# Package parameters for PRE2DUP-R

## General principles for designing parameters:

1. Parameters must reflect ***how medication is used in the real-world***, by real patients in their everyday life. Patients use medications as "units per day", not as "DDDs per day" as DDDs/day doses can be totally arbitrary measures (e.g. meaning that patient would be taking 3/4 tablets per day which almost never happens in the real-world!). That is why package parameters are designed by defining daily dose as units such as tablets per day.
2. ***Duration -related parameters are designed first***, by defining minimum, usual and maximum daily dose for the package. ***Then these are translated into dose parameters*** (lowest and usual dose in DDDs per day) by dividing the number of DDDs in the package with the corresponding duration -related parameter.
3. Parameters must take into account on pharmaceutical details, including dosing interval (e.g. how often injections are administered), whether drug can be divided or not (the general rule is that tablets, except depot tablets, can be halved, whereas capsules cannot), and how long/ if package can be used later after opening (e.g. eye drops often are usable only 1 month/ 28 days after opening).

## Information needed for designing package parameters

Package parameters are crucial for accurate modelling of medication use. For PRE2DUP-R, 3 duration-related parameters and 2 dose-related parameters are needed and these will be described here in detail. The package parameters connect with data through package identifier which separates different strengths, package sizes and drug forms of the same drug. In Nordic countries, they are called VNR numbers (Nordic Article Number, "varunummer" in Swedish). However, good to note that VNR of a drug package in Finland is different than VNR for the same package in Sweden.

For designing package parameters, you will need a complete list of drug packages in your dataset including the following information:

- Package identifier
- ATC code
- Strength
- Package size (as units included in the package)
- Drug form (tablet, depot tablet, injection etc.)
- (preferably also name of the product as often some crucial information is coded in the name instead of drug form, e.g. drug form can be purely "injection" both for Cisordinol-Acutard

and Cisordinol Depot and only the product name will reveal whether it is acute or long-acting injection)

- DDD value of the package: if your dataset does not contain this, you must calculate it based on reference values defined by WHO (ATC DDD index is freely available online: https://atcddd.fhi.no/atc_ddd_index/), or if the reference value is lacking from the ATC index then you must design it yourself, see section *"How to design a DDD reference value if that is lacking from WHO ATC DDD -index, or you want something different (including combination products)?"* starting on page 7). You can also use any other reference system for daily doses if you wish, and code your data with those (e.g. chlorpromazine equivalents, diazepam equivalents).

DDD values for the package are calculated as follows:

$$\frac{strength}{DDD\ reference\ value}\ x\ package\ size$$

For example, package of quetiapine (ATC N05AH04) 300 mg 100 tablets.

DDD reference value is 0.4g =400 mg

DDD value for this package is:

$$\frac{300\ mg}{400\ mg}\ x\ 100 = 75\ DDDs$$

In this calculation, strength and DDD reference value must be in the same unit (e.g. milligrams vs. grams).

Note that DDD reference values provided by WHO can be different for different drug forms (e.g. O=oral vs. P=parenteral) and you cannot just combine values based on ATC but also have to take into account on drug form! There are also two parenteral formulations as parenteral depot can be specified separately.

## What package parameters do?

Here is overall description what package parameters do and how they are defined.

Duration-related parameters

1. ***Maximum duration of the package (dur_max)***: defines the longest refill length for the package. This describes use of a particular medication with the lowest allowed dose (ddd_low). dur_max takes into account also special cases of medication use, e.g. when dose

is slowly titrated up (initiation) or down (discontinuation) and instances where two or more strengths of the same drug are used concurrently. dur_max for tablets/ capsules is calculated either as 0.5 tablet/ day (=multiply package size in tablets with 2), or as 1 tablet/day (or some other typical unit dose -measure, which can be also 2 tablets/day) multiplied by an adherence factor. As PRE2DUP-R does not use traditional grace periods, small allowance for non-perfect adherence must be inserted into dur_max and to corresponding ddd_low. In general, adherence factor is recommended to be 1.3 (=multiply package size in tablets with 1.3; please see also section *"Special cases and things to notice by ATC category*" starting page 9). Adherence factor may be smaller (e.g. 1.2) if less variation and less allowance for any irregularities is wanted, or higher (e.g. 1.4) when medications are used e.g. only on weekdays and not on weekends (for example, ADHD medications). When the lowest allowed dose is half a tablet per day then no adherence factor should be added as this would create unrealistically long refill lengths. dur_max must cover irregularities caused by dispensing system-related irregularities, too, if those exist.

