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# Using SAS to Calculate Statistical Properties of Traditional 3+3 Design

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## ABSTRACT

Traditional 3 + 3 design is a popular design thanks to its simplicity for both modeling and execution. Therefore, it is widely used in Phase I dosing escalation studies to help identifying the maximum tolerated dose(MTD) of a drug for a specific route of administration, it is also used to characterize the most frequent and dose-limiting toxicities, which in turn will be leveraged in Phase II studies design. This paper depicts how to use SAS® to compute and present statistics properties of the 3+3 design without de-escalation. The statistical properties include the likelihood of a dose being chosen as MTD, expected sample size at each dose level, expected dose-limiting toxicity(DLT) incidences at MTD, and both overall dose-limiting toxicities incidences and DLT incidences at each dose level. These statistics properties will help investigators to get some insight. The paper also tries to use SAS to simulate such a trial.



## KEYWORDS

Traditional 3+3 design, PROC IML, PROC SGPLOT, MTD, Expected sample size.

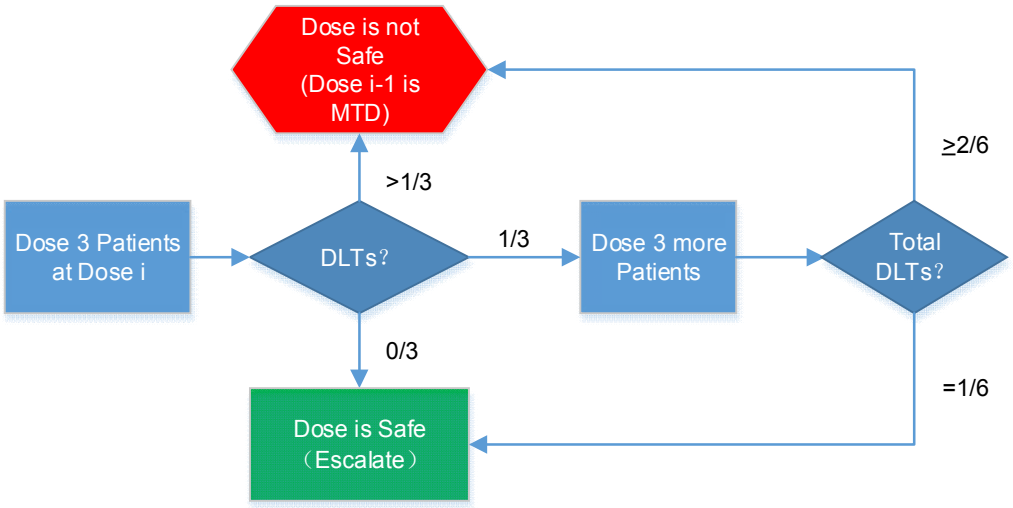

## INTRODUCTION

Traditional 3+3 design remains the widely-used method for conducting phase I cancer clinical trials that help to identify the most tolerable dose (MTD).The recommended dose for phase II trials is conventionally defined as the dose level just below this toxic dose level. This paper will present how to use SAS tools, like SAS/IML, SAS/SGPLOT, to calculate and visualize the statistical properties of the 3+3 design without de-escalation.it will also try to use SAS/IML to simulate such a trial to further explain and confirm these properties.

## TRADITIONAL 3 + 3 DESIGN WITHOUT DOSE DE-ESCALATION

Suppose that there are 3 subjects at dose level i. If less than 1/3 subjects have DLTs, then the dose is escalated to the next dose level i + 1. If more than 1/3 subjects have DLTs, then the previous dose i − 1 will be considered the MTD. If no less than 1/3, 3 more subjects are treated at this dose level i. If no more than 1 of the total of 6 subjects has DLTs, then the dose is escalated; If more than 1 of the total of 6 subjects has DLT, then the previous dose i − 1 will be considered as the MTD.

The schematic of a traditional 3+3 design without dose de-escalation shows the maximum-tolerated dose (MTD) is defined as the highest dose where no more than 1 DLT is observed among six subjects.



