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Establish the Maximum Tolerated Dose in Phase-I Trials using 3+3 Method

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ABSTRACT

The main goal of Phase-I cancer clinical trials is to find the maximum tolerated dose (MTD) of a drug for Phase-II trial for a specific mode of administration. In Phase-I trials there is a critical need to establish MTD by using minimum possible number of patients so as to avoid exposing too many patients to sub-therapeutic doses while preserving safety and maintaining rapid accrual.

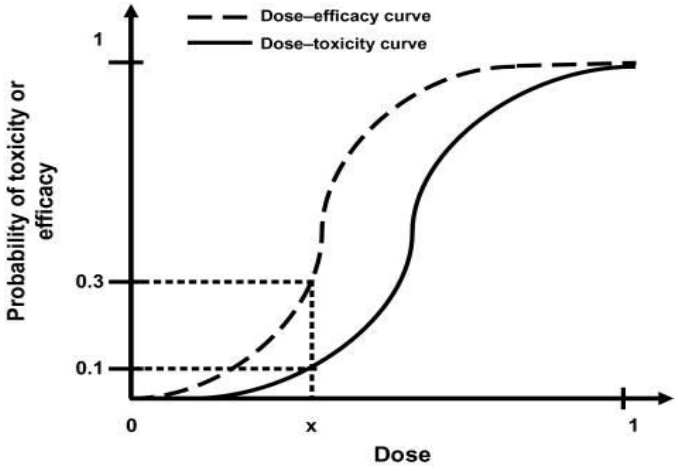
3+3 is a popular rule based design that allows dose escalation and de-escalation based on the number of dose-limiting toxicities observed in a cohort of 3 patients. Its straightforward algorithm and logistical simplicity for the clinical investigators to carry out make it the most widely practiced design for Phase-I trials. This paper explains the 3+3 method along with its advantages and shortcomings. The paper also presents a SAS® macro for simulating a Phase-I clinical trial to determine MTD using the 3+3 design.

INTRODUCTION

The purpose of this paper is to introduce the audience to phase-I oncology trials, in particular to the 3+3 design, a rule based design that is widely used in such trials for determination of the Maximum Tolerated Dose.

Phase-I trials are the first stage of testing experimental drugs/treatments in human subjects where an attempt is made to establish the dose range tolerated by volunteers for single or multiple doses and to determine whether a drug is safe to check for efficacy. Phase-I trials often include healthy volunteers, however; there are some circumstances when real patients are used, such as oncology trials where standard treatment options have been exhausted or when the treatment is likely to make healthy individuals ill. These trials include dose-ranging, also called dose escalation studies, so as to find the best and safest dose-level and to discover the dose-level at which a treatment is too poisonous to administer. This dose-level is called the Maximum Tolerated Dose (MTD) which is further used in phase-II trials. MTD refers to the highest dose of a radiological or pharmacological treatment that will produce the desired effect without unacceptable toxicity. The major difficulty in designing and conducting a phase-I trial is the ethical requirement that the number of patients in the trial who experience toxicity must be limited. For this reason, and because little is known about the actual relationship between dose and the risk of toxicity at the start of the trial, phase-I trials must be conducted adaptively.

This paper would restrict the discussion of finding MTD using 3+3 design, to cytotoxic agents for which the assumption is that a higher dose increases both the probability of toxicity and the probability of any anticancer effect. Since phase-I dose finding typically is concentrated more on toxicity, the former assumption is given more priority than the latter. Thus, the motive of dose escalation is to find a dose that achieves a tolerable toxicity level and that has some efficacy potential. This is the general idea that motivates design methods with an aim to find the MTD.



The adjoining figure represents a typical dose-toxicity and dose-efficacy curve for cytotoxic agents.

It illustrates that at dose x, the probability of efficacy is 0.3 and the probability of toxicity is 0.1.

