tr>
<th>Product name</th>
<th>Drug code</th>
<th>Active Ingredient(s)</th>
<th>ATC</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRILOSEC 00661201/</td>
<td>006612 01 005</td>
<td>Omeprazole</td>
<td>A02BC, Proton pump inhibitors official</td>
</tr>
<tr>
<td>PRILOSEC 00661203/</td>
<td>006612 03 010</td>
<td>Omeprazole magnesium</td>
<td>A02BC, Proton pump inhibitors official</td>
</tr>
</tbody>
</table>

*Figure 3. Search results in WHODrug Insight for ‘Prilosec’."

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) can be selected. The Drug Code system in WHODrug connects all single ingredient products with any salt form of an ingredient by giving them the same DrugRecordNumber (006612 in this example).
Yes, for multi-ingredient records. For multi-ingredient records, the Drug Record Number will differ even though the base form of the ingredients is the same, as seen in Figure 4. This makes it important to know how analysis is done on an ingredient level before selecting a record.

Example: Reported term: ‘Aktil’

<table>
<thead>
<tr>
<th>Product name</th>
<th>Drug code</th>
<th>Active Ingredient(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AKTIL</td>
<td>/00549201/</td>
<td>Auranofin</td>
</tr>
<tr>
<td>AKTIL</td>
<td>/00756801/</td>
<td>Amoxicillin sodium • Clavulanate potassium</td>
</tr>
<tr>
<td>AKTIL</td>
<td>/00852501/</td>
<td>Amoxicillin • Clavulanic acid</td>
</tr>
<tr>
<td>AKTIL</td>
<td>/02043401/</td>
<td>Amoxicillin trihydrate • Clavulanate potassium</td>
</tr>
</tbody>
</table>

**Figure 4. Search results in WHODrug Insight for ‘Aktil’**

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

If the organisation SOP requires coding to the Preferred Name (Sequence 2=001), this can be done, but still requires thought about to which one of the ingredient combinations to choose.

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.

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

<table>
<thead>
<tr>
<th>Product name</th>
<th>Drug code</th>
<th>Active Ingredient(s)</th>
<th>ATC</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLOMAX</td>
<td>00889901/003</td>
<td>Morniflumate</td>
<td>M01AX, Other antiinflammatory and antirheumatic agents, non-steroids official</td>
</tr>
<tr>
<td>FLOMAX</td>
<td>01280302/013</td>
<td>Tamsulosin hydrochloride</td>
<td>G04CA, Alpha-adrenoreceptor antagonists official</td>
</tr>
</tbody>
</table>

**Figure 5. Search results in WHODrug Insight for ‘Flomax’**
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 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.

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

<table>
<thead>
<tr>
<th>Product name</th>
<th>Name specifier</th>
<th>Drug code</th>
<th>Active Ingredient(s)</th>
<th>ATC</th>
<th>Country of sales</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCAL</td>
<td>0000270202/ old form/</td>
<td>000027 02 002</td>
<td>Acetylsalicylate calcium</td>
<td>B01AC, Platelet aggregation inhibitors excl. heparin official • N02BA, Salicylic acid and derivatives unc-assigned</td>
<td>Netherlands</td>
</tr>
<tr>
<td>ASCAL</td>
<td>0080000002/ 100-300-38-38-600 Tablet-600</td>
<td>008000 02 006</td>
<td>Carbassalate calcium</td>
<td>B01AC, Platelet aggregation inhibitors excl. heparin official • N02BA, Salicylic acid and derivatives official</td>
<td>Morocco • Morocco</td>
</tr>
</tbody>
</table>

*Figure 6. Search results in WHODrug Insight for ‘Ascal’.*

As seen in Figure 6, ‘Ascal’ is a non-unique trade name having two different Drug Codes (different active ingredients) in the Netherlands, of which one is /old form/. Assuming that the reported drug is the marketed one, code the reported term to 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.

Example: Reported term: ‘Noval eye drops’.

