TITE-CRM Phase I Clinical Trials: Implementation Using SAS

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1 Introduction to the TITE-CRM

1.1 Phase I Clinical Trial

Clinical trials are carefully controlled experiments involving human participants that are designed to test the safety and efficacy of a new treatment or drug. Typically, clinical trials are performed in several phases with the intent of collecting initial safety data in the first phase, initial efficacy data in the second phase, and confirmatory data based on a larger sample size in subsequent phases.

The primary purpose of a Phase I clinical trial is to determine whether the experimental treatment is safe and can be reasonably tolerated by patients. This involves administering the treatment to a small number of human subjects (usually 25 to 40) at various dose levels and measuring the incidence of treatment-related toxicity.

At the outset of the study, investigators define the specific biological conditions and adverse events that constitute a dose-limiting toxicity (DLT), and specify the target probability of DLT which represents the largest proportion of patients that experience toxicity that would be acceptable, such as 20% or 30%. The goal of the study is to establish the maximum tolerated dose (MTD), the largest administered dose with a probability of dose limiting toxicity that does not exceed the pre-specified target value. Subsequent studies aimed at determining how well the treatment works would be performed using dose levels that do not exceed the MTD.

1.2 Summary of the TITE-CRM Design

The Time-to-Event Continual Reassessment Method (TITE-CRM) proposed by Cheung and Chappell (*Biometrics* 2000) is an adaptive Phase I design that extends the Continual Reassessment Method (CRM) originally presented by O'Quigley et al. (*Biometrics* 1990). In a TITE-CRM clinical trial patients enroll as they become available to be studied. Each participant is assigned to a dose level from a set of dose levels pre-defined by investigators and is monitored for DLTs over time. The design is adaptive in that the dose level assigned to a newly enrolled patient depends on the dose level assignments and dose limiting toxicity outcomes of the patients already in the study.

A patient's observation period ends at the occurrence of a DLT or, if a DLT does not occur, after a fixed time T of follow-up. The trial ends when a fixed number of patients, n, have been observed. Once the final patient has been observed, the MTD can be estimated using the available data. Dose level escalation and de-escalation restrictions can be integrated into the design as needed.

The TITE-CRM differs from the traditional CRM in that the estimation process is weighted to account for the proportion of the observation period that each currently enrolled patient has been observed. While the CRM only makes use of information from patients that have completed the observation period, the TITE-CRM can additionally account for information from patients whose observation period has not yet ended. By not requiring complete observation before the enrollment of the next patient, new participants can be assigned a dose and begin evaluation as they become available, subsequently shortening the overall duration of the study.

1.3 Planning a TITE-CRM trial

When planning a TITE-CRM clinical trial, investigators will need to specify:

1. clinical definitions of what constitutes a DLT
2. target dose limiting toxicity rate, for which the MTD is defined
3. length of the fixed time period during which patients are observed for toxicities
4. the set of potential dose levels to be administered over the course of the study (typically four to six)
5. an initial estimate of the dose limiting toxicity rate for each dose level to be used as a starting point
6. the dose level to assign to the first participant
7. any other rules or restrictions regarding dose escalation, de-escalation, or trial stopping

Consider, for example, a study where the target probability of dose limiting toxicity has been set to be 20% and six doses are to be administered over the course of a clinical trial involving $n = 30$ patients. Dose levels should be chosen such that the target value is suspected to be within the range of the studied doses. It is not

specifically required that one of the dose levels have an initial dose limiting toxicity estimate that is exactly equal to the target dose. Table 1 provides an example set of doses with initial dose limiting toxicity estimates.

Table 1: Planning the TITE-CRM design

Dose level	Dose	Initial toxicity estimate
1	25 mg	0.075
2	40 mg	0.125
3	55 mg	0.150
4	70 mg	0.200
5	85 mg	0.225
6	95 mg	0.250

