Drug Groupings and workflow options for the processing and review of concomitant medication data

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Abstract

Drug groupings combine medicines having one or more properties in common (e.g. indication, chemical, pharmacodynamic and/or pharmacokinetic properties). They can be used to support the identification of drugs of interest for defined business needs (e.g. identification of protocol deviations, statistical analysis, search for prohibited drugs) whenever the existing WHO-DD classification by ATC codes is not sufficient.

Standardized Drug Groupings (SDGs) are provided by the Uppsala Monitoring Center. Internally developed Bayer Drug Groupings (BDGs) are created based on combinations of defined relevant substances, ATC codes, WHO-DD drug codes (DRECNOs) and/or trade names. BDGs are needed to translate existing SDGs into the current Bayer WHO-DD version and as SDGs are not available for all areas of interest. BDGs are provided and maintained by the Global Medical Coding function.

A global drug grouping table, (Global BDG reference list (GBRL), contains all BDGs together with the WHO-DD codes included in them. A summary table ("BDG overview") with available drug groupings is used by Medical Experts to select Drug Groupings for defined areas of interest on the project/study level. Based on this overview file the study specific BDG reference list (SBRL) with all drug groupings relevant for the study is created. This study specific table is a subset of the GBRL. By merging the study specific (WHO-DD coded) concomitant medication data with the SBRL and, in addition, WHO-DD assignment data (ATC codes and substance names) various reports are provided.

Complementary to the ATC system, drug groupings provide an efficient and consistent way of identifying patients/patient groups having taken specific types of medications.

Keywords: WHO-DD, ATC, Trade Name, Drug Grouping

Introduction

The WHO-DD is an international standard for coding of concomitant medications. Within the WHO-DD each drug is classified according to the ATC system. Moreover the WHO-DD provides the active ingredients/substances for each included drug.

For cases where the inherent ATC classification does not identify defined drugs of interest, drug groupings provide an alternative solution. Standardized Drug Groupings (SDGs) are provided by the UMC together with the WHO-DD.

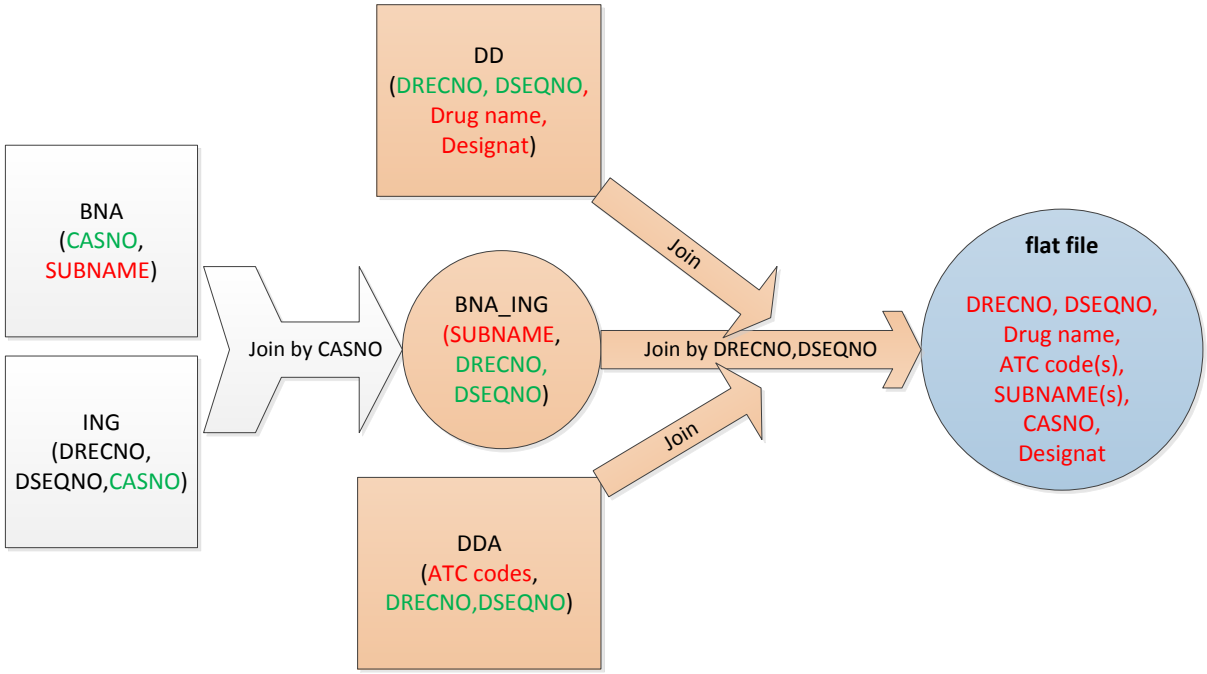
The intention of drug groupings is to provide an easy way to identify or aggregate medicines having one or more several properties in common, e.g. indication, chemical, pharmacodynamics and/or pharmacokinetic properties.