DOSE ESCALATION

The principle aim of dose escalation in phase-I trials is to minimize the number of patients allocated to excessively toxic doses, while identifying the MTD. In phase-I oncology trials the drug is examined in the target population of diseased patients. Subjects included in these trials often suffer from advanced cancer, and may have often exhausted the standard treatment options. Therefore in addition to the appropriate detection of the MTD, dose escalation designs should enroll the majority of subjects to therapeutic levels of the drug, while controlling the numbers of toxic events. These competing objectives for dose escalation designs make it unlikely that one design or methodology will be the best in all circumstances. The selection of the dose escalation strategy has an impact on the recommended dose level and inadequate dose escalation schemes may put the whole drug development program at risk.

Dose escalation methods for phase-I oncology trials fall into two broad classes: the rule-based designs and the model-based designs. The rule-based designs assign subjects to dose levels according to pre-specified rules based on actual observations of target events (e.g., dose-limiting toxicity or DLT) and the MTD or recommended dose for phase-II trials is also determined using some pre-specified rules. On the other hand, the model-based designs assign subjects to dose levels and define the recommended dose for phase-II trials based on the estimation of the target toxicity level by a model depicting the dose-toxicity relationship.

RULE-BASED DESIGN

The main characteristic of rule-based designs is that they do not stipulate any prior assumption of the dose-toxicity curve. These designs comprise of the so-called “up-and-down” designs as they allow dose escalation and de-escalation. The general principle of this design is to escalate or de-escalate the dose with diminishing fractions of the preceding dose depending on the absence or presence of severe toxicity in the previous cohort of treated subjects. Typically, a small group of subjects is treated at gradually escalating doses of the drug in question. Escalation continues until the number of subjects experiencing a given degree of toxicity meets some set criterion, at which point the stopping dose or the next lower dose is considered as the MTD. The first rule-based design to be used widely in clinical practice is the traditional 3+3 design.

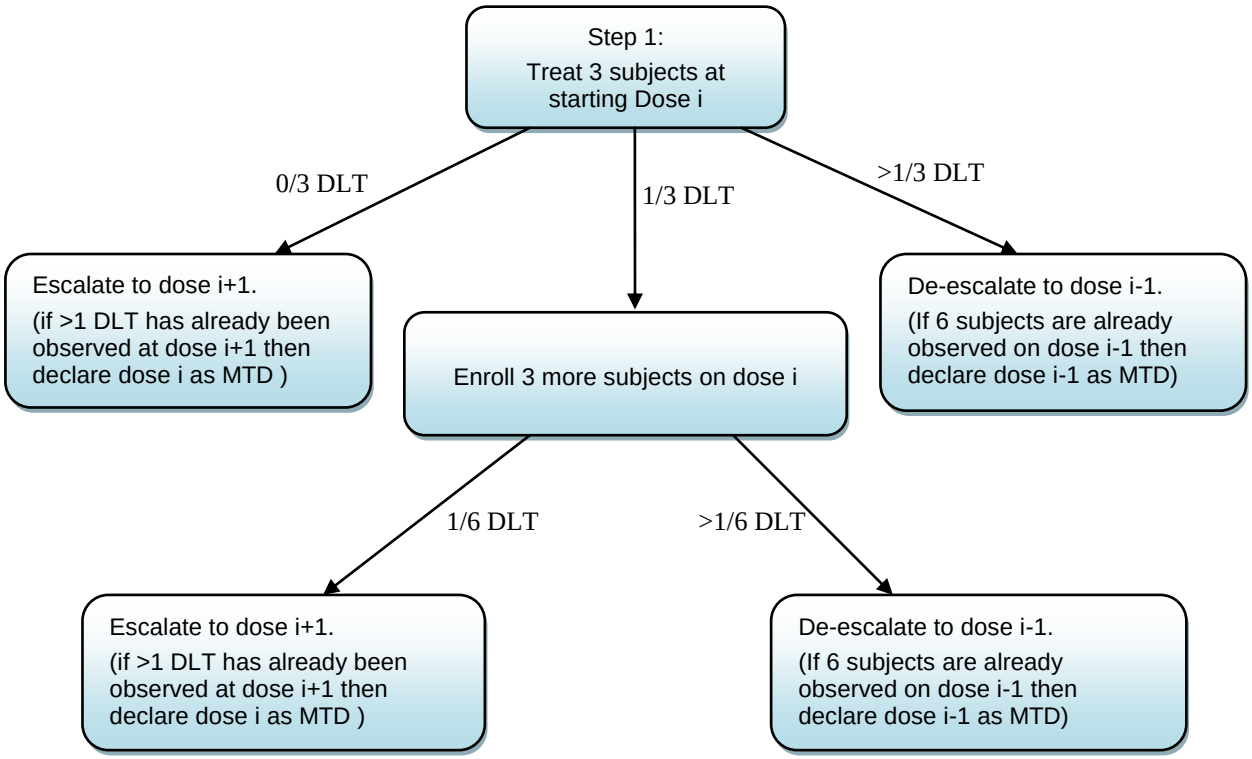
For determination of the MTD, there is a danger that model-based designs may be perceived to be something of a `black box' in which the process underlying the recommendations is not transparent and to improve the understanding of the methodology one would require a closer co-operation between the investigators of the trial and the statistician at the design stage. In contrast, a rule-based design requires no modeling of the dose-toxicity curve beyond the classical assumption for cytotoxic drugs.

