

Identifying Medications that are Protocol Violations

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- ▶ Manual selection, by medical expert
- ▶ Documenting the selected medications

Coding of medications

Based on WHO Drug Dictionary

Investigator: medication name

coding dept.

Aspirine

dictionary term

dictionary logic

Aspirin/00017001/

preferred term

Acetylsalicylic acid

Coding of medications

dictionary term

~~Aspirin~~ /00017001/

dictionary logic

Anatomic Therapeutic Chemical (ATC) codes

~~N05BA~~, B01AC, M02AC, N02BA

Coding of medications

Anatomic Therapeutic Chemical code

N05BA

- ▶ N Nervous system
- ▶ N05 Psycholeptics
- ▶ N05BA Benzodiazepine derivatives

Programmed pre-selection

- ▶ Protocol violations section in protocol
 - Types of medications
 - Time periods of use

Use of any drug product containing estrogens, progestins, androgens or tibolone within the last 4 weeks prior to start of IMP

- ▶ Coding Dept. provides corresponding ATC codes

G03AA, G03AB, G03C, G03CA, L02AA, L02BA, D11AE, ...

Programmed pre-selection

```
* ATC-code violation-classes (taken from SAP);  
  
%let estrogens_etc = 'G03AA' 'G03AB' 'G03C' 'G03CA'  
    'G03CB' 'G03CC' 'G03EA' 'G03EB' 'G03F' 'G03FA'  
    'G03HB' 'G03XC' 'L02AA' 'L02BA' 'G03AA' 'G03FB'  
    'G03XB' 'L02AB' 'D11AE' 'G03B' 'G03DA' 'G03EA'  
    'G03EB' 'G03EK' 'G03H' 'G03HA' 'G03HB' 'L02BB';  
  
%let antidepress_etc='N06A' 'N06AX' 'N06CA' 'A03AE'  
    'A04AA' 'C02KD' 'C02LN' 'N02CC' 'N06AB' 'C02KC'  
    'C02LL';
```

Programmed pre-selection

```
* mark medication for types of violation-medication it belongs to ;  
data cm;
```

```
set cm;
```

```
array atc{*} cmatc;;
```

```
estrogy=0; antidepy=0;    * initialize indicators as 'No' ;
```

```
do i=1 to dim(atc);
```

```
    if atc{i} in (&estrogens_etc)    thenestrogy=1;
```

```
    if atc{i} in (&antidepress_etc) thenantidepy=1;
```

```
    * stop search if beyond filled set-of-possible-ATC-values ;
```

```
    if i<dim(atc) then
```

```
        if atc{i+1}=' ' then i=999;
```

```
end;
```

```
drop i;
```

```
run;
```

Programmed pre-selection

SAS System Viewer - [cm.sas7bdat]										
File Edit View Window Help										
	Reported Name of Drug, Med, or Therapy (CMTRT)	Standardized Medication Name (CMDECOD)	ATC code 1 (CMATC01)	ATC code 2 (CMATC02)	ATC code 3 (CMATC03)	ATC code 4 (CMATC04)	ATC code 5 (CMATC05)	ATC code 6 (CMATC06)	Class: estrogens, progestins, etc. (ESTROGY)	Class: tricyc. antide pressants, SNR Is, etc (ANTIDEPY)
17	Flax seed oil	FLAXSEED OIL	V03AX						0	0
18	Climera	CLIMARA	G03CA	L02AA					1	0
19	Progesterone	PROGESTERONE	G03DA						1	0
20	Percogesic	PERCOGESIC	N02BE						0	0
21	Advair	ADVAIR	R03AK						0	0
22	Combivent	COMBIVENT /01261001	R03AK						0	0
23	Singular	SINGULAIR /01362601	R03DC						0	0
24	Calcium	CALCIUM /00751501/	A12AA						0	0
25	Paxil	PAXIL	N06AB						0	1
26	Flexeril	FLEXERIL	M03BX	N06AA					0	0
27	Activelle 1 / 0.5	ACTIVELLE	G03FA						1	0
28	Aspirin	ASPIRINE	A01AD	B01AC	M02AC	N02BA			0	0
29	Vitamin c	VITAMIN C	A11GA	G01AD	S01XA				0	0
30	Multivitamin	MULTIVITAMINS	A11AB						0	0
31	Ibuprofen	IBUPROFEN	G02CC	M01AE	M02AA				0	0
32	Tylenol	ACETAMINOPHEN	N02BE						0	0
33	Ibuprofen	IBUPROFEN	G02CC	M01AE	M02AA				0	0
34	Tylenol	ACETAMINOPHEN	N02BE						0	0
35	Alkamints	ALKA-MINTS	A02AC	A12AA					0	0
36	Sodium chloride	SODIUM CHLORIDE	A12CA	B05CB	B05XA	R01AX	R05CB	S01XA	0	0
37	Ibuprofen	IBUPROFEN	G02CC	M01AE	M02AA				0	0