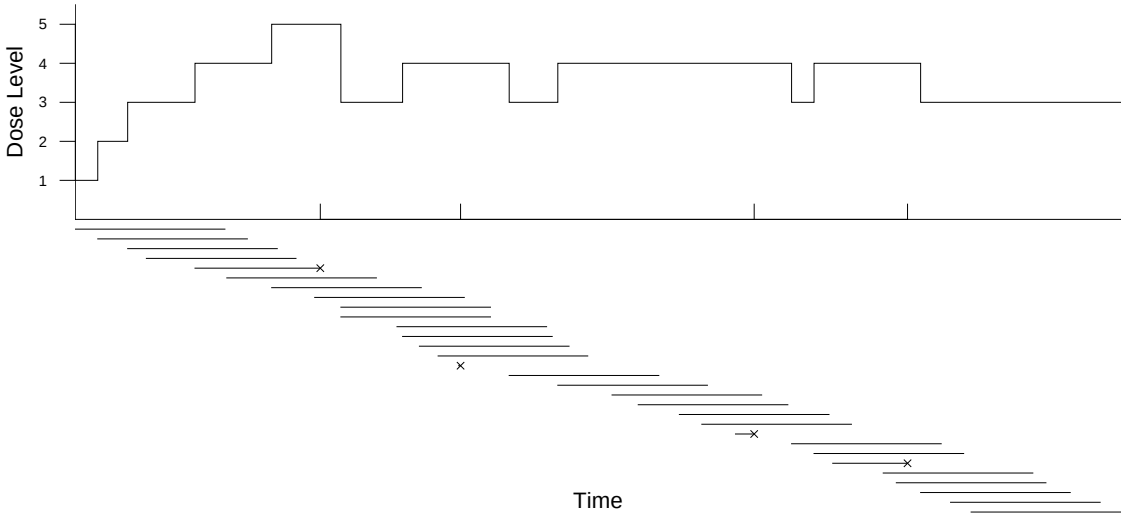
A schematic of a completed trial is provided in Figure 1. The upper portion of the figure displays the working dose level with respect to calendar time as the trial progresses. The lines beneath the graph show the observation times of each of the 30 study participants. For patients that were observed to have a DLT, an X marks the occurrence of dose limiting toxicity (these toxicity times are also displayed as ticks along the time axis). Starting at dose level 1, the adaptive nature of the TITE-CRM design "hones in" on the MTD, eventually settling on dose level 3 as the level with observed toxicity rate "closest" to the target. Dose level assignments are determined as each new patient is ready to enroll in the study by running the `titecrm.sas` program described in more detail in Section 4.

1.4 Implementing the TITE-CRM Using SAS

The Biostatistics Unit of the University of Michigan Comprehensive Cancer Center has developed a program `titecrm.sas` for SAS 9 (SAS Institute, Inc.; Cary, NC) that makes all of the calculations necessary to determine dose allocation of a trial in real-time. The code has been developed by Daniel Normolle PhD. The program also includes the ability to simulate complete trials in order to evalute the operating characteristics of a design prior to implementation. Instructions for using the program

begin in Section 3. First, though, some of the technical aspects of the TITE-CRM design are reviewed.

Figure 1: Diagram of a completed trial



2 Methodological Details

2.1 Investigator-defined Components

As noted in the previous section, when planning a TITE-CRM clinical trial investigators will need to set:

- the target toxicity probability $p^* \in (0, 1)$
- the fixed number of subjects, n, to be evaluated
- the set of K doses to be administered over the course of the study, $\{d_1, \ldots, d_K\}$
- initial estimates for the probability of dose limiting toxicity for each of the k-th dose levels $\{\hat{p}_{01}, \ldots, \hat{p}_{0k}\}$

A summary of these and other notation used throughout this section is given in Table 2.

2.2 Specification of the Dose-Toxicity Model

A fundamental component of any CRM design is a parametric dose-toxicity model that specifies how dose level relates to the probability of dose limiting toxicity. This function should be monotone increasing and usually consists of a single parameter. While there are many possible models, a common choice is to use a logistic dose-toxicity model given by

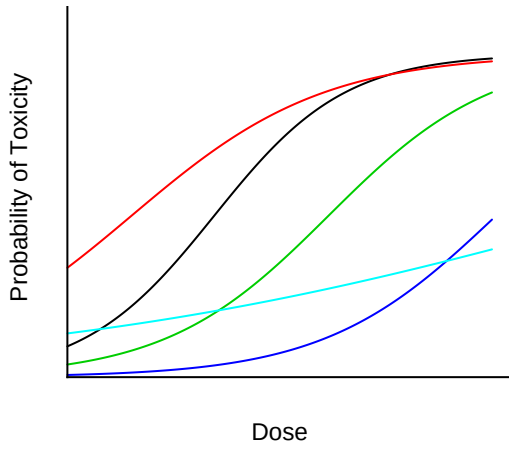
$$p_k = \phi(d_k; \alpha) = \frac{e^{3+\alpha d_k}}{1 + e^{3+\alpha d_k}}.$$

Several different examples of logistic dose-toxicity response curves are displayed in Figure 2. The parameter α influences the rate of change of the dose-toxicity function as it relates increasing dose level to increasing probability of DLT. As part of the Bayesian approach to estimation, α has a prior distribution $\pi(\alpha)$. Here, a normal prior with mean 1 and variance σ^2 is used. The value for the prior variance is fixed at the outset of the trial and modifies the behavior of the dose allocation procedure for the earliest patients to enroll by attenuating the influence of poor initial dose limiting toxicity estimates.