<table>
<thead>
<tr>
<th>Product name</th>
<th>Drug code</th>
<th>Active Ingredient(s)</th>
<th>ATC</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOVAL</td>
<td>002000 01 796</td>
<td>Paracetamol</td>
<td></td>
</tr>
<tr>
<td>NOVAL</td>
<td>000398 01 020</td>
<td>Ethinyestradiol • Megestrol acetate</td>
<td>G03AA, Progestogens and estrogens, fixed combinations official • G03AB, Progestogens and estrogens, sequential preparations official • G03FA, Progestogens and estrogens, fixed combinations umc-assigned • G03FB, Progestogens and estrogens, sequential preparations umc-assigned</td>
</tr>
<tr>
<td>NOVAL</td>
<td>003712 02 050</td>
<td>Timolol maleate</td>
<td>C07AA, Beta blocking agents, non-selective official • S01ED, Beta blocking agents official</td>
</tr>
<tr>
<td>NOVAL</td>
<td>016420 01 013</td>
<td>Estradiol • Noreggestrol acetate</td>
<td>G03AA, Progestogens and estrogens, fixed combinations official • G03FB, Progestogens and estrogens, sequential preparations umc-assigned</td>
</tr>
</tbody>
</table>

Figure 7. Search results in WHODrug Insight for ‘Noval’.

As seen in Figure 7, there are three records in WHODrug 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 a record 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 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.

Example: Reported term: ‘Espaven pediatrico’.

<table>
<thead>
<tr>
<th>Product name</th>
<th>Name specifier</th>
<th>Drug code</th>
<th>Active Ingredient(s)</th>
<th>ATC</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESPAVEN</td>
<td>Pediatrico</td>
<td>001595 01 050</td>
<td>Dimeticone</td>
<td>A01AD, Other agents for local oral treatment umc-assigned • A03AX, Other drugs for functional gastrointestinal disorders umc-assigned • D02AA, Silicone products umc-assigned • D90, ANTI-ACNE PREPARATIONS umc-assigned • P03AX, Other ectoparasiticides, incl. scabicides official • S01K, SURGICAL AIDS umc-assigned • S01X, OTHER OPHTHALMOLOGICALS umc-assigned</td>
</tr>
<tr>
<td>ESPAVEN</td>
<td></td>
<td>005508 02 328</td>
<td>Ranitidine hydrochloride</td>
<td>A02BA, H2-receptor antagonists official</td>
</tr>
<tr>
<td>ESPAVEN</td>
<td></td>
<td>014775 01 003</td>
<td>Calcium pantothenate • Dimeticone</td>
<td>A03AX, Other drugs for functional gastrointestinal disorders umc-assigned</td>
</tr>
</tbody>
</table>

Figure 8. Search results in WHODrug Insight for ‘Espaven’.
There is no record with the complete reported term in the product name field, but for one of the ‘Espaven’ products, ‘pediatrico’ is available in the Name Specifier field, and can therefore used 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. 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.


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.

Examples:

After eliminating all possible records 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 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.
If no other options exist, one of the two Umbrella Records in Figure 10 can be chosen.

<table>
<thead>
<tr>
<th>Product name</th>
<th>Drug code</th>
<th>Active Ingredient(s)</th>
<th>ATC</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL OTHER NON-THERAPEUTIC PRODUCTS</td>
<td>900475 01 001</td>
<td></td>
<td>V07, ALL OTHER NON-THERAPEUTIC PRODUCTS</td>
</tr>
<tr>
<td>ALL OTHER THERAPEUTIC PRODUCTS</td>
<td>900425 01 001</td>
<td></td>
<td>V03, ALL OTHER THERAPEUTIC PRODUCTS</td>
</tr>
</tbody>
</table>

Figure 10. Umbrella Records available when no other options exist.

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 Enhanced subscriber can at any time submit a request for a new drug. This can be done by contacting WHODrug@who-umc.org. This chapter describes the Best Practices for when a coder cannot find an appropriate drug name.

![Figure 11. Schematic explanation of how to handle a coding situation where a drug is missing in WHODrug (Y= Yes; N = No).](image)

3.1. Submitting a Change Request

Before submitting a Change Request, please check that the drug name does not exist in the current version of WHODrug.

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

**Example: Reported term: ‘Omeprazole/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.

However, 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 ‘place holder’ (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 has to 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 re-coding 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 up-versioned.

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 term 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 time-span until the new dictionary version is released, and bearing in mind that the Change request may be declined. If the Change Request is declined, 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 WHODrug Insight, shown in Figure 12. The file Ingredient_LongText is another resource where all Drug Codes with their substance combinations in long text format can be found.

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.

![Figure 12. 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. For multi-ingredients, the preferred name is not always the generic name. For single ingredients, the Preferred and generic name will always be the same.](image-url)
3.3.2. Preferred Name
For single ingredients, the Preferred Name is always generic. For multi-ingredient records, the
generic name is not always the Preferred Name.

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. You will, in the approval response, get information about the corresponding Preferred
Name, the assigned ATC classes, etc. This enables you to create a temporary record in your dic-
tionary to be used until the next version is released.