Ready

Hdn cols:3

Obs 1-2780 of 2780

NUM

Programmed pre-selection

Use of any drug product containing estrogens, progestins, androgens or tibolone within the last 4 weeks prior to start of IMP

- ▶ Medical reviewer: further specification
e.g. depending on route of administration:
 topical: within 7 days
 vaginal: within 14 days
- ▶ To be specified in SAP

Programmed pre-selection

Create separate listings, conform wishes of reviewer:

Possible protocol violations ...

- ▶ pre-treatment hormonal drug use
- ▶ pre-treatment drug use (excl. hormonal)
- ▶ in-treatment drug use, excl. medications started on day after day of last IMP
- ▶ in-treatment drug use, for medications started on day after day of last IMP

Manual selection, by medical expert

Listing 3 Possible protocol violations for in-treatment drug use, excl. those started on day after day of last IMP.

Subj.	Inv.descr. \ WHO drugname	Indication	Potentially violating medication						IMP dates		
			Reg- imen	Daily dose	Unit	Route	Begin	End	Begin	End	
10510	Biclar uno \ BICLAR	Trachitis	od	500	mg	Per os	28JAN05	01FEB05	19NOV04	13FEB05	?
11401	Azitromycin \ AZITHROMYCIN	Upper airway infection	od	500	mg	Per os	14DEC04	16DEC04	16NOV04	10FEB05	?
	Okacin \ OKACIN	Worsened vision	tid	3	drops	Conjun.	14JAN05	20JAN05	16NOV04	10FEB05	?
11920	Actira (r) \ ACTIRA	Bronchiectasis	cc	400	mg	Per os	17AUG05	22AUG05	19JUL05	12OCT05	?
12725	Lotrisone \ LOTRISONE	Skin rash	cc	unk	cream	Topical	28JUN05	25JUL05	23JUN05	18SEP05	?
16913	Canesten \ CANESTEN	Vaginal infection	od	200	mg	Vaginal	27DEC04	29DEC04	01NOV04	30JAN05	?

This review listing presents potentially violating medications from day of IMP begin upto/incl. the day of last IMP, based on ATC codes and -conservative- date comparisons.

Medications that started before IMP begin date are already reported elsewhere as possible MAJOR violations, and NOT reported here.

Last column gives review finding: 'V' for identified as violation; 'x' for identified as non-violation

Manual selection, by medical expert

```
data violmed_intrt;  
  set possviolmed_intrt;  
  
  violmark='x';      * initialize: not a violation ;  
  
  * change VIOLMARK into 'V' for medications  
    identified as violation by CRS ;  
  
  %violats(ViolMeds_InTrt) ;  
  
run;
```

Documenting the selected medications

```
%macro violats(violid) ;  
  %if &violid=ViolMeds_InTrt %then  
    %do;  
      %* WHO drug names identified by CRS as violating  
        in-treatment medications in Blinded Data Rev listings ;  
      if whodrug in  
        ('BICLAR' 'TOLVON' 'APOREX' 'BIAXIN' 'PAMELOR')  
        then violmark='V' ;  
  
      %* specific subject/WHO drug name combinations for  
        medications that were identified as 'violation' by CRS  
        in Blinded Data Review listings ;  
      if usubjid=10408 and cmdecod='EFFORTIL' then violmark='V' ;  
      if usubjid=11920 and cmdecod='ACTIRA' then violmark='V' ;  
    %end;  
  %mend violats ;
```

Documenting the selected medications

Listing 3 Possible protocol violations for in-treatment drug use, excl. those started on day after day of last IMP.