As the version of drug groupings needs to match the WHO-DD version of the coded data, and to cover areas of interest where no SDGs are available, we have developed so-called "Bayer Drug Groupings (BDGs)". BDGs are collections of drug codes derived on the basis of substances, ATC codes, WHO-DD drug codes (DRECNOs) and/or trade names.

WHO-DD "flat" file

The main table supporting the creation of BDGs and listings is the so called WHO-DD flat file. It contains all WHO-DD information considered relevant, namely the drug name, the active ingredients (substances), designation information and ATC codes for each drug code. It is created by joining the relevant information from the standard WHO-DD B2 format tables.

Figure 1 Creation of flat file

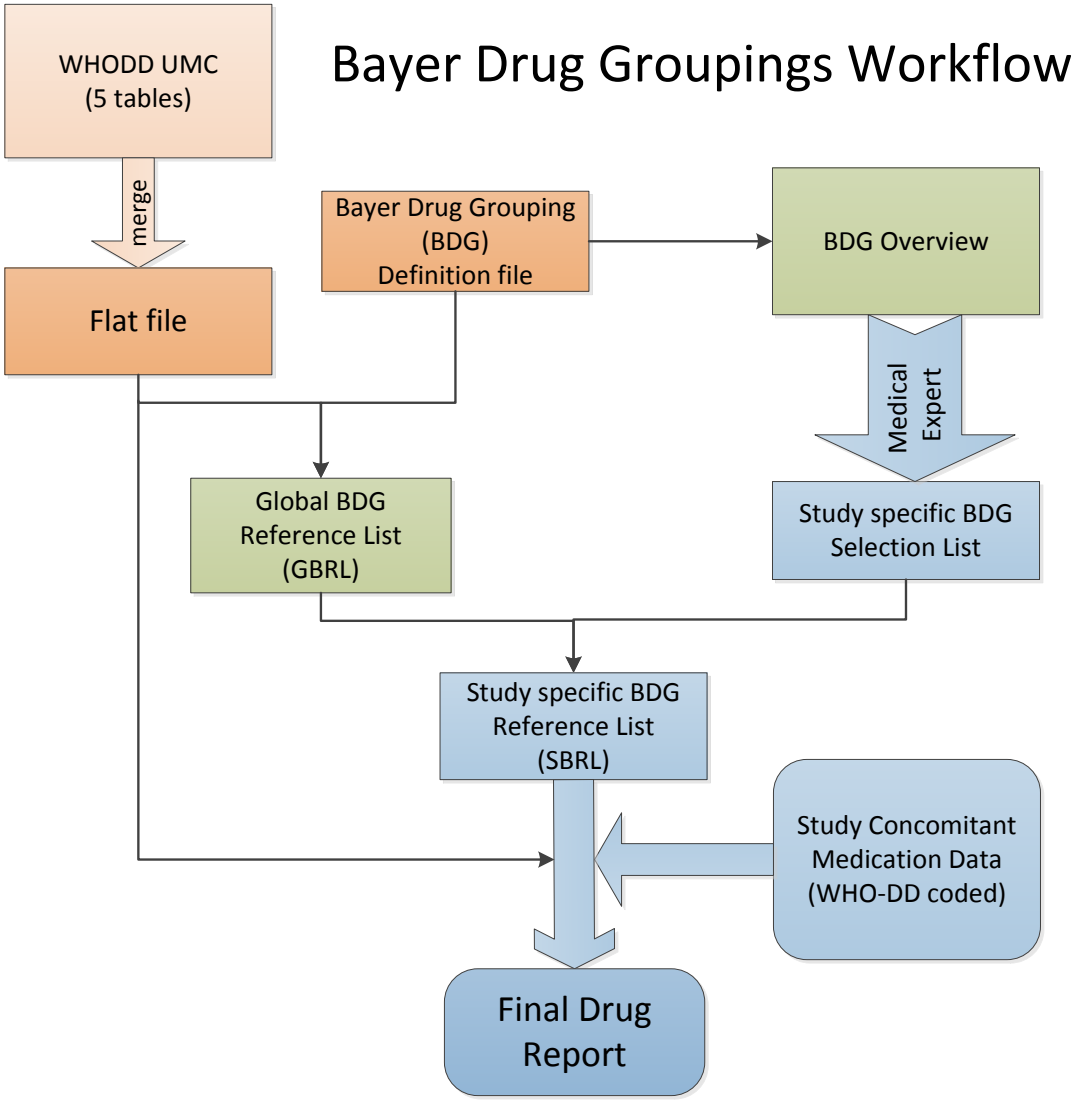


Please note: the WHO-DD flat file contains one record per ingredient, i.e. single ingredient drugs have one record while multi-ingredient drugs have as many records as they have ingredients. In case of multiple ATC codes these are concatenated within the ATC code field. A separate program exists which separates the ATC codes into a flat file with on record per ATC code and substance.

Global BDG Reference List

The GBRL is derived from the WHO-DD flat file through the so-called “BDG Definition file”. The GBRL is the basis for the derivation of the the SBRL on the study level. The SBRL supports the identification of drugs of interest for a specific project or study. The WHO-DD flat file is also used for the creation of tables and listings by deriving ATC codes and ingredient information for the corresponding concomitant medication codes . An overview is given in the following flow chart:

Figure 2 Overview on WHO-DD flat file and BDG architecture



BDG Definition file

The BDG definition table is an Excel file in which the content definition for each drug grouping is included. Hierarchical drug groupings with "Parent Child" architecture can be distinguished from non-hierarchical "standalone" BDGs . The BDG definition file is maintained by the Global Medical Coding function.

The BDG definition file is imported into SAS and then used to derive the content of each drug grouping on either one of the following four different search levels (sorted from broadest to narrowest):

- ATCCODE
- SUBNAME
- DRUGRECNO
- TRADENAME

Each search level can be combined with either one of the three following user-friendly operators:

