Data Doesn't Lie – Real Time Monitoring and Projecting on Clinical Trial Enrollment Progression

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ABSTRACT

Determining enrollment target and projecting realistic enrollment rates are challenging in conducting a clinical trial. Underperforming participant recruitment has been a long-time problem for clinical trials. To address the question whether the ongoing recruitment will enable a trial to reach the planned target number fast enough while staying within budget, the real-time monitoring is key to a successful trial. This paper shows how to use SAS® to automatically visualize the dynamic accrual progression, and simultaneously make a data-driven projection on the accrual rate and the completion date of enrollment target. This real data driven projection can work as a reference for the study team and sponsors to make necessary future amendment to enrollment planning and timeline scheduling.

INTRODUCTION

Determining and projecting realistic enrollment rates is one of the most challenging aspects of conducting a clinical trial. Ninety percent of worldwide clinical trials were delayed due to under-performing participant recruitment. Study timelines are typically extended to nearly double their original duration to meet desired enrollment levels for all therapeutic areas. Among the reasons that delay the recruitment, the optimism bias in clinical trial recruitment can lead to underutilized staff, which is always the biggest expense of a clinical trial. For grant-funded research, recruitment delays can jeopardize the research effort, the failure to reach target sample size post the run-out-of-funding would result in amending the eligibility criteria to meet the enrollment goal. Another "wait-and-see" approach occurs to researchers although they are aware of that 90% of clinical trials are delayed due to recruitment but they assume that their clinical trial would fall into the other 10% of trials not to be delayed in recruitment.

To proactively prevent recruitment disaster that might result from overestimation based on intuition, it is critical for research institute to both build effective pre-recruitment strategies and keep closely monitoring the progress in participants recruitment and the rate of participants drop-out due to exclusion or early termination at each stage of the typical enrollment. The derived real time data driven projection on enrollment rate and completion date of enrollment target make it possible to fit the real-time enrollment funnel model and make appropriate updates in the enrollment plan to meet the final enrollment goal.

SAS® procedures and MACRO facility make it easy to automatically report the recruitment/enrollment data and visualize the progress of study accrual to help the study team get updated timely on the issues occurred in screening, randomization/intervention, subject-specific protocol deviation and early termination, which may have the negative impact on a successful fulfillment of the enrollment goal. The SAS/STAT procedures are useful tools to help generate the projected target completion date and forthcoming rate in trial enrollment.

In this paper we present examples using SAS® to keep track of a multi-site clinical trial study accrual by real-time monitoring raw eCRF data and to make the projection on study enrollment target completion, which can be used as the reference for sponsors to identify and prevent possible under-enrollment in the trial.

CASE STUDY 1: USING METRICS TO MONITOR STUDY ACCRUAL

This section shows using SAS® to track participants enrollment.

INTRODUCTION TO CLINICAL TRIAL WORKFLOW

Figure 1 is the representation of a typical clinical trial enrollment process once the clinical site is activated with the determined maximum number of participants. The screening process evaluates potential participants for their eligibility to take part in a study. The enrollment and randomization processes register participants into a clinical trial, assigning them to the appropriate treatment arm. Once participants are enrolled, they can receive the assigned study product or intervention
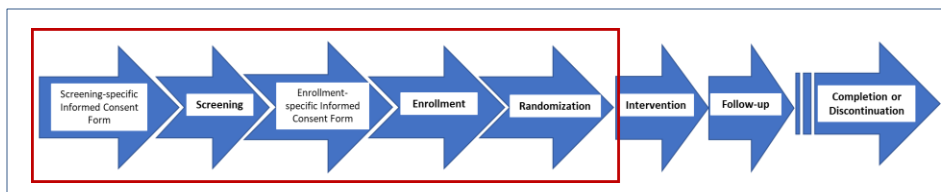
Figure 1. Schematic Illustration of Typical Clinical Trial Workflow Post Site Activation

METRICS REPORT TO REPRESETN ENROLLMENT ACCRUAL

The Case Report Forms (CRFs or eCRFs) such as Screening Failure Checklist (SFC), Enroll (ENR), Demographic (DEM), Consent Agreement (CS), Visit Documentation (VD) are to be used to retrieve the real time data for Trial Metrics Report. As shown in Figure 2 the example trial accrual report to monitor study accrual at each individual trial site as well as the allover accrual, the study team can keep updated with the accumulation in screening failures, average enrollment ready for randomization each week. To make SAS® programming more efficient, a derived comprehensive dataset has been generated and used for programming, which includes all useful variables from multiple different types of eCRF, such as participant's ID, start date of screening, date when the participant was determined to be a screening failure, whether to meet the eligibility criteria, and what this criterion is, etc.

