

# Programming TFLs When No Data is Collected – A Farsighted Approach to Win The Race Against Time in Clinical Research

*Sakthivel S, Manager – Biostatistics, Quartesian LLC*  
*Kameswari P, Statistical Programmer, Quartesian LLC*

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# *Motto of the approach?*

- Provide a cost-effective and efficient solution in terms of proactive programming, by getting the TFLs ready before the first data transfer for any Clinical study



# *Why is this proactive approach needed?*

- Reduce the turnaround time and help in meeting the tight timelines of Project Milestones in fast paced Clinical research industry
- Helps meet Quality vs Time Balance
- Lead time put to best use



- Simulate and mimic the actual data in size and structure by using
  - Simple DO-Loops
  - Random number Generation

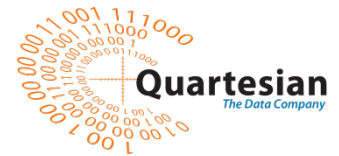


## Random Number Generation

- Many Functions in SAS for random number generation – RAND, RANUNI, RANBIN etc.
- RAND function generates random numbers for continuous and discrete distributions
- Ex: RAND function with Uniform distribution generates random decimal numbers between 0 and 1

```
u = rand("Uniform");
```

## Random Number Generation Continued....



- Scale them to get random decimal numbers in the interval  $[a, b]$

```
a = -1; b = 1; /* example values */  
x = a + ((b-a*u);
```

- Use FLOOR or CEIL functions to transform (continuous) random values into (discrete) random integers

```
m = min + floor (1+Max-Min*u); /* uniform integer in Min..Max */
```

- To get the same set of random numbers generated every time the RAND function is executed, Call Streamint function can be used

```
call streaminit (123); /* set random number seed */
```

- Proactive approach- So nothing at our disposal except the study documents
- How to Kick start crucial!
- Key information taken from study documents like
  - Protocol
  - CRF/aCRF
  - SAP
  - Data Transfer agreement
  - Mock Shells



- Simulate the data that would fit into the standard structures of the clinical trial data domains SDTM
- Determination of the SDTM Data Class to which the simulated data might belong to?
- Comprehend to the standard structure of the dataset as needed during the simulation process



- Number of subjects enrolled in study
- Treatment design- number and type of treatments, plan of administration
- Creation of dummy randomization schedule



| Screening | Dose Level 1    |         | Dose Level 2     |         | Dose Level 3     |         | Dose Level 4     |         | Dose Level 5                    |         | Dose Level 6                    |
|-----------|-----------------|---------|------------------|---------|------------------|---------|------------------|---------|---------------------------------|---------|---------------------------------|
| DAY -2    | DAY 1           |         | Day 8            |         | DAY 15           |         | DAY 23           |         | DAY 43                          |         | DAY 58                          |
|           | Drug A<br>75 mg | Washout | Drug A<br>150 mg | Washout | Drug A<br>450 mg | Washout | Drug A<br>950 mg | Washout | Drug A<br>150 mg<br>+<br>Drug B | Washout | Drug A<br>450 mg<br>+<br>Drug B |

**Example of Study design**

# Dummy randomization schedule

- Generate random numbers using RAND function
- Translate the generated random numbers into the treatment assignment

```
data treat;  
alpha = "ABCD";  
do patient = 1 to 5;  
  trt= (1 + floor ((1+3-1) *rand("uniform")));  
  treatment = SUBSTR (alpha, trt, 1);  
  output;  
end;  
run;
```

| Patient | Treatment |
|---------|-----------|
| 1       | B         |
| 2       | A         |
| 3       | A         |
| 4       | C         |
| 5       | B         |

**Output**

- Simulate data strategically and sequentially using information like planned assessments and interventions and their day of commencement in respect to study day from the Schedule of events table

|                                                           | Screening     | Day of dosing        | Day after dosing     |
|-----------------------------------------------------------|---------------|----------------------|----------------------|
|                                                           | day -45 to -2 | 1, 8, 15, 23, 43, 58 | 2, 9, 16, 24, 44, 59 |
| Informed Consent                                          | x             |                      |                      |
| Medical History                                           | x             |                      |                      |
| Complete Physical Exam                                    | x             |                      |                      |
| Vital Signs                                               | x             | x                    | x                    |
| Triplicate pharmacodynamics ECG extraction's <sup>g</sup> |               | x                    | x                    |