2. ***Usual duration of the package (dur_usual):*** describes assumed most common or usual pattern of use. Dur_usual is utilized when assigning durations for single purchases (i.e. when person has purchased the medication only once ever, or with too long intervals so that modelling cannot make calculations for that particular individual and ATC). Most common usual duration for tablets/ capsules is 1 unit per day (=package size in tablets). In cases of long-term medications which are known to be initiated with lower dose (e.g. "use 0.5 tablet per day for the first two weeks and then 1 tablet per day"), dur_usual can be designed to describe this initiation pattern as most single purchases are initiation attempts. However, keep in mind that single purchases represent failed initiation attempts, which means that very likely the whole package has not been used so avoid overestimation. No adherence factor is used for dur_usual. Suggestion to replace dur_usual is calculated from the dataset (based on most common refill length among regular users) when PRE2DUP-R has run for the first time and those values can be used instead of original dur_usual if and when researcher wants to use them.
3. ***Minimum duration of the package (dur_min):*** defines the shortest refill length of the package, i.e. when package is used with the highest assumed dose. For the smallest strength preparations, the highest dose could mean use of ≥10 tablets per day, which is not reasonable if there are higher strength preparations available. Most commonly the highest assumed dose should be around 3 tablets per day. For some medications, there is only one official use pattern (often 1 tablet/day) and then minimum duration can be 1 tablet/ day, too.

<u>Dose-related parameters</u>

4. ***The lowest dose in DDDs/day (ddd_low):*** the lowest allowed dose for the drug package. Calculated as **amount of DDDs in the package divided by dur_max**. Modelling does not allow doses that are lower than this. All the considerations for this were described in dur_max description.

5. ***The usual dose in DDDs/day (ddd_usual)***: the assumed usual dose for the drug package. Ddd_usual is calculated as **amount of DDDs in the package divided by dur_usual**. All the considerations for this were described in dur_usual description.

**Examples of package parameters**

Basic example of tablet medication:

Example (1), package parameters for quetiapine (ATC N05AH04) 300 mg 100 tablets:

We will define that it can be used 0.5-3 tablets per day.

dur_max is 100/0.5= 200 days, corresponding to 0.5 tablets per day use

dur_usual is 100/1= 100 days, corresponding to 1 tablets per day use

dur_min is 100/3= 33 days, corresponding to 3 tablets per day use

Then we translate these into dose parameters by dividing the number of DDDs per package (calculated above, for this package 75 DDDs) with the corresponding duration-related parameter:

ddd_low is 75 DDDs/ dur_max 200 days = 0.375 DDDs/day

ddd_usual is 75 DDDs/ dur_usual 100 days = 0.75 DDDs/day

Tablet/ capsule which cannot be halved:

Example (2), package parameters for atomoxetine (ATC N06BA09) 60 mg 28 capsules:

It can be used 1-2 capsules per day (any capsules cannot be divided) and we will insert adherence factor of 1.4 as some people use ADHD medications only on weekdays and weekends off.

dur_max is 28 * 1.4 =39 days

dur_usual is 28/1 = 28 days

dur_min is 28/2 = 14 days

DDD value for atomoxetine is 80 mg and the package contains 60/80 *28 =21 DDDs

ddd_low is 21 DDDs / 39 days =0.538 DDDs/day

ddd_usual is 21 DDDs / 28 days = 0.75 DDDs/day

Some more examples for different drug forms and dosing intervals:

Example (3), package parameters for aripiprazole long-acting injectable 400 mg 1 injection/package:

DDD reference value for aripiprazole PD (parenteral depot) is 13.3 mg.

Thus, the package contains 400 mg / 13.3 mg *1 = 30.08 DDDs.

Injection is taken every 28 days. As package includes only 1 injection, we can estimate that it may be dispensed e.g. one week after the previous one so we will allow that.

dur_max is 28 * 1.3=36 days, corresponding to injection interval multiplied by adherence factor 1.3

dur_usual is 28 days, corresponding to injection interval

dur_min is 7 days, corresponding to approximated minimum dispensing interval

ddd_low is 30.08 DDDs / 36 days = 0.836 DDDs/day

ddd_usual is 30.08 DDDs / 28 days = 1.074 DDDs/day

Transdermal forms can be tricky and you must find out the interval for plaster change:

Example (4), buprenorphine transdermal 10 microg/hour 12 plasters.