3+3 DESIGN

The main reason for the popularity of the 3+3 design results from its straightforward algorithm and logistical simplicity for the clinical investigators to carry out, whereas most model based designs often require considerable logistic burden and complexity to implement.

The 3+3 design consists of a set of deterministic rules that dictate dose escalation or de-escalation decisions based on observed patient outcomes (DLT).The traditional 3+3 design proceeds with cohorts of three subjects; where the first cohort is treated with a starting dose which is considered safe based on extrapolation from animals toxicological data or from past experience, and the subsequent cohorts are treated at dose levels that have been fixed in advance.

Below is a schematic of a traditional 3+3 design where the maximum-tolerated dose (MTD) is defined as the highest dose at which not more than one dose-limiting toxicity(DLT) is observed among six subjects.

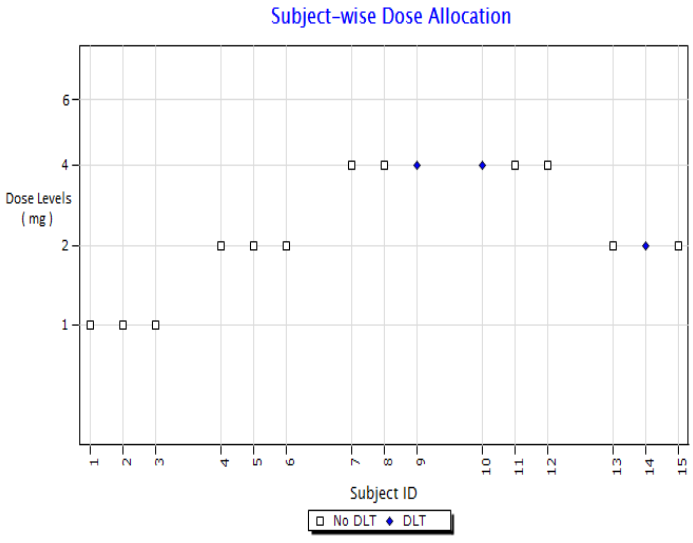


CASE STUDY

Let us look at a study that was conducted to determine the MTD of HB-110 and assess the safety, immunogenicity and efficacy of HB-110 DNA therapeutic vaccine administered by Electroporation in combination with Entecavir in chronic hepatitis B patients.

The 3+3 design was used to reach the MTD. Subjects were enrolled and treated in cohorts of three and each were observed for a minimum of 28 days before the next group of patients would be enrolled and receive the study drug. Each subject was administered HB-110 by Electroporation based on the protocol and one pill of Entecavir (0.5 mg) per day during the study period.

The dose-levels of HB-110 used were 1 mg, 2mg, 4mg and 6mg and it was believed that the probability of toxicity at the dose levels were 0.1, 0.2, 0.35 and 0.45 respectively.