Site	Number of Subjects enrolled for screening	Number of Screen Failures	Number of Subjects in Screening	Number of Subjects Randomized	First Screening Date	Most Recent Screening Date	Most recent Randomization Date	Duration of Accrual (Weeks)	Average Subjects Randomized per Week	Percent Randomized (Based on the Target)
All Participants (Target = 450)										
Site A	6	-	-	6 (100%)	06MAY2021	22MAR2022	29MAR2022	98	0.1	0.2%
Site B	7	1 (14.3%)	-	6 (85.7%)	04MAY2022	05AUG2022	19AUG2022	46	0.1	0.2%
Site C	22	7 (31.8%)	-	15 (68.2%)	24MAY2021	03AUG2022	17AUG2022	95	0.3	3.3%
Site D	22	8 (36.4%)	-	14 (63.6%)	06OCT2021	02AUG2022	17AUG2022	76	0.2	3.1%
All Sites	57	16 (28.1%)	-	41 (71.9%)	06MAY2021	05AUG2022	19AUG2022	98	0.7	9.1%

Table 1. Metrics Report – Study Accrual by Site

GRAPHS TO REPRESENT ENROLLMENT FUNNEL

In addition, by creating a dataset with the average drop-out rate for each of the different stages of enrollment, we can generate the graph to represent the enrollment funnel for randomized participants at each site. Based on the example graph shown in Figure 3, Site A and B need to screen about 150 participants for ~70 enrollments ready for randomization, whereas Site C and D demonstrate a lower drop-out rate. By comparing the graphs of Enrollment Funnel, it makes it easy to compare the performance of different site in trial recruitment.

In the case of clinical trial study of different protocols, the real data driven enrollment funnel can help determine whether the trial is an average or difficult study regarding participants recruitment, but also forecast how many recruitments would need at top of the recruitment funnel in order to hit the enrollment/randomization goal.
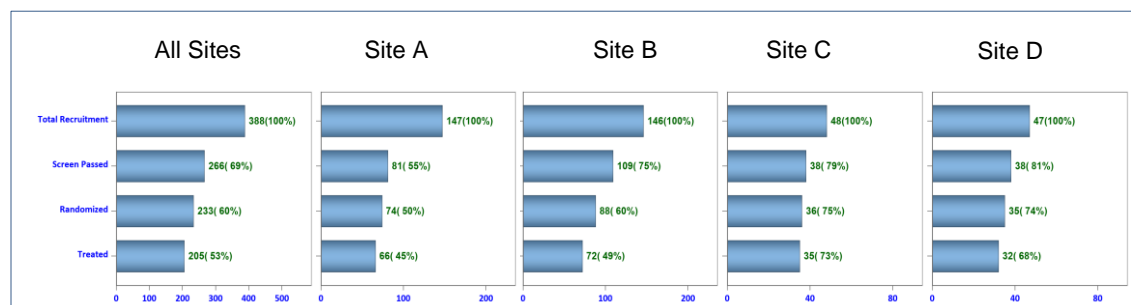
Figure 2. Enrollment Funnel for each site or overall

EXAMPLE DATASET AND SAS PROGRAM TO GENERATE THE GRAPH OF ENROLLMENT FUNNEL

Following is an example dataset read in by the example SAS® program used to generate the Enrollment Funnel.

	COUNT	PERCENT	CAT	txt
1	147	100	0	147(100%)
2	81	55.102040816	1	81(55%)
3	74	50.340136054	2	74(50%)
4	66	44.897959184	3	66(45%)

VIEWTABLE: Work.Temp

```
proc format;
      value catf 0="Total Recruitment"
                 1="Screen Passed"
                 2="Randomized"
                 3="Treated";
run;
%macro enrfunnel(dsn);
   proc sgplot data=&dsn.;
        format cat catf.;
        hbarparm category=CAT response=COUNT
              / dataskin=Pressed datalabel=txt
                datalabelpos=data
                datalabelattrs=(color=darkgreen Family="Arial" size=14 Weight=bold
style=normal)
                barwidth=0.7;
        xaxis display=(nolabel) offsetmin=0 offsetmax=0.15
           valueattrs=(size=14 weight=Bold color=blue)values=(0 to 200 by 100);
        yaxis display=(nolabel) offsetmax=0.15 offsetmin=0.15
           valueattrs=(size=14 weight=Bold color=blue);
   run;
%mend enrfunnel;
%enrfunnel(temp)
```

CASE STUDY 2: PROJECTION ON COMPLETION DATE TO MEET ENROLLMENT TARGET

This section introduces SAS® program to generate graphs to keep track of the progress in randomization and the projected data driven enrollment completion date.

