

Keeping Patients on Schedule, The Art of Visit Windows and Cycle Slotting

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ABSTRACT

It would be so much easier if the patients enrolled in a clinical trial would simply follow the visit schedule. The scheduled visits reported at the top of most case report forms would align to the data collected and programming would be so much simpler. Alas, this is reality and nothing could be further from the truth. Generally all clinical trials have to deal with taking “unscheduled” or “off cycle” visits and aligning them with the planned visits in order to make sense of the data collected.

This paper covers a few of the different methodologies used to align the data collected with the visit in which it was intended to occur. Typical approaches will include the visit window calculations and cycle slotting. We will also cover how to handle different epochs of treatment. All solutions will be presented using SDTM domains as source and ADaM implementations for the derivations.

OVERVIEW

WHY, OH WHY....

For almost any programmer starting a study, the problem seems to always come up, “Why can’t these people follow the schedule. My code would be so much easier if...” If you think back to when you started in this business, you probably uttered the very same statement, and possibly still do. So, let’s discuss some of the background and how all of this has evolved.

There can actually be a number of reasons. If we start looking at subjects, or patients, in a study we need to know that, while they are participating on a study, their primary concern is not the study. Some may have jobs and others may have a serious disease that is of higher concern than participating on the study. Add in other demands that may consume their time and we are probably lucky that they even get close to the planned visit date. The other cause of problems is the investigator themselves who may either be physicians or other health care providers. For those individuals as well, patient care is of greater concern than the participation in the study.

Because of these reasons, it will always be up to the programmer to develop algorithms for getting the actual visits to align with the planned visits. Of course, there are plenty of documents to review before you start this endeavor, such as the protocol (which probably contains a visit schedule) and of the statistical analysis plan (which may contain some details on the intended algorithm). There are also some logical data sets to look at before you do much else such as the labs (LB), the vital signs(VS), ecgs (EG), and physical examinations (PE). Be especially aware of any visits that might be labeled as unscheduled, unplanned, or missing. Take some notes and then get ready to analyze.

WHICH ONE SHOULD I USE?

For this paper, we are going to look at a couple of general rules. For the most part, you are going to use the approach of visit windows when a detailed visit schedule is provided with either the protocol or statistical plan. This detailed plan usually provides the study days throughout the study on which subjects should be at the investigators site for some type of assessment. Frequently this type of assessment occurs when subject dosing happens once at the beginning of the study or regularly for the duration of the study.

On the other hand, some studies conduct visits in association with study treatment. As an example, an oncology study where the subjects visit coincides with each exposure to the medication (either placebo or actual medication). For this reason, the visit number is data driven based on one of the databases within a study (such as the EX domain). This methodology will require the creation of a database for mapping the study visits for each subject back to the planned exposure visit. This is referred to as cycle slotting.

THE BASIC VISIT WINDOWS.

Once you have reviewed the protocol and statistical analysis plan and determined that the right approach is to use the visit window, the next step is to evaluate the data. Since visit windows are usually based on study days, the first step is to calculate the study days based on the specification in the SAP. Once you have calculated the study days you would then perform a frequency evaluation on those days. Be aware that each type of data, such as laboratory or vital signs, may have different study day frequencies that will need to be evaluated. [Consider the case where the subject has a blood sample drawn two days prior to the actual visit.]

As an example, let's evaluate the laboratory data for the UBERCURE study. Based on the SAP, the study days are based on number of days after a subject is randomized on the study, with the day of randomization being day 1. Based on the protocol, the subject is supposed to show up every two weeks for 2 months. After you have calculated the study days, creating a frequency table on the study days for the WBC yields the results in Table A. This gives you the basic data to identify the visit windows to be used for the study.

Based on our protocol, you would expect the visits to happen on days 1, 12, 26, 40, and 54 or 2 days prior to the actual office visit. However, in reviewing the data, you can tell that we have laboratory visits on day 10, 34 and 60. If you were to look at the data, you might also find that the recorded visits don't actually match to the visit schedule. For the purposes of this example, we are just going to look at the visit frequencies, but be aware there may be other issues to consider. Once again, it is good to review this data with the study team to make sure you have taken into consideration all the potential permutations.