<sup>g</sup>triplicate 12-lead ECGs will be at the following times in relation to dosing on Day of dosing: -1.0, -0.75, and -0.5 hours predose and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12 and 24 hours post dose

- Descriptor information about variables obtained from Data Transfer Agreement

| EGTESTCD | EGTEST                                          | EGCAT          | EGORRESU  | EGSCAT            | EGORRES                                     |
|----------|-------------------------------------------------|----------------|-----------|-------------------|---------------------------------------------|
| QTCB     | QTcB –<br>Bazett's Correction<br>Formula        | INTERVAL       | msec      |                   |                                             |
| QTCF     | QTcF –<br>Fridericia's<br>Correction<br>Formula | INTERVAL       | msec      |                   |                                             |
| HRMEAN   | Summary<br>(Mean) Heart<br>Rate                 | MEASUREMENT    | BEATS/MIN |                   |                                             |
| RRMEAN   | Summary<br>(Mean) RR<br>Duration                | INTERVAL       | msec      |                   |                                             |
| EGINT    | ECG<br>Interpretation                           | INTERPRETATION |           | ECG<br>EVALUATION | NORMAL<br>ABNORMAL<br>UNABLE TO<br>EVALUATE |

**Mapping Table**

- Perplexity regarding the consideration of date for the Study Day 1
- Diligent to consider a date that would help us simulate meaningful data
- Protocol finalization date can be considered as DAY 1 date so that the previous and subsequent dates generated are suggestive and purposeful





## Case Study- EG Data Set Creation

\*Creating triplicate records for 10 EG-tests for 16 time points for 6 periods for 10 parameters for 16 subjects;

```
data dummy;  
  do patid=1 to 16;  
    do egtestcd=1 to 10;  
      do period=1 to 6;  
        do EGTPNUM= -1, -0.75, -0.5, +0.5, +1, 1.5, 2, 3, 4,  
                5, 6, 7, 8, 9, 10, 12, 24;  
          do repeatid=1 to 3;  
            output;  
          end;  
        end;  
      end;  
    end;  
  end;  
run;
```

- Protocol finalization date considered for study day 1
- Tentative time of study drug administration taken from protocol and subsequent times calculated based on respective timepoint

```
data dummy1;  
  set dummy;  
  by patid egtested period EGTPTNUM;  
  fir_dt=input ("12JAN2016", DATE9.);  
  fir_tm=input ("07:00", time5.);  
  adt=fir_dt+((period-1) *7);  
  time=fir_tm+(EGTPTNUM*60*60);  
  format adt date9. time time5.;  
run;
```



# Test Result Values Generation:

- Values of test result generated using random number generation
- Normal Reference Range values of the test in healthy adults used as limits during result value simulation

\*Sub setting for creating the AVAL using random number generation;

```
data HRMEAN EGINT;  
  set dummy1;  
  if egtestcd=1 then output HRMEAN;  
  if egtestcd=8 then output EGINT;  
run;
```



# Test Result Values Generation: Continued..

- Test specific result generation using rand functions
- Can be made robust by including extreme values as they can be part of real data

```
%macro rand (dat=, num=, min=, max=);  
  data &dat;  
  set &dat nobs=&num ;  
  %let n=&num;  
  do i=1 to &n;  
    call streaminit(123);  
    aval=(&min + floor(((1+&max-&min) *rand("uniform"))));  
  end;  
run;  
%mend;  
%rand (dat=HRMEAN, num=num, min=30, max=130);  
%rand (dat= EGINT, num=num, min=1, max=2);
```

# *Missing cant be ignored!*

- However, well planned study is presence of missing values is a common scenario due to many reasons like unfriendly case-report forms, technical and manual errors, subjects drop out from the studies, lost to follow up etc.
- These missing values can not be ignored as they can have a significant effect on the conclusions that can be drawn from the data
- In order to make the simulated dataset resemble the real time data, missing values can be created in a random fashion
- This practice helps the programmer to program defensively with missing values and their imputations