Having set the prior mean for α to be 1, the doses are relabeled so that the dose-toxicity model with $\alpha = 1$ fits the initial estimates for the probability of dose limiting toxicity. This relabeling is used in all future calculations and can be accomplished by finding the dose d_k that solves $\phi(d_k; \alpha = 1) = \hat{p}_{0k}$. That is,

$$d_k = \log\left(\frac{\hat{p}_{0k}}{1 - \hat{p}_{0k}}\right) - 3.$$

Figure 2: Several examples of dose-toxicity relationships modelled by a logistic function



2.3 Dose Allocation

The first patient in the study is assigned to the pre-defined starting dose. At the time a new patient becomes available for enrollment in the study, the estimate of α is updated to reflect both the observed data up to this point in time and the prior distribution for the parameter.

Suppose J patients have been enrolled in the trial and the J+1-th patient is ready to be enrolled. The information available to estimate α consists of the set of doses $\{x_1, \ldots, x_J\}$ administered to the J patients, the set of toxicity outcomes $\{y_1, \ldots, y_J\}$ where $y_j = 0$ if no toxicity and $y_j = 1$ if toxicity, and the amount of time each patient has been observed $\{u_1, \ldots, u_J\}$ where $0 < u_j \leq T$.

2.4 Weighted Likelihood

Having enrolled J patients, the information about α is given by the weighted likelihood function

$$L_J(\alpha) = \prod_{j=1}^{J} (w_j \, \phi(x_j; \alpha))^{y_j} (1 - w_j \, \phi(x_j; \alpha))^{1-y_j}$$

where the weights account for the proportion of the observation period that each currently enrolled patient has been observed. Specifically,

$$w_j = \begin{cases} \frac{u_j}{T} & \text{if } y_j = 0 \\ 1 & \text{if } y_j = 1 \end{cases}$$

where u_j is the current length of follow-up for patient j.

This simple weighting scheme can be represented graphically by the plot provided in Figure 3. The weight given to a patient's outcome increases at a constant rate while being monitored for dose limiting toxicity, achieving full weight upon making it to the end of the observation period. In other words, the outcomes are weighted as if the time-to-toxicity is uniformly distributed. Depending on how conservative investigators want to be about counting the contributions of patients at the earliest portion of their respective observation periods, the distribution of weights over time can be modified.

In a standard TITE-CRM clinical trial the contribution of each patient to the estimation process is weighted at a constant rate based on the amount of time each has been observed to be toxicity-free. It is possible, though, to assign weights that vary at different rates depending on the amount of time under observation.

Two example variable weighting schemes are shown in Figure 4. The plot on the left shows a conservative weighting approach, where patients without dose limiting toxicity in the early portion of the observation period receive substantially less weight than patients that are toxicity-free in the later portion of the observation period. In this case, patients do not contribute much to the dose limiting toxicity rate estimation process until they have made it more than half-way through the observation period without experiencing toxicity.