Table A: Study Day Frequencies

studyday	Frequency	Cumulative Frequency
1	72	72
10	8	80
12	40	120
13	16	136
14	8	144
26	40	184
27	16	200
28	8	208
34	8	216
40	48	264
41	16	280
42	8	288
54	40	328
55	16	344
56	8	352
60	8	360

APPLYING THE VISIT WINDOWS

Now that we have the frequencies, we can take a look at where to make the logical breaks and bring that into a macro. While this could be incorporated into each program that needs to reassign the visit windows, the use of a macro will make the algorithm more transportable. It will also aid in the review and documentation of the algorithm, which may occur over the course of the study.

Based on the algorithm, we should probably schedule visit 1, or the baseline visit, to occur just on day 1. From there, visit two would occur from day 10 to 14, visit three on day 26 to 28, visit 4 on visit 34 to 42, and visit 5 on day 54 thru 60. Notice that we are not including the days outside of the visit windows. For those dates, we actually want to build into our macro a clause so that days not accounted for are logged somewhere. This allows us to review them later in case the macro needs to be adjusted.

Also be aware that these dates are planned for the laboratory data for our study. Just because we have a visit window doesn't mean it applies equally to all of the data.

A sample macro for applying a visit window is included in Table B.

Table B: Macro for Visit Windows

```
%macro makewin (wintyp=LB, stdyvar=,visvar=);
  %if &wintyp="B" %then %do;
    If &stdyvar = 1 then &visvar = 1;
    Else if 10 <= &stdyvar <= 14 then &visvar=2;
    Else if 26 <= &stdyvar <= 28 then &visvar=3;
    Else if 34 <= &stdyvar <= 42 then &visvar=4;
    Else if 54 <= &stdyvar <= 60 then &visvar=5;
  If &visvar = .
    Then put "War" "ning: Visit window error";
  %end;
%mend makewin;
```

WHAT ABOUT THE SV DOMAIN

The SV domain of the Study Data Tabulation Model can also be used for visit windows. It does track when each visit for each subject begins and ends. It is also created, generally, based on all the known visits that have been tracked for a clinical trial. Based on my experience, the SV domain does not allow visit date differences to occur between two other domains. Consider where the LB domain would allow a subject up to 4 days prior to a planned visit to be assigned to that visit but that possibly a PE domain would not allow any days. For that reason, I prefer the use of a macro.

CYCLE SLOTTING, AN OVERVIEW

As simple as visit windows are, cycle slotting is a much more complicated approach. Cycle slotting will be based on particular events occurring within a clinical trial such as an exposure to the medication or some form of imaging data. Since each subject will have these events at different times, you will need to create a database of when each event occurs for each subject. Once you have this data, the algorithm will merge the data in which visits need to be slotted to the slotting data.

Because the algorithm is going to be data dependant, you are probably going to want to place th[Type a quote from the document or the summary of an interesting point. You can position the text box anywhere in the document. Use the Text Box Tools tab to change the formatting of the pull quote text box.] is data into an analysis dataset. For the purposes of this paper, we are going to use the Basic Data Structure as defined in the ADaM specifications version 1.2. As we proceed through the cycle slotting algorithm, we will determine the appropriate visits for the laboratory results of the TUMORGONE project. For this project, the randomized subject receives a treatment of TUMORGONE every 4 weeks. And of course they perfectly follow the schedule (or why would we be writing this, right.).

CREATING THE SLOTTING DATABASE

Using the TUMORGONE trial, we know that the visits should be based on when each subject receives a dose of the medication. This means that we should build an analysis dataset based on data collected in the EX domain. Since this is dependent on the data of exposure, we do not need to calculate study day at this time. This is a simple study, so we are going to create the ADSV (Subject Visit) database by extracting the dates on which the subject EXDOSE value is greater than 0. An example of this database is shown in Table C.