3.4.2. Change Request declined
If the Change Request is declined, 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 Figure 10 may represent alternative coding
options.
4. 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 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 Herbal. 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 can be classified in WHODrug with additional ATC codes to reflect the main use of the particular 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 B2- and C-format

In the B2-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 C-format 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 and Preferred Names in the C-format are assigned ATC codes in the same manner as in the B2-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 B2- and C-format.

<table>
<thead>
<tr>
<th>Drug name (ingredient)</th>
<th>ATC in B2 format</th>
<th>ATC in C format</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylsalicylic acid (acetylsalicylic acid)</td>
<td>A01AD</td>
<td>A01AD</td>
</tr>
<tr>
<td></td>
<td>B01AC</td>
<td>B01AC</td>
</tr>
<tr>
<td></td>
<td>M02AC</td>
<td>M02AC</td>
</tr>
<tr>
<td></td>
<td>N02BA</td>
<td>N02BA</td>
</tr>
<tr>
<td>Alidor (acetylsalicylic acid)</td>
<td>A01AD</td>
<td>N02BA</td>
</tr>
<tr>
<td></td>
<td>B01AC</td>
<td></td>
</tr>
<tr>
<td></td>
<td>M02AC</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N02BA</td>
<td></td>
</tr>
<tr>
<td>Casprin (acetylsalicylic acid)</td>
<td>A01AD</td>
<td>B01AC</td>
</tr>
<tr>
<td></td>
<td>B01AC</td>
<td></td>
</tr>
<tr>
<td></td>
<td>M02AC</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N02BA</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Illustration of the difference in ATC assignment for the ingredient erythromycin in B2- and C-format.

<table>
<thead>
<tr>
<th>Drug name (ingredient)</th>
<th>ATC in B2 format</th>
<th>ATC in C format</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythromycin (erythromycin)</td>
<td>D06AX</td>
<td>D06AX</td>
</tr>
<tr>
<td></td>
<td>D10AF</td>
<td>D10AF</td>
</tr>
<tr>
<td></td>
<td>J01FA</td>
<td>J01FA</td>
</tr>
<tr>
<td></td>
<td>S01AA</td>
<td>S01AA</td>
</tr>
<tr>
<td>Emina (erythromycin)</td>
<td>D06AX</td>
<td>D10AF</td>
</tr>
<tr>
<td></td>
<td>D10AF</td>
<td></td>
</tr>
<tr>
<td></td>
<td>J01FA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>S01AA</td>
<td></td>
</tr>
<tr>
<td>Eritrovit (erythromycin)</td>
<td>D06AX</td>
<td>J01FA</td>
</tr>
<tr>
<td></td>
<td>D10AF</td>
<td></td>
</tr>
<tr>
<td></td>
<td>J01FA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>S01AA</td>
<td></td>
</tr>
</tbody>
</table>

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 C-format assignments in the B2-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 text file is available, named ‘DDA Exclusive’. This file is designed to increase the efficiency of ATC coding in the B2-format by implementing C-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 particular 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>
<thead>
<tr>
<th>Method</th>
<th>Definition and description</th>
</tr>
</thead>
<tbody>
<tr>
<td>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>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 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.</td>
</tr>
<tr>
<td>Classification using a system other than ATC</td>
<td>Classification using a 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 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.</td>
</tr>
<tr>
<td>No classification of medication</td>
<td>No classification of medication is 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.</td>
</tr>
</tbody>
</table>
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).

<table>
<thead>
<tr>
<th>Method</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>All possible ATC pathways</td>
<td>Coding to all possible ATC selections saves time and resources, thus saving money on the study budget. Changes of ATC classification in WHODrug can be automatically updated without manual revision since no specific ATC has been chosen. Coding to all possible ATC pathways means that there is a reduced risk of missing a signal and signals can be more easily recognised. No need to store ATC codes in the database. The ATC classification can be derived directly from WHODrug.</td>
<td>Requires a more experienced analysis team to interpret the data correctly. 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 multiaxiality of ATC. Often this can lead to literal translation of figures and misleading interpretations of the data.</td>
</tr>
<tr>
<td>Single ATC selection</td>
<td>Allows data to be grouped in a more medically relevant manner and categories of interest to be reviewed in more detail. Facilitates and promotes consistency in specific drug classification based on the reported indication. Supports the medication coding process such as in checking the consistency between the Drug Code and the reported indication, route and dosage. Groups medications according to their ATC codes with no double counting/reporting.</td>
<td>Means that changes in ATC classification need to be reviewed manually during upversioning. Is often time-consuming, putting a strain on tight study budgets. 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). Could generate more queries when a substance is used ‘off-label’, or if the indication is missing, especially for a non-unique drug name.</td>
</tr>
<tr>
<td>Classification using a system other than ATC</td>
<td>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.</td>
<td>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.</td>
</tr>
</tbody>
</table>
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 (1) 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 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 multiaxial representation.