The example showed in table 1 will be used to illustrate how a traditional 3+3 design performs and its properties. With an assumption of increasing DLT rates associated with increasing dose level, the following information could be obtained: 1) the likelihood of a dose being chosen as MTD; 2) expected sample size at each dose level, etc.

**Table 1 Example for 3+3 design without dose de-escalation**

| Dose level | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|
| Dose Level (mg) | 10 | 20 | 33 | 50 | 70 | 93 | 124 |
| DLT Rate | 0.010 | 0.021 | 0.055 | 0.173 | 0.489 | 0.848 | 0.983 |

### Step 1: Calculation of the probability of dose escalation at Dose j

It's assumed 3 subjects are enrolled into a given dose cohort j ($1 \leqslant j \leqslant n$, n is the number of dose cohort). The probability of the number of DLT observed in any of these subjects is actually turned to be a binomial problem, and the probability of no DLT observed can be given by:

$$P_0^j = \mathrm{Prob}(\mathrm{No\ DLT}) = p_j^0(1-p_j)^3$$

If one subject develops a DLT at a specific dose, additional 3 subjects are enrolled into that same dose cohort. In probability theory, for two independent events, the joint probability can be expressed as the product of their probabilities of occurrence:

$$Q_0^j = \mathrm{Prob}\begin{pmatrix} 1\ DLT\ in \\ first\ 3\ subjects \end{pmatrix} * \mathrm{Prob}\begin{pmatrix} No\ more\ than\ 1\ DLT \\ in\ additinal\ 3\ subjects \end{pmatrix}$$

Its SAS implementation can be written as follows:

```
……
%DO i=1 %TO &dose_cnt;
    %LET k= 1;
    %LET cnt=%EVAL(1-&k);
           q0  = PDF('Binomial',&k, ptox, 3) *
                 CDF('Binomial',&cnt, ptox, 3)  ;
%END;
……
```

### Step 2: Identify the probability of a dose level claimed as MTD

If MTD is identified as the dose cohort i, we can tell that all previous doses are not too toxic to stop. Statistically, the probability to make the decision of entering into the next dose cohort at dose i could be written as,

$$p\_go = \mathrm{Prob}\begin{pmatrix} Escalate\ at\ dose\ \mathrm{i}\ and \\ MTD \geq Dose\ \mathrm{i} \end{pmatrix} = \prod_{k=1}^{i}(P_0^k + Q_0^k)$$

On the other side, if MTD is identified at dose cohort i, we can tell that dose i+1 is too toxic to continue. Hence the probability of stopping dose escalation at dose i+1 is given by

$$p\_stop = \mathrm{Prob}\begin{pmatrix} Stop\ at\ dose\ \mathrm{i{+}1}\ and \\ MTD < Dose\ \mathrm{i{+}1} \end{pmatrix} = 1-(P_0^{i+1} + Q_0^{i+1})$$

The probability that dose i claimed as MTD is given by

$$P\_\mathrm{MTD}_i^* = \Pr ob(MTD = Dose\ \mathrm{i}) = (1 - P_0^{\mathrm{i}+1} - Q_0^{\mathrm{i}+1})(\prod_{k=1}^{\mathrm{i}} (P_0^k + Q_0^k)), 1 \le i < K$$

Under the general context of traditional 3 + 3 design, MTD will be dose i in case of the development of DLTs in more than 1 of 6 subjects in dose cohort i+1.