DDD reference value for buprenorphine TD is 1.2 mg (=1200 microg).

This plaster is changed every 7 days, meaning that one plaster releases:

10 microg/hour * 24 hours * 7 days = 1680 microg

Thus, the package contains 1680 microg/ 1200 microg * 12 = 16.8 DDDs

dur_max is 12 plasters * 7 days (change interval) = 84 days multiplied with adherence factor 1.3 = 109 days

dur_usual is 12 plasters * 7 days = 84 days

dur_min could be 12 plasters * 7 days / 2 = 42 days, corresponding to 2 plaster per time use

ddd_low is 16.8 DDDs / 109 days = 0.154 DDDs/day

ddd_usual is 16.8 DDDs / 84 days = 0.2 DDDs/day

Analgesics and other medications for “when needed” type of use:

Example (5), package parameters for oxycodone 10 mg 28 capsules /package:

DDD reference value for oxycodone (oral) is 75 mg.

Thus, the package contains 10 mg / 75 mg *28 = 3.73 DDDs.

Analgesics are typically used “when needed” and thus, quite restrictive parameters are needed and the general rule is that no doses less than 1 unit/day are allowed. Dose can vary from 1-6 calpsules/day.

dur_max is 28 * 1.3=36 days, corresponding to 1 caps/day use multiplied by adherence factor 1.3.

dur_usual is 28 days, 28 / 2 = 14 days, assuming that 2 caps/day would be most common dose.

dur_min is 28 / 6 =4.67 days, corresponding to 6 capsules per day.

ddd_low is 3.73 DDDs / 36 days = 0.104 DDDs/day.

ddd_usual is 3.73 DDDs / 14 days = 0.266 DDDs/day.

Antibiotics (when used as a short course):

Example (6), package parameters for cefalexin 500 mg 20 tablets/package:

DDD reference value for cefalexin is 2 g (=2000 mg).

Thus, the package contains 500 mg / 2000 mg *20 = 5 DDDs.

Cefalexin is typically used as 500 mg tablet twice a day for 10 days. In some cases, severe infections might require doubling the dose so we can define that dose varies from 2 to 4 tablets/day.

dur_max is 20/2 * 1.3=13 days, corresponding to 2 tablets/day dose multiplied by adherence factor 1.3.

dur_usual is 20/2 = 10 days, corresponding to usual course of 2 tablets/day.

dur_min is 20/4 = 5 days, corresponding to maximum dose of 4 tablets/day.

ddd_low is 5 DDDs / 13 days = 0.385 DDDs/day.

ddd_usual is 5 DDDs / 10 days = 0.500 DDDs/day.

Eye drops (e.g. for glaucoma, meant for regular use):

Example (7), package parameters for bimatoprost eye drops 0.3 mg/ml 3ML package (1 bottle):

DDD reference value does not exist but is defined according to package and administration frequency as 30 EDs (30 day package). Package has to be used within 30 days after opening.

Package should cover 1 month use unless administration is difficult and drops are often missed from eye. In these cases we will allow shorter refill length.

dur_max is 30 * 1.3=36 days, corresponding to typical duration multiplied by adherence factor 1.3.

dur_usual is 30 days

dur_min is 14 days, corresponding to approximated minimum dispensing interval

ddd_low is 30 DDDs / 36 days = 0.833 DDDs/day

ddd_usual is 30 DDDs / 30 days = 1.000 DDDs/day

**How to design a DDD reference value if that is lacking from WHO ATC DDD -index, or you want something different (including combination products)?**

If there is no DDD reference value in the WHO ATC DDD index database (nor in national databases which some medicines agencies publish), you can design DDD reference value yourself. Please also note that WHO has recommendations for combination products:

https://atcddd.fhi.no/ddd/list_of_ddds_combined_products/

It is also possible to change an existing DDD value e.g. in cases of combination products when you are interested in the use of a particular component of the combination. DDD reference values for combination products are usually 1 unit/ day or 2 units/day if that is the assumed dose (exceptions include e.g. levodopa combinations which are coded according to dose of levodopa, regardless of other drug/drugs included in the combination). In some cases, researcher may want to derive use of a particular drug and derive it equally also from combination products (then we may want to change ATC codes, too, so that the drug is coded with the same ATC from all sources). Another option is that researcher wants to model parts of the combination separately (i.e. as if two different drugs would have been used). This can be done by duplicating (or triplicating if combination includes 3 different drugs) the rows and re-coding ATC codes and package identifiers for each component (please see below, “complex example”). Changes to ATC and DDD values are possible as long as you know which codes or values you have used and how data was coded (good idea to keep good care of version control/ keep a data management log where you can find what was done).