This SAS® program is composed of three components, as shown in Figure 4. The first macro is to use FREQ procedure to get the cumulative enrollment by each group and date. The second macro is using GLM procedure (as an example) to predict the date to meet the required enrollment target for randomization. The third macro is to use SGPLOT procedure to generate the graph. Figure 5 is an example output to visualize the enrollment progress and the estimated completion date, 05JUL2022, based on the average enrollment observed More details can be found in the following SAS® program with an example dataset included.
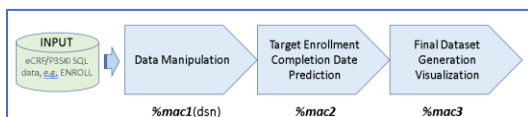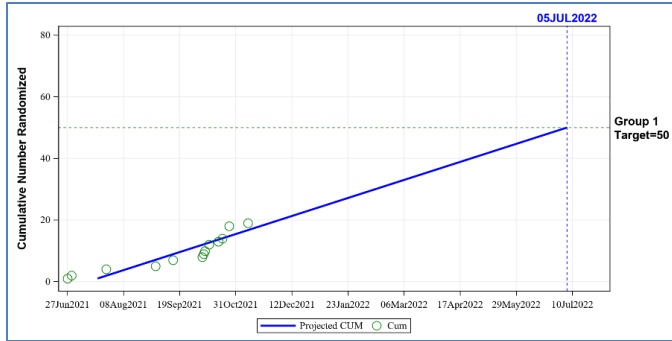

Figure 3. Flowchart of SAS® program to track study accrual and to make projection on enrollment target completion date

Figure 4. Enrollment Progress and Projection on the Target Completion Date

EXAMPLE CODE TO GENEREATE GRAPH OF THE ENROLLMENT PROGRESS MARKED BY PROJECTED ENROLLMENT COMPLETION DATE TO MEET THE ENROLLMENT TARGET

Following is an example dataset Temp read in by the example SAS® program

	Grp	STARTDT	COUNT	Cum	grpc
1	1	27JUN2021	1	1	1
2	1	30JUN2021	1	2	1
3	1	26JUL2021	2	4	1
4	1	01SEP2021	1	5	1
5	1	14SEP2021	2	7	1
6	1	06OCT2021	1	8	1
7	1	07OCT2021	1	9	1
8	1	08OCT2021	1	10	1
9	1	11OCT2021	2	12	1
10	1	18OCT2021	1	13	1
11	1	21OCT2021	1	14	1
12	1	26OCT2021	4	18	1
13	1	09NOV2021	1	19	1

```
/*PART 1: Add new variable _grp.
        _grp="projected" when CUM=50, the Target Enrollment */
proc sort data=temp;
    by grp STARTDT;
run;
data temp1;
    format _grp $9.;
    set temp;
       by grp STARTDT;
       _grp="observed";
       output;
       if last.grp then do;
          STARTDT=.;
             COUNT=.;
             CUM=50;
             _grp="projected";
             output;
       end;
run;
/*PART 2: Use GLM to fit the Model Stardt = CUM.
        Predicted value is the projected completion data for the Enrollment Target, says CUM=50*/
ods output ParameterEstimates=pars;
Proc GLM data=temp1;
     Model startdt=cum;
     output out=temp2 predicted=fit;
run;
quit;
ods output close;
data temp3;
    format _grp $9. fit date9.;
    set temp2;
    _grp="projected";
    startdt=fit;
    output;
```

4

```
        keep _grp grp grpc STARTDT CUM;
run;
/*PART 3: Combine two datasets _grp="observed" and _grp="projected". Output the graph. */
data temp4;
        set temp2(where=(_grp="observed"))
            temp3(rename=(CUM=pCUM));
run;
proc sql noprint;
        /*To assign the predicted completion date to macro variables */
        select STARTDT format=f5. into: projdt_1  trimmed
               from temp4
               where _grp in("projected") and grp=1 and pCUM=50;
        select STARTDT format=date9. into: projdt_1c  trimmed
               from temp4
               where _grp in("projected") and grp=1 and  pCUM=50;

        select min(STARTDT) format=f5.0 into: min_dt  trimmed  from temp4;
        select max(STARTDT) format=f5.0 into: max_dt  trimmed  from temp4;
quit;
ods graphics on;
proc sgplot data=temp4;
        label pCUM="Projected CUM";
        series  x=STARTDT y=pCUM /lineattrs=(thickness=3 color=blue   pattern=solid);
        scatter x=STARTDT y=CUM  /markerattrs=(size=13 color=green  symbol=circle);
        refline 50/axis=y LINEATTRS=(pattern=shortDash color=green ) label=('Group 1 Target=50')
                    labelattrs=(size=8 weight=bold family=arial)
                    LABELLOC = outside LABELPOS=MAX splitchar="*";
        refline &projdt_1/axis=x LINEATTRS=(pattern=shortDash color=blue ) label=("&projdt_1c")
                    labelattrs=(size=8 weight=bold family=arial color=blue)
                    LABELLOC = OUTSIDE LABELPOS=max;
        xaxis display=(nolabel) VALUES= (&min_dt to %eval(&max_dt+30) by 7) grid;
        yaxis label = 'Cumulative Number Randomized'   values=(0 to 80 by 20) grid;
run;
ods graphics off;
```

CONCLUSION

Underperforming participant recruitment is a long-time problem for clinical trials. Determining enrollment target and projecting realistic enrollment rates are challenging in conducting a clinical trial. In this paper we present examples using SAS® to keep track of study accrual by generating the metrics report, enrollment funnel graph, and making projection on the date to meet study enrollment target, to help sponsors identify and prevent under-enrollment.

CONTACT INFORMATION

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

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