Note that, the probability of last dose (dose K) chosen as MTD is

$$\prod_{k=1}^{\mathrm{K}} (P_0^k + Q_0^k)$$

After data are read into a matrix using IML, the probability a dose claimed MTD can be computed as follows:

```
PROC IML;
……
     READ ALL VAR{"p_go" "p_stop" "p0" "p1" "ptox" "q0"};

     ** Probability of MTD;
     DO i = 1 TO &dose_cnt-1;
        p_go_i   = REPEAT(., i, 1);
        p_go_i   = p_go[1:i];
        p_mtd[i] = p_go_i[#,]*p_stop[i+1];
     END;
……
     p_mtd[&dose_cnt] = p_go[#,];

……
QUIT;
```

### Step 3: Expected number of subjects needed

Through the probability of toxicity at each dose, we can find the expected number of subjects treated at each dose. To get the expected number of subjects in each dose cohort, we need to resolve this mathematical expectation calculation for a discrete variable:

$$N_j^* = \sum_{i=0}^{K-1} N_{ji} P_i^*$$

$$\text{where } N_{ji} = \begin{cases} \dfrac{3P_0^j + 6Q_0^j}{P_0^{\mathrm{j}} + Q_0^j}, & if\ j < i+1 \\ \dfrac{3(1 - P_0^{\mathrm{j}} + P_1^j) + 6(P_1^{\mathrm{j}} - Q_0^j)}{(1 - P_0^{\mathrm{j}} - Q_0^j)}, & if\ j = i+1 \\ 0, & if\ j > i+1 \end{cases}$$

SAS/IML snippets for this step can be written as:

```
exp_go = (3 * p0 + (3 + 3) * q0)/(p0 + q0);
exp_stop = (3 * (1 - p0 - p1) + (3 + 3) * (p1 - q0))/p_stop;
……
DO k=1 TO &dose_cnt;
   exp_ss[k] = exp_stop[k] * mtd2[k] + exp_go[k] *
                                       mtd2[(k + 1):(&dose_cnt + 1)][+,];
END;
```

### Step 4: Expected DLT incidences at MTD

The MTD is defined as the dose that has the risk of DLT which equals to a chosen target toxicity level (TTL), usually between 17–33% in oncology trials.
Similar to expected number of subject calculation, expected DLT incidences at dose j can be given by

$$DLT_j^* = \sum_{i=1}^{K} N_i^* Ptox_i$$

The results from above calculations are presented in table 2, 50 mg would be chosen as the target dose which could be worthy of further investigation since it has the highest probability.

**Table 2 Calculation Results for 3+3 design without dose de-escalation**

| Dose Level (mg) | 10 | 20 | 33 | 50 | 70 | 93 | 124 |
|---|---|---|---|---|---|---|---|
| Sample size | 3.1 | 3.2 | 3.4 | 3.9 | 3.1 | 0.4 | 0.0 |
| Toxicity | 0.03 | 0.07 | 0.19 | 0.68 | 1.50 | 0.37 | 0.00 |
| Prob. Of MTD | 0.01 | 0.03 | 0.22 | 0.60 | 0.13 | 0.00 | 0.00 |

## STATISTICAL PROPERTIES VISUALIZATION

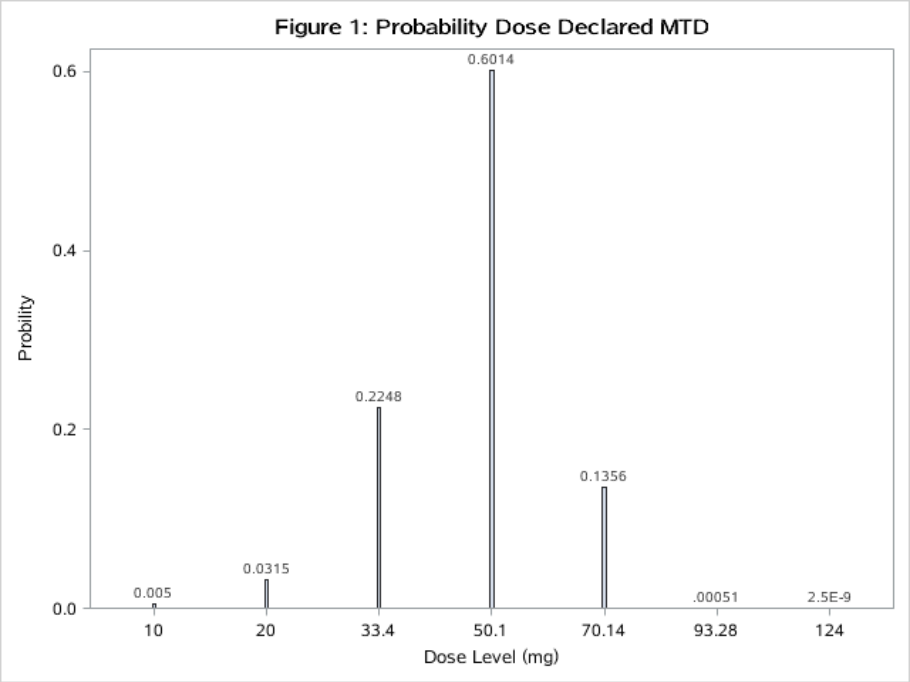
SAS/Graph provides a handful of tools to facilitate data visualization. SAS SGPLOT in this case can be used to visually check the properties of such a 3+3 design. With the help of SAS SGPLOT, investigators can easily get a clear insight into the traditional 3+3 design.

