Assigning Treatment Group in Cross-over Studies:
A Practical Approach
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ABSTRACT:
Cross-over studies in clinical studies are always complicated but are manageable when certain key variables are generated and merged with related data sets to assign correct treatment groups. With a brief introduction of cross-over studies, this paper demonstrates methods and ideas of how to assign treatment groups based on the raw treatment code data set, with the help of a new variable called periods (one of the key variables to assign treatment groups correctly). Once key variables, treatment group and period, are created, new data sets can be merged with the help of these key variables. Listings and tables can be generated based on these newly created treatment groups. However, AE (adverse events) counts are another issue statistical programmers are facing. The second part of this paper clearly introduces steps of how to select AE counts before the dosage, during the wash-out period and after the last dosage, with SAS code, which is ready to apply. Thus, a complicated concept of cross-over studies becomes normal programming concept again. To assist programmers, SAS code is included in the paper and can be applied by other programmers with ease.

INTRODUCTION:
In clinical trials, we generally conduct two types of clinical studies. One consists of several treatment groups with distinct subjects (patients); another involves cross-over studies in which same subjects enter into different treatment groups after an amount of set days of wash-out period in the same clinical study with different study medications. Even some very experienced SAS programs who never have come across a cross-over study before may face some challenge when they are asked to assign the treatment group correctly. This paper addresses some key concepts, issues and techniques of how to assign the treatment groups correctly in this topic. Mainly it consists of a study trt (treatment group) design, one way of assigning trt variable, and an example of AE counts to illustrate how we handle this concept.

1. An example of a cross-over study design. Let us take a four-way cross over study design for an illustration:

   A B C D
   B C D A
   C D A B
   D A B C

   One of the key time sequence is the period in which a patient takes the first dose, second dose and so on. In the above design, the first treatment in period one is “A”, followed by “B”, “C” and then “D”. Generally, we have a raw trt (treatment) data set which includes some of the following variables: patient (randomization number), tgroup (treatment groups) and trtdesc (treatment description). An example of the data can look like the following:

<table>
<thead>
<tr>
<th>Trtdesc</th>
<th>tgroup</th>
<th>patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>a/b/c/d</td>
<td>1</td>
<td>1001</td>
</tr>
<tr>
<td>b/c/d/a</td>
<td>2</td>
<td>1002</td>
</tr>
<tr>
<td>c/d/a/b</td>
<td>3</td>
<td>1003</td>
</tr>
<tr>
<td>d/a/b/c</td>
<td>4</td>
<td>1004</td>
</tr>
</tbody>
</table>

   When we are given the above data set, we can assign trt groups in the following code.

2. Some SAS code to assign the treatment groups with the help of a newly created variable – period, after we merge the above variables with the patient data set:
data trt_new;
  set raw.trt;
  by patient;
  do i=1 to 4; /* we have four treatment periods */
    if scan (trtdesc, i , '/')='a' then trt=1;
    else if scan (trtdesc, i , '/')='b' then trt=2;
    else if scan (trtdesc, i,  '/')='c' then trt=3;
    else if scan (trtdesc, i,  '/')='d' then trt=4;
    period=i; /* we assign different periods in this loop */
    output;
  end;
run;

After this trt_new data set being merged with PAT data set by patient, you may merge this data set with any other data sets by centre, subject, period in order to assign the correct trt variable. However, AE counts are more complicated than traditional AE tables. We need more code to determine which AE counts occur in which treatment periods.

3. How to handle AE counts in different treatment groups. As we, who have worked with cross-over studies before, know that we can not merge AE data set with the above trt_new data set. If we do so, the assignment of the trt for the AE table might be wrong. What can be done then? We need to bring in drugacct(drug account data set) and then merge it with AE data set to determine each period as to get the correct treatment groups. The following code solves this problem:

data drug;
  set raw.drugacct;
  by centre subject;
  retain visitid;
  if first.subject then  visitid=2; /* prepare for the following logic */
    else  visitid=visitid+1;
run;

data drugtrt;
array astr{*}  start1-start4;
array aend{*} end1-end4;
set drug;
  by centre subject;
  retain start1-start4 end1-end4;
if first.subject then 
  do;
    do i=1 to 4; astr{i}=.; aend{i}=.;
    end;
  end;
astr{visitid-1}=sdsdtn;
aend{visitid-1}=sdedtn;
  if last.subject then output;
  drop visitid i;
run; /* merge AE data set with drug account data set */
data ae ;
merge anyae drugtrt;
by centre subject;
  if aeondtn<start1 then visit=1;
  if .<start1<=aeondtn<start2 then visit=2;
  if .<start2<=aeondtn<start3 then visit=3;
  if .<start3<=aeondtn then visit=4;
  period=visit-1; /* variable period is created here */
if anyaes="1";
drop visit;
run;
proc sort;
  by study centre subject period;
run;
  /* Merge the above AE data set with the TRT data set */
data account;
  merge trt_new ae(in=a); /* if we only keep the population in AE dataset */
  by centre subject period;
  if a;
run;
CONCLUSION:
With the above code, we have created the correct treatment group variable to count AE occurrence. This concept can be applied for lab tables if we need to consider visit days to determine different periods. Cross-over studies are similar to regular clinical trials, except the fact that we need to assign the correct trt variable as I have illustrated in the previous paragraphs. One may argue that there are other ways that can handle a cross-over study, but the approach addressed here can be easily applied and can make the cross-over study less complicated as it appears.
ACKNOWLEDGMENTS:
Many thanks to my manager, Dan Godoy, and my co-workers, for their suggestions and support for this paper.
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