4.3.2.2. Choose Single ATC selection (2) 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 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 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 (3) 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 (4) 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 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 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 (1)

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 (2)
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.

Example: Acetylsalicylic acid is linked to four different ATC codes.

![Figure 13. Search results in WHODrug Insight for 'Acetylsalicylic acid'.](image)

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.

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

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

![Figure 14. Search results in WHODrug Insight for 'Aciclovir'.](image)
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.

Example: Finasteride is classified with different ATC codes 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>Drug code</th>
<th>Active Ingredient(s)</th>
<th>ATC</th>
</tr>
</thead>
<tbody>
<tr>
<td>FINASTERIDE</td>
<td>011300 01 001</td>
<td>Finasteride</td>
<td>D11AX, Other dermatologicals official • G04CB, Testosterone-5-alpha reductase inhibitors official</td>
</tr>
</tbody>
</table>

Figure 15. Search results in WHODrug Insight for ‘Finasteride’.

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, contact UMC via e-mail: WHODrug@who-umc.org.

Example: Methadone is officially classified in N07BC – Drugs used in opioid dependence. However, on request from WHODrug users the ATC N02AC – Diphenylpropylamine derivatives, is also assigned.

<table>
<thead>
<tr>
<th>Product name</th>
<th>Drug code</th>
<th>Active Ingredient(s)</th>
<th>ATC</th>
</tr>
</thead>
<tbody>
<tr>
<td>METHADONE</td>
<td>000689 01 001</td>
<td>Methadone</td>
<td>N02AC, Diphenylpropylamine derivatives umc-assigned • N07BC, Drugs used in opioid dependence official</td>
</tr>
</tbody>
</table>

Figure 16. Search results in WHODrug Insight for ‘methadone’.

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 (3)

The UMC does not provide best practice for this option since the medications in WHODrug are not classified according any other such 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 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 Tabulation Model (SDTM) (reference 1) 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 (1).

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.

4.5.3. References

Study Data Tabulation Model Implementation Guide: Human Clinical Trials. Version 3.1.2. CDISC.
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. UMC releases four WHODrug versions per year, and users can choose to subscribe to one, two or all four of these versions. Upversioning may be conducted for all versions included in the subscription but may be conducted 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.

Normally, upversioning is performed between two versions of the same dictionary type, but the procedure can be followed also when upgrading from one dictionary type to another (e.g. WHODrug Enhanced to WHODrug Enhanced with WHODrug Herbal).

The procedure however assumes that the same dictionary format (B2 or C) is used in both versions.
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)**
  CAT is a UMC application, available for all users of WHODrug Enhanced, 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 WHO-Drug 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 B2-format is that trade names may have /Drug Record Number Sequence 1/ 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. Aspar used to be a unique trade name, but became non-unique in the March 1, 2014 version.

<table>
<thead>
<tr>
<th>Trade name</th>
<th>WHOD DDE B2 December 1, 2013</th>
<th>WHOD DDE B2 March 1, 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspar</td>
<td>Aspar /00398701/</td>
<td>Aspar /01281401/</td>
</tr>
<tr>
<td>Drug Code</td>
<td>00398701001</td>
<td>00398701001</td>
</tr>
<tr>
<td>Ingredients</td>
<td>Bentiamine</td>
<td>Bentiamine</td>
</tr>
<tr>
<td></td>
<td>Magnesium aspartate</td>
<td>Magnesium aspartate</td>
</tr>
<tr>
<td></td>
<td>Potassium aspartate</td>
<td>Potassium aspartate</td>
</tr>
<tr>
<td></td>
<td>Pyridoxine hydrochloride</td>
<td>Pyridoxine hydrochloride</td>
</tr>
</tbody>
</table>

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 C format, incorrect name specifiers, Marketing Authorisation Holders and strengths can be adjusted. The old form status may also change.

Table 6. In March 1, 2014, P01CX was added to Miltefosine in addition to L01XX.

<table>
<thead>
<tr>
<th>Trade name</th>
<th>WHOD DDE B2 December 1, 2013</th>
<th>WHOD DDE B2 March 1, 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miltefosine</td>
<td>Miltefosine</td>
<td>L01XX – Other antineoplastic agents</td>
</tr>
<tr>
<td></td>
<td>01282001001</td>
<td>P01CX - Other agents against leishmaniasis and trypanosomiasis</td>
</tr>
</tbody>
</table>

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 March 1, 2014, Bubo kok with Drug Code 00695501134 was, due to incorrect information regarding ingredients, deleted and replaced by 01504501022.