The adjoining figure shows us how the dose-levels were escalated and de-escalated based on the DLTs observed among 3 subjects in each cohort using the above specified algorithm.

The 1st cohort was treated at a starting dose of 1mg where no DLTs were observed. The 2nd cohort also observed no DLT which was treated at a higher dose-level of 2mg. The third cohort was treated on a dose-level of 4mg on which 1 DLT was observed and so another set of three subjects were treated on the same dose-level. Now it was observed that out of the total six subjects 2 DLTs were observed and thus the next cohort was treated on a de-escalated dose-level of 2mg. A set of three subjects had already been treated on this dose level and of the three new subjects 1 DLT was observed. And as per the pre-specified rules of 3+3 design we declare this dose-level of 2mg as MTD.

SAS® MACRO FOR SIMULATING 3+3 DESIGN:

The appendix contains a SAS® Macro which simulates a 3+3 design using the algorithm as specified in the above schematic diagram. The purpose of this macro is to identify the dose level most likely to be the MTD.

The macro requires the following inputs

- SAS® dataset in the work directory with the name 'dose_escalation'
  The 'dose_escalation' dataset must contain the following columns;
  DOSEID : serial numbers specifying the different doses
  DOSEVALUE : actual dose level
  PROB : probability of toxicity corresponding to each dose level
  Note that the dose levels specified in the dataset must be strictly in increasing order.
- Starting Dose: the DOSEID corresponding to the starting dose level, i.e. the dose level assigned to the first cohort of subjects.
- Number of Simulations: the total number of simulations of the trial to be run.
- Sample Size: the maximum sample size that must be used in each simulation of the trial.

ILLUSTRATION:

Input dataset: 'dose_escalation'

	DOSEID	DOSEVALUE	PROB
1	1	1	0.1
2	2	2	0.2
3	3	4	0.35
4	4	6	0.45

Running the Macro with the above input datset and with a starting dose =1 and maximum sample size = 30, with 1000 simulations would produce an Output dataset named 'Simulation_summary' as shown below.

Output dataset: 'Simulation_summary'

	DoseLevels	count	%
1	1	314	31.4
2	2	372	37.2
3	4	157	15.7
4	6	0	0
5	MTD below lowest Dose	89	8.9
6	MTD above highest Dose	68	6.8
7	Inadequate SS	0	0

The output dataset contains the number of times a dose was selected as MTD and the corresponding percentage. In addition, it also provides the count and percentage of simulations in which an MTD was not obtained, along with the reason. In addition to this the macro provides the simulation-wise details of number of subjects and DLTs observed on each dose.

In the current illustration it is observed that dose-level 2mg has been selected as the MTD most of the times (372 times of 1000). From the Output it is observed that dose-level 2mg approximately has a 37% chance of being the MTD. The macro can be used to confirm our selection of MTD that we have done in the trial.

ADVANTAGES AND DISADVANTAGES OF 3+3 DESGN

The main advantages of the traditional 3+3 design is that it has a simple and intuitive algorithm which is easy to understand and implement and no assumptions related to dose-response curve are required. In addition, the accrual of three subjects per dose level provides additional information about pharmacokinetic inter-patient variability.
3+3 design is often used as a starting step before moving over to more complex dose-escalation designs.

However, the design has been widely criticized for being inefficient and inflexible due to escalation and de-escalation decisions being based on outcomes from only the most recently recruited subjects. The other disadvantage of this design is that it involves an excessive number of escalation steps, which results in a large proportion of subjects who are treated at low (i.e., potentially sub-therapeutic) doses while few subjects actually receive doses at or near the recommended dose for phase II trials.

VARIATIONS IN 3+3 DESIGN

The 3+3 design discussed in this paper is known as '3+3 L'. There are other variations to this 3+3 design which can be used as per our design requirement. Alternative rules besides "3+3 L" that have been proposed include the "3+3+3," and "3+1+1" ("best of five") rules.