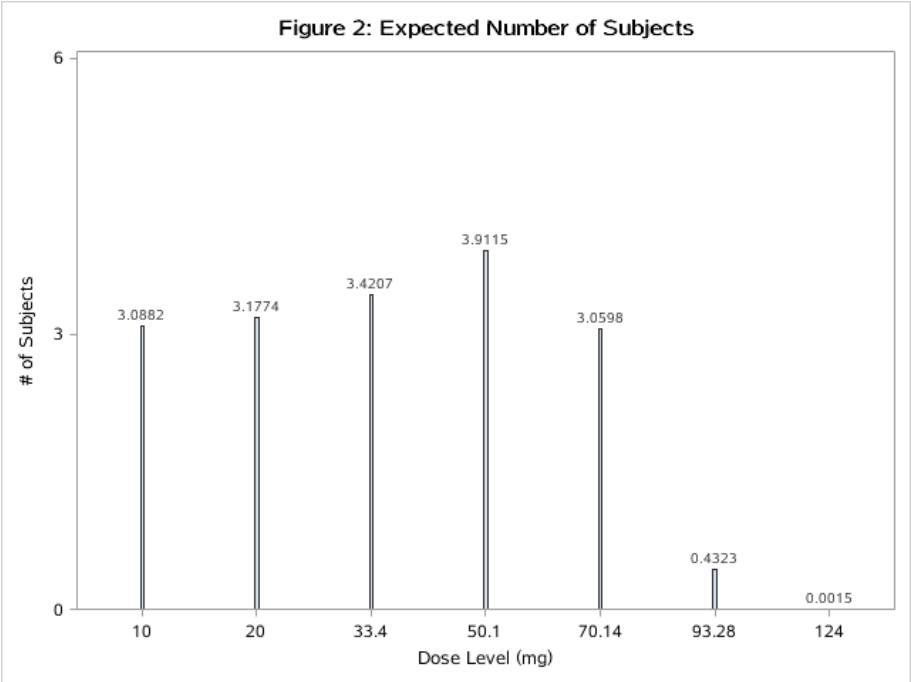
Some observations from the figure 1 and figure 2:

- ✓ Dose 50 mg/kg has the highest probability to be claimed as MTD. Starting from cohort 70 mg/kg, the probability descends.
- ✓ Starting from dose cohort 70 mg/kg, the number of subjects needed drops obviously, which may also reveal that dose would not need to be escalated after 70 mg/kg.

SAS code to create figure 1:

```
PROC SGPLOT DATA = final;
     YAXIS LABEL="Probility";
     XAXIS LABEL="Dose Level (mg)";
     VBAR dose_level /response= p_mtd  BARWIDTH = 0.03
                      TRANSPARENCY = 0.2 DATALABEL;
     TITLE 'Figure 1: Probability Dose Declared MTD';
RUN;
```




## SIMULATING A 3+3 DESIGN WITHOUT DE-ESCALATION

After getting the knowledge of statistical properties of a 3+3 design, it becomes easy to simulate a 3+3 traditional escalation trial. Besides, the simulation could also be used to verify the result as above.