<table>
<thead>
<tr>
<th>Trade name</th>
<th>WHOD DDE B2 December 1, 2013</th>
<th>WHOD DDE B2 March 1, 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bubo kok</td>
<td>Bubo kok</td>
<td>Diphtheria vaccine</td>
</tr>
<tr>
<td></td>
<td>00695501134</td>
<td>Hepatitis B vaccine</td>
</tr>
<tr>
<td>Ingredient(s)</td>
<td>Hepatitis B vaccine</td>
<td>Pertussis vaccine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tetanus vaccine</td>
</tr>
</tbody>
</table>
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. Cometriq is an example of a salt change.

<table>
<thead>
<tr>
<th>WHO DDE B2 March 1, 2015</th>
<th>WHO DDE B2 June 1, 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trade name</td>
<td>Cometriq</td>
</tr>
<tr>
<td>Drug Code</td>
<td>07198100002</td>
</tr>
<tr>
<td>Ingredient</td>
<td>Cabozantinib</td>
</tr>
<tr>
<td></td>
<td>07198102002</td>
</tr>
<tr>
<td></td>
<td>Cabozantinib s-malate</td>
</tr>
</tbody>
</table>

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 recommend 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 in order 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

<table>
<thead>
<tr>
<th>Verbatim</th>
<th>Indication</th>
<th>Route</th>
<th>Trade Name</th>
<th>Ingredient(s)</th>
<th>Preferred Name</th>
<th>ATC Code</th>
<th>ATC Text 4</th>
<th>ATC Text 3</th>
<th>ATC Text 2</th>
<th>ATC Text 1</th>
<th>Version</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robitussin</td>
<td>Cough</td>
<td>Oral</td>
<td>ROBITUSSIN NIGHTTIME COUGH DM</td>
<td>Dextromethorphan hydrobromide; Doxylamine succinate</td>
<td>VICKS FORMULA 44 /02685101/</td>
<td>R05DA</td>
<td>COUGH SUPPRESSANTS, EXCL. COMBINATIONS WITH EXPECTORANTS</td>
<td>COUGH AND COLD PREPARATIONS</td>
<td>RESPIRATORY SYSTEM</td>
<td></td>
<td>WHO DDE B2 31st March 2016</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Ear Infection</td>
<td>Otic</td>
<td>ANTIINFECTIVES, OTOLOGICAL</td>
<td>ANTIINFECTIVES, OTOLOGICAL</td>
<td>ANTIINFECTIVES, OTOLOGICAL</td>
<td>S02A</td>
<td>ANTIINFECTIVES OTOLOGICAL</td>
<td></td>
<td></td>
<td></td>
<td>WHO DDE B2 31st March 2016</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>Ankle Pain</td>
<td>Oral</td>
<td>ACETAMINOPHEN</td>
<td>Paracetamol</td>
<td>PARACETAMOL</td>
<td>N02BE</td>
<td>OTHER ANALGESICS AND ANTIPYRETICS</td>
<td>ANALGESICS</td>
<td>NERVOUS SYSTEM</td>
<td></td>
<td>WHO DDE B2 31st March 2016</td>
</tr>
</tbody>
</table>

*Figure 18. 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 /########/ appended to the trade name?
The /########/ 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.

Why is the preferred name a different trade name than the reported term?
In some cases, the Preferred Name in WHODrug is the first trade name entered into the dictionary representing that combination of ingredients, rather than the active ingredients themselves. This is also fixed within the dictionary structure and unable to be modified by the coder or programmer. The active ingredients can be retrieved in e.g. WHODrug Insight or in the Ingredients_LongText file in the additional features folder.

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).
INSPIRE. ENGAGE. TRANSFORM.

Uppsala Monitoring Centre advances the science of pharmacovigilance and inspires patient safety initiatives all over the world. As an independent, non-profit foundation, we engage stakeholders who share our vision and collaborate to build a global patient safety culture. As a leader in the research and development of new scientific methods, we explore the benefits and risks of medicines to help minimise harm to patients, and offer products and services used by health authorities and life-science companies worldwide. Our unique expertise makes us an organisation with the capacity to transform patient safety from an ambition into a reality. For almost 40 years, we have provided scientific leadership and operational support to the WHO Programme for International Drug Monitoring, expanding the global pharmacovigilance network to reach more than 95% of the world’s population (www.who-umc.org).