- In the "3+3+3" design, a third cohort of three subjects is added if two of six subjects in the first two cohorts experience a DLT at a certain dose level. The trial terminates if at least three of nine subjects experience a DLT.
- The "best of five" design is a more aggressive than the traditional 3+3 design where one additional patient is added if one or even two DLT are observed among the first three subjects. Another patient is added if two DLTs are observed among the four treated subjects. Dose escalation is allowed if DLTs are observed among none of three, one of four, or two of five subjects, but the trial will terminate if three or more DLTs are observed.

CONCLUSIONS

Although there are a host of other, more efficient design methods which can be used to determine the MTD in phase-I clinical trials, 3+3 remains the most popular method among clinicians and researchers. This is largely due to its simple concept and operational ease. It can be implemented without any complex statistical considerations and computations. The operating characteristics of the design method can be studied with the help of simulations. In addition 3+3 design is used as a starting step for carrying out more complex designs.

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APPENDIX

Macro for simulating a 3+3 design

```
data dose_escalation;
input DOSEID DOSEVALUE PROB;
datalines;
1 1 0.1
2 2 0.2
3 4 0.35
4 6 0.45
;
run;

%MACRO MTD_3x3(treatment=1,no_sim=10,sample_siz=30,sort=);
%macro a; %mend a;
options spool ;;
proc sql noprint;
select distinct strip(put(max(doseid),best.)) as d, strip(put(max(dosevalue)+1,best.)) as dd
into :maxtrt , :maxval
from work.dose_escalation ;
quit;

data trtx1;
set work.dose_escalation(rename= (doseid=_doseid dosevalue=_dosevalue prob=_prob)) end=a;
array did[&maxtrt] did1 - did&maxtrt;
array didv[&maxtrt] didv1 - didv&maxtrt;
array prob[&maxtrt] prob1 - prob&maxtrt;
array ss[&maxtrt] ss1 - ss&maxtrt;
array dlt[&maxtrt] dlt1 - dlt&maxtrt;

do i=1 to dim(did);
retain did: ss: dlt: prob:;

if _n_ = i then did[i]= _doseid;
if _n_ = i then didv[i]= _dosevalue;
if _n_ = i then prob[i]=_prob;
if _n_ = i then ss[i]=0;
if _n_ = i then dlt[i]=0;
end;

if a;
drop _: i;
run;

data Simulation_Detail;
stop;run;
%do t= &treatment %to &treatment;
%do sim= 1 %to &no_sim;
data work.trt&t._&sim.;
length rsn_stop mtd $25 sum_ss start i 8;
set  work.trtx1;

array did[&maxtrt] did1 - did&maxtrt;
array didv[&maxtrt] didv1 - didv&maxtrt;
array prob[&maxtrt] prob1 - prob&maxtrt;
array ss[&maxtrt] ss1 - ss&maxtrt;
array dlt[&maxtrt] dlt1 - dlt&maxtrt;

start =&t ;
do i= 1 to dim(did)+1;
i = start;

resp = rand('bernoulli',prob[i]) + rand('bernoulli',prob[i])  + rand('bernoulli',prob[i]);
ss[i]=ss[i]+3;
```

```
dlt[i]+resp;
sum_ss = sum (of ss:);

if sum_ss > &sample_siz then
do; *---------------Checking Sum of all SS is greater then sample_siz or not------------------*;
rsn_stop = "Sum of sample size is gt &sample_siz";
mtd = "Inadequate SS";
i= dim(did) +1;
end; /* end loop of, if sum_ss > &sample_siz then */

else
do;
if ss[i] = 3 then
do; *------------------------Checking DLT is 0 or not---------------------------------*;
if    dlt[i]= 0 then
do; *----------Checking current treatment is last treatment or not------------*;
if i = dim(did) then
do;
mtd = "MTD above highest Dose";

rsn_stop=   "SS of trt "||strip(put(start,best.))||" = 3 and DLT of trt"||strip(put(start,best.))||
          " = 0 and it's last treatment, so MTD shold be [MTD above highest Dose]";