- Operator "Begins with" -> LIKE 'search string%'
- Operator "Contains" -> LIKE '%search string%'
- Operator "Equals" -> EQUALS 'search string'

Figure 3 Examples for selected search conditions within various drug groupings

BDG_NAME	SEARCHLEVEL	OPERATOR	SEARCHSTRING	SEARCHSTRING DESCRIPTION
Adrenergic receptor antagonists - Beta blocking agents	ATCCODE	EQUALS	C07	Beta Blocking Agents
Corticosteroids	ATCCODE	BEGINS WITH	D07	Dermatological preparations, corticosteroids
Vasodilators (others)	DRUGRECNO	EQUALS	900117	C01DB - Quinolone vasodilators
Centrally acting antihypertensives (adrenergic receptor agonists)	SUBNAME	EQUALS	Clonidine	
Analgesia producing opioids	SUBNAME	CONTAINS	Alfentanil	

Each BDG can contain an unlimited number of search conditions. In case the same drug is identified on two different search levels it is only included once. In case the same drug has a narrow scope on one search level and a broad scope on another search level it will be included with narrow scope only.

SAS macro extracts GBRL from flat file based on BDG Definition file

All conditions in the BDG definition file are translated into SAS code, run in a batch process against the up-to-date WHO-DD flat file and the results transferred to interim tables.

Figure 4 contains examples for complete search conditions in combination with drug codes retrieved for the specific condition from the WHO-DD flat file.

Please note: Within the processing, DSEQNO2 is defaulted to NULL unless the search level is trade name in which case the true value of DSEQNO2 is extracted in addition.

Figure 4 Example for the selection by search level "ATC code" and operator "Begins with":

parent_bdg	bdg_name	cond	drecno	dseqno1	atccode
Antidepressants	Monoamine oxidase A inhibitors	LIKE N06AG%	006274	01	N06AG
Antidepressants	Monoamine oxidase A inhibitors	LIKE N06AG%	008045	01	N06AG
Antidepressants	Monoamine oxidase A inhibitors	LIKE N06AG%	008766	01	N06AG
Antidepressants	Monoamine oxidase A inhibitors	LIKE N06AG%	015507	01	N06AG
Antidepressants	Monoamine oxidase A inhibitors	LIKE N06AG%	017661	01	N06AG

Figure 5 Example for the selection by search level "Subname" and operator "Contains":

parent_bdg	bdg_name	cond	drecno	dseqno1	subname
Antidepressants	Adjunct antidepressant therapy	LIKE %AMISULPRIDE%	009256	01	AMISULPRIDE

Based on the interim tables illustrated in figures 4 and 5, the Global BDG reference list is created.

