PhUSE 2010

Paper CS02

Identifying Medications That Are Protocol Violations

John van Bemmelen, MSD, Oss, The Netherlands

ABSTRACT

Each protocol typically specifies medications whose use is prohibited during the trial because of possible interactions with the Investigational Medicinal Product. The identification of such medications in the actual trial data typically involves a programming effort followed by manual review by a medical expert. This paper presents a method for the identification while simultaneously documenting the whole selection process.

INTRODUCTION

A protocol prescribes the procedures to be followed during the study to ensure that the data that are being collected are a good representation of the effect that the Investigational Medicinal Product (IMP) has. Therefore the protocol also describes pretrial and concomitant medications whose use is prohibited because they are known to interfere with the IMP or have an effect similar to that as expected from the IMP.

Because medications can use many different names, the prohibited medications are often described as classes of medications, e.g. hormonal contraceptives. Prohibited medications descriptions typically also include time interval details. For example:

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

Serious deviations from protocol procedures with a possible impact on the validity of the efficacy analysis are called violations. Such violations lead to the exclusion from the Per Protocol analysis of efficacy data that may have been influenced by the violation.

The medications used in a study need to be judged by a medical expert, to see whether any of these medications are in violation. In this process amongst others the route of administration, the dosage and the time period of usage are taken into account.

Fortunately, the programmer can help to make the identification of violating medications more efficient, by creating clever review listings: limited to the medications that are at least a possible violation. Also, a division into separate logical listings will help the reviewer.

With minor additional programming effort the identified violating medications can also be indicated in listings, and thus provide for a more complete study documentation.

This paper first explains how the medication data are coded. Then, based on these codes, with a few SAS statements the possibly violating medications are identified. These are then listed, so that a medical expert can identify the definitive set of violating medications. Finally this definitive set is flagged within the medication data, so that the definitive violations can be indicated in listings and used to determine the efficacy data that need to be excluded from Per Protocol analysis.

CODING OF MEDICATIONS

In most studies the medications are coded using the WHO Drug Dictionary. For each medication name a best matching dictionary name is looked up in the dictionary, resulting also in a preferred name and Anatomic Therapeutic Chemical codes (ATC codes). A medication can have several ATC codes.

For example:

Medication description	**Preferred name**	**ATC codes**					
CMTRT	**CMDECOD**	**CMATC01**	**CMATC02**	**CMATC03**	**CMATC04**	**CMATC05**	**CMATC06**
Flexerile	Flexeril	M03BX	N06AA				
Progesteron	Progesterone	G03DA					
Climera	Climera	G03CA	L02AA				
Sodium chlorid	Sodium chloride	A12CA	B05CB	B05XA	R01AX	R05CB	S01XA
Paxil	Paxil	N06AB					

The first letter of an ATC code describes the anatomical main group, i.e. the body system on which the medication acts. Together with the next two digits an ATC code describes the therapeutic subgroup of the medication. The full 5 character code describes the chemical subgroup.
For example, for N06AB:

N	Nervous system
N06	Psychoanaleptics
N06AB	Selective serotonin reuptake inhibitors

PROGRAMMED PRE-SELECTION OF POSSIBLY VIOLATING MEDICATIONS

The department that performs the coding of the data can also provide collections of ATC codes for the medications that fall within the prohibited medication classes. These collections of codes will be used in our programming, so we choose to store them in a macro variable per defined prohibited medication class. By doing so, we also separate these data-like settings from actual programming code and thus enhance the readability and documentation of our code.

```
* ATC codes for estrogens, progestins and androgens, from Coding Dept. ;
%let estrogens_etc = 'G03AA' 'G03AB' 'G03B'  'G03C'  'G03CA' 'G03CB' 'G03CC' 'G03DA'
                     'G03EA' 'G03EB' 'G03EK' 'G03F'  'G03FA' 'G03FB' 'G03H'  'G03HA'
                     'G03HB' 'G03XB' 'G03XC' 'D11AE' 'L02AA' 'L02AB' 'L02BA' 'L02BB';

* ATC codes for tricyclic antidepressants, SNRIs and SSRIs, from Coding Dept. ;
%let antidepr_etc =  'A03AE' 'A04AA' 'C02KD' 'C02KC' 'C02LL' 'C02LN' 'N02CC' 'N06A'
                     'N06AB' 'N06AX' 'N06CA';
```

For each class of medications a flagging variable is added that indicates whether the medication belongs to that class. The code below adds flagging variables ESTROGFL and ANTDEPFL.

```
data cm (drop=i);
  set cm;

  array atc{*} cmatc:;

  estrogfl='N'; antdepfl='N';  * initialize as 'No' ;

  do i=1 to dim(atc) while(atc{i}^=' ');
    if atc{i} in (&estrogens_etc) then estrogfl='Y';
    if atc{i} in (&antidepr_etc)  then antdepfl='Y';
  end;
run;
```

Note that this code does not explicitly mention the number of CMATC*nn* variables, because this may vary depending on the available coded data. Some medications have more than 10 ATC codes assigned to them, and thus as many variables in the data. But if such medications do not occur in the data then fewer variables may be available.