i= dim(did) +1 ;
end; /* end loop of, if i = dim(did) then */

else
do; *---------------Checking for DLT of next treatment----------------*;

if dlt[i+1] ge 2 then
do;

rsn_stop = "SS of trt "||strip(put(start,best.))||" = 3 and DLT of trt "||
          strip(put(start,best.))||" = 0 and it's not a last trt and DLT"||
          " of next trt is "||strip(put(dlt[i+1],best.))||
          ", so re-run cycle again for same treatment "||strip(put(start,best.));
start = i;
i=i;
end; /* end loop of, if dlt[i+1] ge 2 then */

else
do;
rsn_stop=   "SS of trt "||strip(put(start,best.))||" = 3 and DLT of trt "||
          strip(put(start,best.))||" = 0 and it's not a last trt and DLT"||
          " of next trt is "||strip(put(dlt[i+1],best.))||
          ", so re-run cycle again for next treatment "||strip(put(start,best.));

start = i +1;
i=1;
end; /* end loop of, if dlt[i+1] ge 2 then# else */

end; /* end loop of, if i = dim(did) then # else */

end; /* end loop of, if dlt[i]= 0 then */

else if  dlt[i] = 1 then

do; *-------------------------Checking DLT is 1 or not-------------------------*;
rsn_stop =  "SS of trt "||strip(put(start,best.))||" = 3 and DLT of trt "||strip(put(start,best.))||
          " = 1, so re-run cycle again for same treatment "||strip(put(start,best.));

start = i;
i=i;
end; /* end loop of, else if  dlt[i] = 1 then */

else if  dlt[i] > 1 then
```

```
do; *--------------------Checking DLT is greater then 1 or not-----------------*;
if    i = 1 then
do; *--------------Checking treatment is first or not-----------------*;
mtd = 'MTD below lowest Dose';
rsn_stop =  "SS of trt "||strip(put(start,best.))||" = 3 and DLT of trt "||strip(put(start,best.))||
          " in (2,3) and it's first treatment, so stop the step with MTD value [MTD below lowest Dose]";

i= dim(did) +1;
end; /* end loop of, if i = 1 then */

else
do; *-----------------Checking treatment is not first-----------------*;

if ss[i-1] = 6 then
do;*--Checking sample size of previous treatment is 6 or not--*;
mtd = strip(put(didv[i-1],best.));
rsn_stop =  "SS of trt "||strip(put(start,best.))||" = 3 and DLT of trt "||
          strip(put(start,best.))||" in (2,3) and it's not a first treatment "||
          "and the value of previous treatment is "||strip(put(SS[i-1],best.))||
          ", so stop the cycle with MTD value ["||strip(put(didv[i-1],best.))||"]";

i= dim(did)+1;
end; /* end loop of, if ss[i-1] = 6 then */

else
do;*----------Sample size of previous treatment not 6-------*;


rsn_stop =  "SS of trt "||strip(put(start,best.))||" = 3 and DLT of trt "||
          strip(put(start,best.))|| " in (2,3) and it's not a first treatment "||
          " and the value of previous treatment is "||strip(put(SS[i-1],best.))||
          " not 6, so re-run cycle for previous treatment";

start = i - 1;
i=1;

end; /* end loop of, if ss[i-1] = 6 then # else */

end; /* end loop of, if       i = 1 then # else */

end; /* end loop of, else if  dlt[i] > 1 then */

end; /* end loop of, if ss[i] = 3 then */

else if ss[i] = 6 then
do;

if    dlt[i]= 0 then
do; *----------------------Checking DLT value is 0 or not---------------------*;

mtd = strip(put(didv[i],best.));

rsn_stop =  "SS of trt "||strip(put(start,best.))||" = 6 and DLT of trt "||
          strip(put(start,best.))|| " = 0, so stop the cycle with MTD value ["||
          strip(put(didv[i],best.))||"]";

i= dim(did) +1 ;
end; /* end loop of, if dlt[i]= 0 then */

else if  dlt[i] = 1 then