Subj.	Inv.descr. \ WHO drugname	Indication	Potentially violating medication						IMP dates		
			Reg- imen	Daily dose	Unit	Route	Begin	End	Begin	End	
10510	Biclar uno \ BICLAR	Trachitis	od	500	mg	Per os	28JAN05	01FEB05	19NOV04	13FEB05	V
11401	Azitromycin \ AZITHROMYCIN	Upper airway infection	od	500	mg	Per os	14DEC04	16DEC04	16NOV04	10FEB05	x
	Okacin \ OKACIN	Worsened vision	tid	3	drops	Conjun.	14JAN05	20JAN05	16NOV04	10FEB05	x
11920	Actira (r) \ ACTIRA	Bronchiectasis	cc	400	mg	Per os	17AUG05	22AUG05	19JUL05	12OCT05	V
12725	Lotrisone \ LOTRISONE	Skin rash	cc	unk	cream	Topical	28JUN05	25JUL05	23JUN05	18SEP05	x
16913	Canesten \ CANESTEN	Vaginal infection	od	200	mg	Vaginal	27DEC04	29DEC04	01NOV04	30JAN05	x

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Documenting the selected medications

The details of VIOLMARK='V' medications are used to limit data that can be used for efficacy analysis.

- ▶ All data following start of such medication
- ▶ ... upto X days after stop of such medication

- ▶ Minor vs. Major

Documenting the selected medications

SAS System Viewer - [violinfo.sas7bdat]					
File Edit View Window Help					
	USUBJID	VIOLNUM	VIOLBECD	VIOLENDD	VIOLINFO
1	10115	7	26MAY2005	15JUN2005	Estrace (per os) from 26MAY2005 (Day 92) and Ongoing
2	10408	1.4	.	.	Effortil (per os) from 01APR2005 (Day -12) and Ongoing
3	10510	7	28JAN2005	19MAR2005	Biclar uno (per os) from 28JAN2005 (Day 71) until 01FEB200
4	10510	7	14FEB2005	.	Activelle (per os) from 14FEB2005 (Day 88) and Ongoing
5	10512	1.4	.	.	Carvediol (per os) from 01SEP2004 (Day -78) and Ongoing
6	10522	1.3	.	.	Livial (per os) from 01MAR2004 (Day -332) until 27NOV2004
7	10524	1.4	.	.	Dafalgan codeine (per os) from 17FEB2005 (Day -5) to 20Feb
8	11722	1.4	.	.	Dolol (per os) from2004 and Ongoing
9	11722	1.4	.	.	Hexasoptin r (per os) from2004 and Ongoing
10	11910	1.4	.	.	Ba
11	11920	7	17AUG2005	06SEP2005	Ac
12	12410	1.4	.	.	At
13	12507	1.4	.	.	Se
14	12806	7	13JUN2005	.	Ac
15	12812	7	13JUN2005	.	Ac
16	12820	7	18JUL2005	25JUL2005	Es
17	12904	7	26MAY2005	15JUL2005	Re
18	12935	7	14SEP2005	04OCT2005	Re
19	12939	1.4	.	.	Ap
20	12940	7	24AUG2005	31AUG2005	Ac

SAS System Viewer - [violdes.sas7bdat]		
File Edit View Window Help		
	VIOLTYF	VIOLNUM
2	MAJOR	1.2
3	MAJOR	1.3
4	MAJOR	1.4
5	MAJOR	1.5
6	MAJOR	2
7	MAJOR	3
8	MINOR	4
9	MINOR	5
10	MINOR	6
11	MINOR	7
12	MINOR	8

Possible questions

How is off-label used medication detected?

WHO DD may not (yet) include applic. ATC code!

Title goes here

Subtitle goes here

- ▶ Text goes here
 - Text goes here
 - Text goes here
- ▶ Text goes here

Title goes here