These are the data with the added flagging variables:

Medication description	**Preferred name**	**ATC codes**			**Estrogen etc. class**	**Antidepr. etc. class**	
CMTRT	**CMDECOD**	**CMATC01**	**CMATC02**	**…**	**ESTROGFL**	**ANTDEPFL**	
Flexerile	Flexeril	M03BX	N06AA		N	N	
Progesteron	Progesterone	G03DA			**Y**	N	← *potentially*
Climera	Climera	G03CA	L02AA		**Y**	N	← *violating*
Sodium chlorid	Sodium chloride	A12CA	B05CB	…	N	N	*medications*
Paxil	Paxil	N06AB			N	**Y**	←

MANUAL SELECTION OF DEFINITIVE VIOLATING MEDICATIONS, BY REVIEWER

Using medical judgment the reviewer decides on the medications that definitively are a protocol violation. The reviewer may conclude that a topically administered medication or a medication in a very low dose does not result in a violation. This knowledge can be used to limit the listings of possibly violating medications, and lighten the reviewer's task.

The reviewer may conclude that prohibited medications that are administered topically or vaginally have a shorter lasting impact, so that a general rule that prohibits their use within the 4 weeks prior to IMP can be made more strict:

If administered topically: a possible violation if used within the 7 days prior to start of IMP
If administered vaginally: a possible violation if used within the 14 days prior to start of IMP
Otherwise: a possible violation if used within the 4 weeks prior to start of IMP

Such programmed additional restrictions are best documented in the Statistical Analysis Plan of the study.

To aid the reviewer, the data to be reviewed may be presented in separate listings, each with its own logical selection of possibly violating medications. For example:

1. Possible protocol violations for pre-treatment hormonal medications
2. Possible protocol violations for pre-treatment medications, excluding hormonal ones
3. Possible protocol violations for in-treatment medications, excl. those started on day after day of last IMP[1]
4. Possible protocol violations for in-treatment medications started on day after day of last IMP

This will help the reviewer to focus on the specific choices to be made. Listings 3 and 4 distinguish between the (replacement) medications that often start on the day after day of last IMP and the other in-treatment medications.

The listings must include all details needed for the reviewer to make the definitive choice of violating medications:

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

	Potentionally violating medication							IMP dates		
Subj.	Inv.descr. \ WHO drugname	Indication	Reg-imen	Daily dose	Unit	Route	Begin	End	Begin	End	
10510	Progesteron \ PROGESTERONE	Prophylaxis for hot flushes	od	1	creme	Topical	28JAN05	01FEB05	19NOV04	13FEB05	?
11920	Lotrisone \ LOTRISONE	Skin rash	cc	unk	cream	Topical	28JUN05	25JUL05	23JUN05	18SEP05	?
12725	Canesten \ CANESTEN	Vaginal infection	od	200	mg	Vaginal	27DEC04	29DEC04	01NOV04	30JAN05	?
13013	Paxil \ PAXIL	Hot flushes	od	25	mg	Oral	14DEC04	16DEC04	19JUL04	12OCT05	?
14101	Actira (r) \ ACTIRA	Bronchiectasis	cc	400	mg	Oral	17DEC04	22DEC04	16NOV04	10FEB05	?
	Okacin \ OKACIN	Worsened vision	tid	3	drops	Conjun.	14JAN05	20JAN05	16NOV04	10FEB05	?

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; '-' for identified as non-violation

On listings like these the reviewer indicates the definitive set of violating medications.

ADD FLAG FOR DEFINITIVE SET OF VIOLATIONS TO THE DATA

Below code is used to copy the reviewer's set of violating medications into the data, so that it can be presented in the listing and used in derivations like that of the efficacy data to be excluded. Notice that the actual violation flag settings are done through a macro call, so that these last minute changes to the data are separated from the main program code.

```
data violmed_intrt;
  set possviolmed_intrt;

  violflag='-';    * initialize: not a violation ;

  * change VIOLFLAG into 'V' for medications identified as violation by Reviewer ;
  %violats(ViolMeds_InTrt);
run;
```

[1] In this study the in-treatment period ended on the day after last day of IMP.