do; *----------------------Checking DLT value is 1 or not---------------------*;

if i = dim(did) then
do; *---------------Checking treatment is last or not-----------------*;

mtd = "MTD above highest Dose";
```

```
rsn_stop =  "SS of trt "||strip(put(start,best.))||" = 6 and DLT of trt "||
            strip(put(start,best.))|| " = 0 and it's last treatment ,"||
            " so stop the cycle with MTD value [MTD above highest Dose]";

i= dim(did) +1 ;
end; /* end loop of, if i = dim(did) then */

else
do; *-----------------Checking treatment is not last -----------------*;

if dlt[i+1] ge 2 then
do; *--------Checking DLT of next treatment is 2 or not-------*;

mtd = strip(put(didv[i],best.));

rsn_stop = "SS of trt "||strip(put(start,best.))||" = 6 and DLT of trt "||
       strip(put(start,best.))|| " eq 1 and DLT of next treatment is ge 2 "||
       "so stop the step with MTD value ["||strip(put(didv[i],best.))||"]";

i= dim(did) +1 ;
end; /* end loop of, if dlt[i+1] eq 2 then */

else do; *---------Checking DLT of next treatment is not 2--------*;


rsn_stop =  "SS of trt "||strip(put(start,best.))||" = 6 and DLT of trt "||
            strip(put(start,best.))|| " eq 1 and it's not a last treatment, "||
            "so re-run cycle for next treatment";

start = i +1;
i=1;

end; /* end loop of, if dlt[i+1] eq 2 then # else */

end; /* end loop of, if i = dim(did) then # else */

end; /* end loop of, else if  dlt[i] = 1 then */

else if  dlt[i] eq 2 then
do; *-----------------Checking DLT of treatment is ge 2----------------*;

if i = 1 then
do; *-------------Checking treatment is first or not---------------*;

mtd = 'MTD below lowest Dose';
rsn_stop =  "SS of trt "||strip(put(start,best.))||" = 6 and DLT of trt "||
            strip(put(start,best.))||" eq 2 and it's first treatment "||
            ", so stop the step with MTD value [MTD below lowest Dose]";

i= dim(did) +1;
end; /* end loop of, if i = 1 then*/

else
do; *---------------Checking treatment is not first----------------*;


if ss[i-1] = 6 then
do;*--Checking sample size of previous treatment is 6 or not---*;
mtd = strip(put(didv[i-1],best.));
rsn_stop =  "SS of trt "||strip(put(start,best.))||" = 6 and DLT of trt "||
            strip(put(start,best.))||" eq 2 and it's not a first treatment "||
            "and the value of previous treatment is "||strip(put(SS[i-1],best.))||
            ", so stop the cycle with MTD value ["||strip(put(didv[i-1],best.))||"]";

i= dim(did)+1;
end; /* end loop of, if ss[i-1] = 6 then*/
```

```
else /*if ss[i-1] = 3 then*/
do; *--Checking sample size of previous treatment is 3 or not---*;
rsn_stop =  "SS of trt "||strip(put(start,best.))||" = 3 and DLT of trt "||
            strip(put(start,best.))|| " eq 2 and it's not a first treatment "||
            "and the value of previous treatment is "||strip(put(SS[i-1],best.))||
            " [not 3], so re-run cycle for previous treatment";

start = i - 1;
i=1;
end; /* end loop of, else ss[i-1] = 3 then*/

end;/* end loop of, if i = 1 then# else */

end;/* end loop of, else if  dlt[i] = 2 then*/

else if  dlt[i] gt 2 then
do; *-----------------Checking DLT of treatment is ge 2----------------*;

if i = 1 then
do; *-------------Checking treatment is first or not---------------*;

mtd = 'MTD below lowest Dose';
rsn_stop = "SS of trt "||strip(put(start,best.))||" = 6 and DLT of trt "||
            strip(put(start,best.))||" eq 2 and it's first treatment "||