- Random numbers as result values for Qualitative tests makes no sense
- Apply formats to these random numbers and display them as character results
- Values for the formats can be obtained from accepted values list for the test from Data Transfer agreement/CRF

```
proc format;  
  value EGINT  
    1="ABNORMAL"  
    2="NORMAL";  
run;
```

# Partial Output of EG dataset

| PATID | AVISIT | ADT       | TIME  | ATPT               | EGTESTCD | AVAL | AVALC    |
|-------|--------|-----------|-------|--------------------|----------|------|----------|
| 1     | Day 1  | 1/12/2016 | 6:00  | 1 Hour predose     | HRMEAN   | 48   | 48       |
| 1     | Day 1  | 1/12/2016 | 6:00  | 1 Hour predose     | HRMEAN   | 68   | 68       |
| 1     | Day 1  | 1/12/2016 | 6:00  | 1 Hour predose     | HRMEAN   | 76   | 76       |
| 1     | Day 1  | 1/12/2016 | 8:30  | 1.5 Hours postdose | HRMEAN   | 63   | 63       |
| 1     | Day 1  | 1/12/2016 | 8:30  | 1.5 Hours postdose | HRMEAN   | 78   | 78       |
| 1     | Day 1  | 1/12/2016 | 8:30  | 1.5 Hours postdose | HRMEAN   | 64   | 64       |
| 1     | Day 2  | 1/13/2016 | 7:00  | 24 Hours postdose  | HRMEAN   | 86   | 86       |
| 1     | Day 2  | 1/13/2016 | 7:00  | 24 Hours postdose  | HRMEAN   |      |          |
| 1     | Day 2  | 1/13/2016 | 7:00  | 24 Hours postdose  | HRMEAN   | 71   | 71       |
| 1     | Day 1  | 1/12/2016 | 9:00  | 2 Hours postdose   | EGINT    |      | ABNORMAL |
| 1     | Day 1  | 1/12/2016 | 11:00 | 4 Hours postdose   | EGINT    |      | NORMAL   |
| 1     | Day 2  | 1/13/2016 | 7:00  | 24 Hours postdose  | EGINT    |      | NORMAL   |

- As our motto is to get the final TLF's ready-
- Create analysis datasets from the simulated datasets-
- By adding derived variables required for reporting like the ANL01FL, ANLBFL, PSTBLFL, BASE, CHG etc. based on SAP and mock shells
- These analysis ready data sets can be used for report generation

Table 3  
Absolute and Change from Baseline in Heart Rate Summary Statistics (bpm) by Dose Group and Combined Placebo and by Timepoint