Table C: ADSV database

SUBJECTID	PARAMCD	PARAM	AVALC
001	CYC1	Cycle 1	2010-01-01
001	CYC2	Cycle 2	2010-02-14
001	CYC3	Cycle 3	2010-04-01
001	CYC4	Cycle 4	2010-05-20
002	CYC1	Cycle 1	2010-01-30
002	CYC2	Cycle 2	2010-03-01
002	CYC3	Cycle 3	2010-05-01
003	CYC1	Cycle 1	2010-03-30

Note: Not all BDS variables needed are shown

Of course, for the purposes of this paper we are using a simple approach. In reality there are a number of things the programmer will need to consider. Some of these items include how to handle when a subject takes two partial dosages of the study medication close together. Since we are working with laboratory data, you may also need to consider how many days prior to the start of a slotted visit are allowed in order for that data to be included in a visit. As always, once you have the algorithm designed, be sure to share it with the study team and gather their input.

Since we are creating this as a Basic Data Structure, let's take a moment to describe what is necessary. As a minimum, we need to incorporate the STUDYID, USUBJID, SUBJID, and SITEID fields from the ADSL dataset. You will also need to create a treatment variable, such as TRTP, based on the design of the study and the TRTnnP data in the ADSL dataset. The dates for storing when each new visit occur will be stored in the AVALC in ISO8601 format. In order to identify the actual visits, the PARAM value will be noted as CYCLE n, the PARAMCD will be noted as CYCn, and the PARAMN field will be set to n. For this case, n represents the actual visit number.

SLOTTING THE VISIT

Now that you have the slotting database created it is time to use that data to determine visits, or cycles. As you calculate the visits, you may also need to determine the number of days within a particular visit have occurred as many studies show both study day and days in cycle. Other things to consider, as described above, are how many days preceding the start of a new visit should be taken into account. Since we are working on the lab data for TUMORGONE, we are going to account for two days prior to the start of a visit.

The macro, as shown in Table D, is an example of slotting visits, or cycles, to the laboratory data. Take a look at the first section of the macro code. Remember that since we are creating the ADSV dataset as a BDS, we need to "denormalize" the data in order to apply the dates to the laboratory data. We accomplish this thru the use of the TRANSPOSE procedure and assign the idvar to

Table D: Slotting Macro

```
%macro slot (inset=,inslot=ADSV,studydt=,visit=);
/* Denormalize the ADSV data */
Proc transpose data=&inslot out=adsvwide;
  By subjid; id=paramcd; var=avalc;
Run;

/* Merge the ADSV data to the
Data slotted;
Merge &inset (in=_inset)
  Adsvwide (in=_adsv);
By subjid;
Drop cyc: ;
Array visar [*] cyc: ;
&Visit = .;
Do I = 1 to dim(visar);
  If &studydt >= input(visar[i], yymmdd10.)
    Then &visit = I;
End;
%mend slot;
```

PARAMCD. This creates a wide record for each subject containing the appropriate visits.

APPLICATION OF A CROSSOVER DESIGN WITH SLOTTING

Of course, we have been showing simple study designs. What about slotting windows in a crossover design? While this may seem to be a much more complicated process, it can actually be simplified by just merging the ADSL dataset in the same merge process shown in Table D. Within the ADSL dataset, there are the variables TRTxxP and TRTxxA which defines the planned and actual treatments given to a subject during period xx. In addition to those variables, you also have the variables TRxxSDT, and TRxxEDT which define when period xx begins and ends. By using a new DO loop within the dataset, you can assign the TRTxxP variable to TRTP for the planned visits (and likewise for actual treatments).

Why would we do this? Let's consider the above oncology study where a subject might be on a variety of treatments during the course of the clinical trial. The different treatment periods would coincide to the different treatments a subject might receive.

CONCLUSION

Of course, one should always remember that there are studies where the visit recorded on the CRF actually matches the planned visit. This is frequently the case for Phase I studies and some Phase II. The above tools described above provide some additional tools to use for getting the actual visits recorded to align to the planned visits. This helps when using the visits for categorical analysis of many parameters, such as labs and other evaluable parameters.

Does this mean these are all the potential ways to handle visit windows or slotting? Absolutely not. But after you have reviewed the study documents, these methods can help you start getting the data ready for analysis. Good luck.

REFERENCES

SDTM version 1.2 specifications. the SDTM Implementation Guide, the ADaM version 2.1 specifications, and the ADaM Implementation Guide 1.0 can be downloaded from <http://www.cdisc.org>.

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