            ", so stop the step with MTD value [MTD below lowest Dose]";

i= dim(did) +1;
end; /* end loop of, if i = 1 then*/
else
do; *---------------Checking treatment is not first----------------*;
if ss[i-1] = 6 then
do;*--Checking sample size of previous treatment is 6 or not---*;

mtd = strip(put(didv[i-1],best.));

rsn_stop =  "SS of trt "||strip(put(start,best.))||" = 6 and DLT of trt "||
            strip(put(start,best.))||" eq 2 and it's not a first treatment "||
            "and the value of previous treatment is "||strip(put(SS[i-1],best.))||
            ", so stop the cycle with MTD value ["||strip(put(didv[i-1],best.))||"]";

i= dim(did)+1;
end; /* end loop of, if ss[i-1] = 6 then*/

else
do; *--Checking sample size of previous treatment is 3 or not---*;
rsn_stop = "SS of trt "||strip(put(start,best.))||" = 3 and DLT of trt "||
            strip(put(start,best.))|| " eq 2 and it's not a first treatment "||
            "and the value of previous treatment is "||strip(put(SS[i-1],best.))||
            " [not 3], so re-run cycle for previous treatment";

start = i - 1;
i=1;

end; /* end loop of, else ss[i-1] = 3 then*/

end;/* end loop of, if i = 1 then# else */

end;/* end loop of, else if  dlt[i] gt 2 then*/

end;/* end loop of, else if ss[i] = 6 then*/

end; /* end loop of, if sum_ss > 30 then# else  */

end;/* end loop of, do i= 1 to dim(did)+1; */

run;
```

```
data Simulation_Detail;
length trt sim $25;

set Simulation_Detail trt&t._&sim.(in=a) ;

if a then do;
trt="&t";
sim= "&sim.";
end;

drop trt start i resp did: prob:;
run;
%end;
%end;

proc freq data=Simulation_Detail noprint;
table mtd/out= trtx ;
run;

data trt_dummy;
length mtd $25;
mtd= "MTD below lowest Dose";
output;

mtd ="MTD above highest Dose";
output;

mtd ="Inadequate SS";
output;
run;

data trt_mtd;
length mtd $25;
set dose_escalation(keep=dosevalue) trt_dummy;

if dosevalue ne . then mtd = strip(put(dosevalue,best.));
sort1= _n_;
run;

proc sql;
create table Simulation_Summary(drop= sort1 label="Simulation summary") as
select a.mtd  "DoseLevels"
, case when b.count = . then 0 else b.count end as count
, case when b.percent = . then 0 else b.percent end as percent "%"
, sort1
from trt_mtd as a
left join
trtx as b
on a.mtd=b.mtd
order by

%if %sysfunc(find("&sort",per,i)) %then %do; percent desc, %end;
sort1, mtd;
quit;

/*Delete extra data set from work*/
proc datasets library=work nowarn;
delete trt:;
run;
quit;
```

```
/*************** graphical representation of count of MTD.**********************;*/
*ods rtf gtitle bodytitle notoc_data file  = "/anup/output.rtf" headery = 50 footery  = 25 image_dpi = 90;

options orientation= landscape nonumber nodate byline center missing = "0" formchar = "__" ps=50 ls=180;
proc gchart data=work.Simulation_Summary;
where anydigit(mtd);
     vbar3d mtd /  sumvar=percent
     shape= hexagon
     type=sum
     coutline=black
     raxis=axis1
     maxis=axis2
     gaxis=axis3;
     axis1 label = (a=90 "%" f="Arial/bold" ) order=(0 to 100 by 10) value=(h=8pt);
     axis2 label = ("Dose Levels" f="Arial/bold" ) value=(h=8pt) ;
     goptions htext=13pt htitle=15pt gsfname=chrt12;
     title1 'Establish the Maximum Tolerated Dose in Phase I Trials using 3+3 Method';
run;
title;
footnote;

/***************Close graphic output files and write to disk.**********************;*/
/*ods rtf close;*/
/*ods graphics off;*/

ods rtf close;
ods graphics off;
%MEND MTD_3x3;

%MTD_3x3( treatment=1 , no_sim=1000 , sample_siz=30  /*, sort=*/ );
```