| Timepoint/<br>Statistics       | Drug A 75 mg<br>(N=12) |                    | Drug A 150 mg<br>(N=12) |                    | Drug A 450 mg<br>(N=12) |                    | Drug A 900 mg<br>(N=12) |                    | Drug A 150 mg<br>+ Drug B mg<br>(N=12) |                    | Drug A 300 mg<br>+ Drug B<br>(N=12) |                    | Combined<br>Placebo<br>(N=4) |                    |
|--------------------------------|------------------------|--------------------|-------------------------|--------------------|-------------------------|--------------------|-------------------------|--------------------|----------------------------------------|--------------------|-------------------------------------|--------------------|------------------------------|--------------------|
|                                | At                     | Change<br>from     | At                      | Change<br>from     | At                      | Change<br>from     | At                      | Change<br>from     | At                                     | Change<br>from     | At                                  | Change<br>from     | At                           | Change<br>from     |
|                                | Timepoint baseline     | Timepoint baseline | Timepoint baseline      | Timepoint baseline | Timepoint baseline      | Timepoint baseline | Timepoint baseline      | Timepoint baseline | Timepoint baseline                     | Timepoint baseline | Timepoint baseline                  | Timepoint baseline | Timepoint baseline           | Timepoint baseline |
| <b>Baseline</b>                |                        |                    |                         |                    |                         |                    |                         |                    |                                        |                    |                                     |                    |                              |                    |
| n                              | 12                     |                    | 12                      |                    | 12                      |                    | 12                      |                    | 12                                     |                    | 12                                  |                    | 4                            |                    |
| Mean                           | 84.1                   |                    | 75.9                    |                    | 77.6                    |                    | 82.3                    |                    | 78.7                                   |                    | 75.8                                |                    | 78.4                         |                    |
| SD                             | 16.24                  |                    | 7.77                    |                    | 8.54                    |                    | 12.49                   |                    | 11.55                                  |                    | 6.75                                |                    | 6.78                         |                    |
| Min                            | 53.6                   |                    | 64.8                    |                    | 60.6                    |                    | 53.6                    |                    | 62.1                                   |                    | 64.8                                |                    | 68.7                         |                    |
| Median                         | 87.8                   |                    | 75.4                    |                    | 77.2                    |                    | 85.3                    |                    | 78.2                                   |                    | 76.0                                |                    | 80.1                         |                    |
| Max                            | 109.0                  |                    | 95.4                    |                    | 89.8                    |                    | 95.8                    |                    | 102.0                                  |                    | 88.0                                |                    | 84.5                         |                    |
| Missing                        | 0                      |                    | 0                       |                    | 0                       |                    | 0                       |                    | 0                                      |                    | 0                                   |                    | 0                            |                    |
| <b>30 Minutes<br/>Postdose</b> |                        |                    |                         |                    |                         |                    |                         |                    |                                        |                    |                                     |                    |                              |                    |
| n                              | 12                     | 12                 | 12                      | 12                 | 12                      | 12                 | 12                      | 12                 | 12                                     | 12                 | 12                                  | 12                 | 4                            | 4                  |
| Mean                           | 71.0                   | 13.1               | 85.3                    | -9.4               | 80.6                    | -3.0               | 78.7                    | 3.6                | 79.2                                   | -0.5               | 79.8                                | -4.1               | 83.5                         | -5.2               |
| SD                             | 18.81                  | 18.73              | 21.84                   | 19.92              | 17.28                   | 20.18              | 14.54                   | 16.97              | 14.93                                  | 19.37              | 14.33                               | 14.92              | 10.83                        | 13.59              |
| Min                            | 41.3                   | -13.7              | 54.7                    | -44.3              | 58.7                    | -31.7              | 45.7                    | -28.4              | 48.7                                   | -33.7              | 53.7                                | -22.9              | 67.8                         | -20.9              |
| Median                         | 75.5                   | 11.3               | 84.8                    | -12.4              | 78.5                    | 0.6                | 82.3                    | 1.9                | 81.8                                   | -5.6               | 78.5                                | 0.2                | 87.3                         | -6.0               |
| Max                            | 102.7                  | 45.2               | 124.3                   | 22.2               | 114.7                   | 20.2               | 93.7                    | 29.8               | 100.0                                  | 25.6               | 101.3                               | 20.0               | 91.7                         | 12.2               |
| Missing                        | 0                      | 0                  | 0                       | 0                  | 0                       | 0                  | 0                       | 0                  | 0                                      | 0                  | 0                                   | 0                  | 0                            | 0                  |
| <b>1 Hour<br/>Postdose</b>     |                        |                    |                         |                    |                         |                    |                         |                    |                                        |                    |                                     |                    |                              |                    |
| n                              | 12                     | 12                 | 12                      | 12                 | 12                      | 12                 | 12                      | 12                 | 12                                     | 12                 | 12                                  | 12                 | 4                            | 4                  |
| Mean                           | 75.6                   | 8.4                | 78.0                    | -2.1               | 70.6                    | 7.0                | 75.2                    | 7.1                | 84.2                                   | -5.4               | 73.6                                | 2.2                | 88.6                         | -10.2              |
| SD                             | 13.09                  | 25.26              | 12.45                   | 16.09              | 15.42                   | 19.89              | 15.39                   | 20.68              | 10.90                                  | 15.31              | 15.02                               | 16.41              | 7.00                         | 11.32              |
| Min                            | 55.7                   | -31.8              | 61.3                    | -23.7              | 39.7                    | -24.3              | 50.7                    | -25.8              | 68.3                                   | -41.4              | 46.7                                | -28.6              | 81.9                         | -26.4              |
| Median                         | 74.8                   | 4.5                | 80.5                    | -3.1               | 70.7                    | 6.9                | 72.3                    | 7.7                | 85.3                                   | -6.7               | 72.3                                | 1.1                | 88.7                         | -6.3               |
| Max                            | 103.0                  | 53.3               | 103.7                   | 33.1               | 99.7                    | 50.1               | 108.7                   | 45.1               | 108.3                                  | 12.2               | 107.0                               | 32.4               | 95.1                         | -1.9               |
| Missing                        | 0                      | 0                  | 0                       | 0                  | 0                       | 0                  | 0                       | 0                  | 0                                      | 0                  | 0                                   | 0                  | 0                            | 0                  |