Design DDD values based on the dosing interval and choose a reference value which corresponds to some/ most common use pattern and dose. If there are two strengths of the drug then choose higher strength as reference value (=1 DDD) and for drugs with three different strengths, choose the middle

one. This aims to result into most common dose values 1 DDD/day, 0.5 DDDs/day and 2 DDDs/day and spread the range evenly.

For example, DDD values for losartan/ hydrochlorthiazide combinations (ATC C09DA01) of 50/12,5 mg and 100/25 mg, 30 tablet packages. Assuming that we are interested in losartan use and want to code these according to dose of losartan (C09CA01) component for which DDD reference value is 50 mg. We can then define DDD amounts for these packages as:

50/12,5 mg: 50/50 *30 = 30 DDDs

100/25 mg: 100/50 * 30 = 60 DDDs

**Complex example**: deriving use of each part of the combination product as if they were separate drugs. Assuming that we are interested knowing total duration of use of budesonide and total duration of use of formoterol, we will re-code use of budesonide-formoterol combination product (ATC R03AK07) 160/ 4.5 mikrog/dose of inhalation powder 60 doses package into use of:

- budesonide (ATC R03BA02), DDD reference value for inhalation powder (OBS! There are 3 different inhalation dosage forms for budesonide!!) is 0.8 mg, and
- formoterol (ATC R03AC13), DDD reference value inhalation powder is 24 microg

First, make up package identifier for both components by deriving a package identifier which is not used for any other package in your dataset. Assign ATC R03BA02 for budesonide “package” and ATC R03CA13 for formoterol “package“. Strength of budesonide is 160 microg and 4.5 microg for formoterol. Both packages contain 60 doses.

DDD amounts for these new packages are:

For budesonide package 160 microg/ 800 microg * 60 = 12 DDDs

For formoterol package 4.5 microg/ 24 microg *60 = 11.25 DDDs

## Some special cases and things to notice by ATC category

### B: Blood and blood forming organs

Insulins can be used with very variable doses and this should be reflected in the parameters. dur_min e.g. 7 days and dur_max e.g. 200 days.

### G: Genito urinary system and sex hormones

Note that all drug forms of e.g. estradiol have the same ATC code. If you want derive *systemic* use, you need to separate local preparations (vaginal preparations) from systemic ones as otherwise there is no way to know from drug use periods who has used systemic vs. non-systemic forms. This can be done e.g. by re-coding ATC codes based on drug form. If you wish to model systemic use (without separating whether the use was oral vs. transdermal) you could code only vaginal preparations separately:

| ATC | Drug formulation | New, re-coded ATC |
|---|---|---|
| G03CA03 | Transdermal patch | G03CA03 |
| G03CA03 | Gel | G03CA03 |
| G03CA03 | Vaginal tablets | G03CA03V |
| G03CA03 | Tablets | G03CA03 |

If you wish to separate oral vs. transdermal and all other drug forms, you could code like this:

| ATC | Drug formulation | New, re-coded ATC |
|---|---|---|
| G03CA03 | Transdermal patch | G03CA03T |
| G03CA03 | Gel | G03CA03G |
| G03CA03 | Vaginal tablets | G03CA03V |
| G03CA03 | Tablets | G03CA03O |

T=transdermal, G=gel (in this case, also refers to transdermal and systemic use), V=vaginal, O=oral

### L: antineoplastic and immunomodulating agents

Note that many antineoplastic drugs lack DDD reference values.

### M Musculo-skeletal system

NSAIDs should be coded similarly as oxycodone in Example 5

### N Nervous system

ADHD drugs N06BA can be used only on weekdays and weekends off. Adherence factor of 1.4 has been utilized for these.

**R respiratory system**

For inhalations, any kind of “half” doses are not possible so 1 dose per day is minimum dose always.