Initially macro VIOLATS simply sets the flagging variable holding the reviewer's opinion to a question mark:

```
%macro violats(violid);
 %if &violid=ViolMeds_InTrt %then
 %do;
    %* Reviewer has not yet performed Blinded Review ;
    violflag='?';
 %end;
%mend violats;
```

After the review has been completed the definitive set of violating medications are flagged in the data by replacing part of the code in macro VIOLATS. Many criteria can be used to reflect this definitive set. Here is just an example:

```
%* WHOdrugnames identified by Reviewer as violating in-treatment medications
   in Blinded Data Rev listings ;
if cmdecod in ('PAXIL' 'APOREX' 'BIAXIN' 'PAMELOR') then violflag='V';

%* specific subject/WHOdrugname combinations for medications that were
   identified as violating by Reviewer in Blinded Data Review listings ;
if usubjid=10510 and cmdecod='PROGESTERONE' then violflag='V';
if usubjid=11401 and cmdecod='ACTIRA'       then violflag='V';
```

If the listing is now created once more then the question marks in the last column will be replaced by '–' and 'V' symbols, representing the definitive set of violating medications.

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

	Potentionally violating medication							IMP dates		
Subj.	Inv.descr. \ WHO drugname	Indication	Reg-imen	Daily dose	Unit	Route	Begin	End	Begin	End	
10510	Progesteron \ PROGESTERONE	Prophylaxis for hot flushes	od	1	creme	Topical	28JAN05	01FEB05	19NOV04	13FEB05	**V**
11920	Lotrisone \ LOTRISONE	Skin rash	cc	unk	cream	Topical	28JUN05	25JUL05	23JUN05	18SEP05	**-**
12725	Canesten \ CANESTEN	Vaginal infection	od	200	mg	Vaginal	27DEC04	29DEC04	01NOV04	30JAN05	**-**
13013	Paxil \ PAXIL	Hot flushes	od	25	mg	Oral	14DEC04	16DEC04	19JUL04	12OCT05	**V**
14101	Actira (r) \ ACTIRA	Bronchiectasis	cc	400	mg	Oral	17DEC04	22DEC04	16NOV04	10FEB05	**V**
	Okacin \ OKACIN	Worsened vision	tid	3	drops	Conjun.	14JAN05	20JAN05	16NOV04	10FEB05	**-**

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; '-' for identified as non-violation

These are the data with resulting violation flag variable, also showing medication start and end dates:

Subject identif.	Medication description	Medication start date	Medication end date	…	Estrogen etc. class	Antidepr. etc. class	Violation flag
USUBJID	**CMTRT**	**CMSTDTC**	**CMENDTC**		**ESTROGFL**	**ANTDEPFL**	**VIOLFLAG**
10102	Flexerile	2004-11-15	2004-12-03	…	N	N	
10510	Progesteron	**2005-01-28**	**2005-02-01**	…	Y	N	**V**
11305	Climera	2005-03-06	2005-05-21	…	Y	N	–
11517	Sodium chlorid	2005-04-11	2005-04-25	…	N	N	
13013	Paxil	**2004-12-14**	**2004-12-16**	…	N	Y	**V**

The time intervals for which efficacy data must be excluded from the Per Protocol analysis can now be derived, also dependent on rules given in the Statistical Analysis Plan. Based on the above indicated violations efficacy data need to be excluded for subject 10510 between 28 Jan and 01 Feb 2005 and for subject 13013 between 14 and 16 Dec 2004.

SOME THOUGHTS ON THE PROCESS

Some medications may be used off-label, i.e. for an indication that is not officially accepted. Such medications may perhaps not have an ATC code that matches with the indication, and thus may not be selected as a potentially violating medication, even though reviewer might find it violating.
Fortunately, during the ongoing data review, the consistency between medications and adverse events is checked, so such off-label use of medications should be detected there. If reviewer finds such a medication to be a violation then, with some additional program code, the appropriate medication class flag can be set.

Sometimes medications may be added to the clinical database even after the reviewer has completed his identification of violating medications. By electronically comparing the dataset and/or review listing at database lock against those that were reviewed we can detect whether the review needs to be repeated.

CONCLUSION

With little extra effort the programmer can help the reviewer in identifying the violating medications more efficiently because a major part of the identification process can be automated.
Because each violating medication is marked as such within the data set, it is possible to include these details in medication listings and provide for a more complete documentation.
Of course, for studies with only few pre-trial and concomitant medications it is just as simple for the reviewer to review all medications. Partly automating the process is useful specifically for studies with many medications.

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

John van Bemmelen
MSD
P.O. Box 20
5340 BH Oss
Phone: +31(0)412662366
Email: john.vanbemmelen@merck.com