In case we already have a rough idea of the following parameters:

- Dose increase method;

- Probability of toxicity.

- The underlying true dose-toxicity relationship is given by a logistic model with parameters a = 5.373 and b = 0.076, which gives a true MTD of 50 mg if the DLT rate for MTD is 0.17.

SAS/IML can also be used to simulate a traditional 3+3 trial without de-escalation and to get an insight into the design.

```
%MTD_3x3_simu(Starting_dose=10,
              No_dose_planned=7,
              Dose_increase_method=2, *2 = Modified Fibonachi;
              Inc_factor=%str(2, 1.67, 1.5, 1.4, 1.33, 1.33),
               No_sim =10000);
```

After 10000 simulations, the average MTD is found to be 54 mg although this is not a planned dose level. And, this dosage corresponds to a DLT rate around 0.22.

**Table 3 Simulation results for 3+3 design without dose de-escalation**

| Dose Level (mg) | 10 | 20 | 33 | 50 | 70 | 93 | 124 |
|---|---|---|---|---|---|---|---|
| DLT Rate | 0.010 | 0.021 | 0.055 | 0.173 | 0.489 | 0.848 | 0.983 |
| Prob. of MTD | 0.001 | 0.001 | 0.109 | 0.583 | 0.293 | 0.003 | 0.000 |
| Sample Size | 3.1 | 3.2 | 3.2 | 3.5 | 4.0 | 3.7 | 0.0 |

## FURTHER ILLUSTRATION OF '3+3' DESIGN

### Illustration 1:

Traditional 3+3 design has been criticized for its uncertainty due to escalation decisions being based on outcomes from only the most recently recruited subjects, not all of the data. The 95% exact confidence interval for DLT rate is calculated using SAS as bellows:

| | Confidence Interval (Low, High) | |
|---|---|---|
| 0/3 | 0.00 | 0.63 |
| 1/3 | 0.01 | 0.91 |
| 2/3 | 0.09 | 0.99 |

Although no toxicity is observed in 3 subjects, the chance of getting it could be as high as 63%. Even 3 more subjects are added, the chance could be as high as 40% although no toxicity is observed. However, if there are 2 subjects experienced DLTs which suggest rate ≥0.33, the chance could be only 9%. It may reveal that the choice of MTD is based on relatively weak evidence.

| | Confidence Interval (Low, High) | |
|---|---|---|
| 0/6 | 0.00 | 0.40 |
| 1/6 | 0.00 | 0.64 |
| 2/6 | 0.04 | 0.78 |

### Illustration 2:

As long as the dose-toxicity relationship is appropriately selected, bias could be avoided. But if an inappropriate relationship is assumed, the predictions for the MTD or DLT rate may be not convincing, according to results presented in table 4, 40 mg has the highest probability to be chosen as MTD, but it may be underdosing because its DLT rate is less than 0.17. To address such kind of problem, some Bayesian methods have been developed based on traditional 3+3 design, including mTPI and (modified) CRM, with which dose assignment recommendations are based on the posterior distribution of the DLT rate.

**Table 4 Example for 3+3 design without dose de-escalation**

| Dose Level (mg) | 12 | 24 | 40 | 60 | 84 | 112 |
|---|---|---|---|---|---|---|
| DLT Rate | 0.011 | 0.028 | 0.089 | 0.309 | 0.736 | 0.958 |
| Prob. Of MTD | 0.01 | 0.08 | 0.48 | 0.43 | 0.01 | 0.00 |

## CONCLUSION

Although there are many other design methods that can be used to determine the MTD in phase-I clinical trials, the traditional 3+3 design remains the prevailing method among clinicians and investigators. This is largely due to its simple concept and operational ease which can be explored through its properties mentioned in this paper.

This paper tries to explain traditional 3+3 design and implement by SAS in a practical method. Due to limited space, 3+3 dose escalation with dose de-escalation is not discussed in this paper.

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## CONTACT INFORMATION

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