Note: Baseline presented are period specific according to the Dose levels.

Table 7  
Number (%) of Subjects with HR ≤ 40 bpm by Dose Group and Combined Placebo and by Timepoint and for All Postdose Timepoints Combined

| Timepoint              | Drug A 75 mg<br>(N=12)<br>n (%) | Drug A 150 mg<br>(N=12)<br>n (%) | Drug A 450 mg<br>(N=12)<br>n (%) | Drug A 900 mg<br>(N=12)<br>n (%) | Drug A 150 mg<br>+ Drug B<br>(N=12)<br>n (%) | Drug A 300 mg<br>+ Drug B<br>(N=12)<br>n (%) | Combined<br>Placebo<br>(N=4)<br>n (%) |
|------------------------|---------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------------------|----------------------------------------------|---------------------------------------|
| Baseline               | 0                               | 0                                | 0                                | 0                                | 0                                            | 0                                            | 0                                     |
| 0.5 Hours Postdose     | 0                               | 0                                | 0                                | 0                                | 0                                            | 0                                            | 0                                     |
| 1 Hours Postdose       | 0                               | 0                                | 1 ( 8.3)                         | 0                                | 0                                            | 0                                            | 0                                     |
| 1.5 Hours Postdose     | 1 ( 8.3)                        | 0                                | 0                                | 0                                | 0                                            | 0                                            | 0                                     |
| 2 Hours Postdose       | 0                               | 0                                | 0                                | 1 ( 8.3)                         | 0                                            | 0                                            | 0                                     |
| 3 Hours Postdose       | 0                               | 0                                | 0                                | 0                                | 0                                            | 0                                            | 0                                     |
| 4 Hours Postdose       | 0                               | 0                                | 0                                | 0                                | 0                                            | 0                                            | 0                                     |
| 5 Hours Postdose       | 0                               | 0                                | 0                                | 0                                | 0                                            | 0                                            | 0                                     |
| 6 Hours Postdose       | 0                               | 0                                | 0                                | 0                                | 0                                            | 0                                            | 0                                     |
| 7 Hours Postdose       | 0                               | 0                                | 0                                | 0                                | 0                                            | 0                                            | 0                                     |
| 8 Hours Postdose       | 0                               | 0                                | 1 ( 8.3)                         | 0                                | 0                                            | 1 ( 8.3)                                     | 0                                     |
| 10 Hours Postdose      | 0                               | 0                                | 0                                | 0                                | 0                                            | 0                                            | 0                                     |
| 12 Hours Postdose      | 0                               | 0                                | 0                                | 0                                | 0                                            | 0                                            | 0                                     |
| 24 Hours Postdose      | 0                               | 0                                | 0                                | 0                                | 0                                            | 0                                            | 0                                     |
| All Times Postdose [1] | 1 ( 8.3)                        | 0                                | 2 ( 16.7)                        | 1 ( 8.3)                         | 0                                            | 1 ( 8.3)                                     | 0                                     |

Note: Number (%) of Subjects satisfying the criteria presented are period specific according to the Dose levels.

[1] - Number of Subjects satisfying the criteria at least once anytime during post dose timepoints.

- Latency in the lead time i.e. between the initiation of the programming activity and the execution can be put to best use
- Customary things i.e. the acquaintance with the study documents, dataset generations and TLF creations can be done almost to a lion's share before the actual data arrives
- Will help the programmers in developing the programming skills as the proposed approach is not data driven
- In a nut shell this proactive approach is defensive, dynamic and robust enough to encounter extreme values, missing data and large volume of data