Several program checks ensure that syntax restrictions are followed and mandatory fields are filled. The user receives reports with any findings and a list of all BDGs containing search criteria without corresponding matches in the WHO-DD flat file.

The above interim tables are also of great value for debugging purposes and for content related discussions with Global Medical Coding.

Study specific processing

BDG selection list on the study or project Level

The Medical Expert of a clinical trial has access to the "BDG overview file", a summary table with all currently available BDG's.

In case BDGs are needed for a study she/he uses this file to select/indicate all relevant BDGs and stores this file as "BDG selection list" (Figure 6).

Figure 6 Example of BDG selection by the Medical Expert

PARENT_BDG	B_CODE	BDG_NAME	SBRL_ INCLUDE
Antiarrhythmics (subgroups)	1001	Adrenergic receptor antagonists - Beta blocking agents	x
Antiarrhythmics (subgroups)	1060	Adrenergic receptor antagonists - Combined beta and alpha blocking agents	x
Antiarrhythmics (subgroups)	1002	Antiarrhythmics, class I and III	
Antiarrhythmics (subgroups)	1003	Anticholinergic agents used in bradycardia	x
Antiarrhythmics (subgroups)	1004	Digitalis glycosides	x
Antiarrhythmics (subgroups)	1005	Other antiarrhythmics	
Antiarrhythmics (subgroups)	1006	Selective calcium channel blockers with direct cardiac effects	x
Antidepressants	1099	Adjunct antidepressant therapy	
Antidepressants	1100	Herbal antidepressants	x
Antidepressants	1101	Monoamine oxidase A inhibitors	

The BDG selection list is then used to create a study specific BDG Reference List (SBRL), which contains only the BDG's indicated in the column SBRL_INCLUDE of the BDG selection list.

The WHO-DD coded concomitant medication data is merged with the SBRL via DRECNO and DSEQNO1 as merge keys. One possible output is a list which contains only subjects having taken drugs identified through the study specific BDG reference list (Figure 7).

Figure 7 Example for a patient level listing with patients having taken Antihypertensives

PARENT_BDG	BDG_NAME	DRUGNAME WHO-DD	Reported drug name	SUBJECT ID
Antihypertensives	ACE inhibitors	ENALAPRIL [ENALAPRIL]	ENALAPRIL	6
Antihypertensives	ACE inhibitors	BENAZEPRIL HYDROCHLORIDE	BENAZEPRIL HYDROCHLORIDE	1
Antihypertensives	Angiotensin II receptor antagonists	COZAAR PLUS	COZAAR PLUS	1
Antihypertensives	Angiotensin II receptor antagonists	VALSARTAN	Valsartan Capsules	3
Antihypertensives	Calcium channel blockers	NIFEDIPINE	Nifedipine Controlled Release Tablet	5
Antihypertensives	Calcium channel blockers	ADALAT OROS	ADALAT OROS	2
Antihypertensives	Calcium channel blockers	FELODIPINE	Felodipine Sustained Release Tablets	1
Antihypertensives	Calcium channel blockers	AMLODIPINE BESYLATE	Amlodipine Besylate Tablets	8

Additional tables and listings are available. These mainly combine coded concomitant medication data with information from the WHO-DD flat file and BDG information.

Please note: Tables which combine coded concomitant medication data with BDG information and WHO-DD assignment information allow for a cross-check between BDGs and the WHO-DD. It is hence possible to identify relevant substances possibly not included in a drug grouping or to identify substances which should not be included in a drug grouping .

Conclusions

The above workflow supports an expert- controlled and easy to adjust handling of drug groupings in clinical trials and projects. The Study Medical Expert only has to define in which drug groupings she/he is interested. Based on this standardized approach, no additional programming is needed on the study level to create listings for specific drugs of interest or in support of specific processes. Globally defined standard objects (e.g. in JReview, a global reporting tool) can be used instead of a case-by-case approach. The maintenance of the BDG definition file is done centrally by the Medical Dictionary Experts within Global Medical Coding as Drug Groupings are project and study independent. The central approach ensures consistency on the project level. At the same time, resouces are saved by avoiding redundant programming and maintenance.