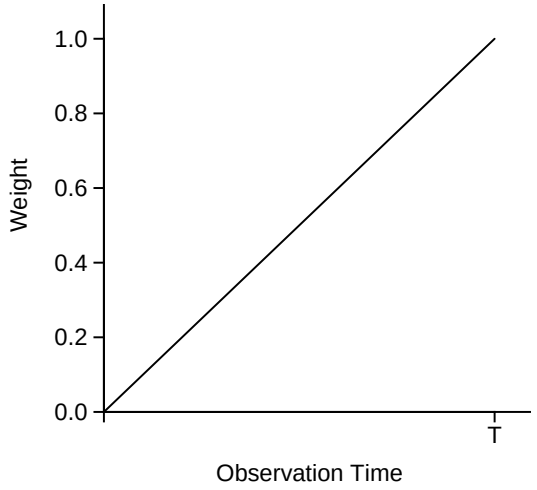


Figure 3: Plot of standard TITE-CRM weighting scheme

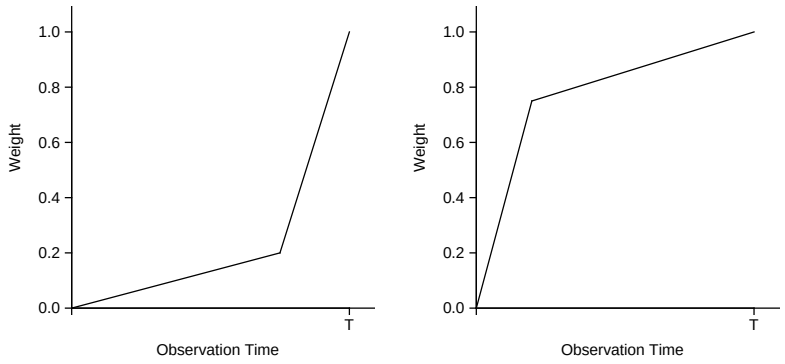


Figure 4: Plot of two different variable weighting schemes

Alternatively, the plot on the right shows a more aggressive approach, where patients still early in the observation period can be given nearly as much weight as those patients that have made it to the end of the observation period without dose limiting toxicity. Note that, regardless of the approach, the weights are always non-decreasing over time, and patients observed to be toxicity-free at the end of the fixed observation period are always given full weight (i.e., weight = 1). If a patient has had a delay during the observation period and has not yet reached the end of their follow-up period the calculation of the weight for that patient is modified. In the case of uniform weighting the weight is number of days on study divided by the sum of T and delay. In the case of variable weighting the times of the break points in the weight function are multiplied by (T+delay)/T.

2.5 Parameter Estimation

The estimate of α conditional on the data from the J patients enrolled in the study is the posterior mean given by

$$\hat{\alpha}_J = \frac{\int_0^\infty \alpha \, L_J(\alpha) \, \pi(\alpha) \, d\alpha}{\int_0^\infty L_J(\alpha) \, \pi(\alpha) \, d\alpha}.$$

Using $\hat{\alpha}_J$ the estimated probability of dose limiting toxicity for dose level k, $k = 1, \ldots, K$ is given by $\hat{p}_{Jk} = \phi(d_k; \hat{\alpha}_J)$. The J+1-th patient is assigned to the dose level with $\hat{p}_{Jk}$ close to the target probability p^*. $\hat{p}_{Jk}$ is a summary of the posterior distribution of $\phi(d_k; \alpha)$, it is an approximation of the median of this posterior distribution.

2.6 Posterior intervals

In addition to the calculation of point estimates $\hat{\alpha}_J$ and $\hat{p}_{Jk}$ the program also calculates the uncertainty intervals for the probability of toxicity. The 95% credible intervals for the posterior probability are calculated by estimating the exact cutoff points that give the 2.5% probability for α in each tail of the posterior distribution. These cutoff points of α are then transformed to give the posterior probability intervals for p_k. The program also provides the posterior probability that $p_k > target + E$, calculated in a similar way, where E is a user specified value called the excess. In the current version of the code these are provided for information only and are not incorporated in decision making of the next dose.

Table 2: List of notation that will be used to describe the TITE-CRM design

Notation	Description
n	fixed number of subjects to be enrolled in the study
p^*	target dose limiting toxicity probability $\in (0, 1)$
p_k	true (unobserved) dose limiting toxicity rate of the k-th dose level ($k = 1, \ldots, K$)
$\hat{p}_{0k}$	initial estimate of probability of dose limiting toxicity for the k-th dose level
$\hat{p}_{jk}$	estimated probability of dose limiting toxicity for the k-th dose level having observed j subjects ($j = 1, \ldots, J; J \leq n$)
d_k	dose value for the k-th dose level (relabeled)
x_j	dose administered to j-th subject (relabeled)
y_j	binary response for j-th subject (1 if toxicity, 0 if no toxicity)
α	single parameter for dose-toxicity model $\phi(d_j; \alpha)$
$\pi(\alpha)$	probability distribution function for the prior distribution of α
T	fixed follow-up time to observe toxicities
u_j	amount of time j-th subject has been observed $0 < u_j \leq T$
$delay_j$	delay during follow-up for j-th subject
E	Excess over target representing unacceptable toxicity rate

3 Guidelines for choosing inputs required for Phase I trial

3.1 Number of dose levels

This will be largely determined by the goals of the study and logistical considerations. The number will typically be between 3 and 8. If the number of levels is large then more patients will typically be required to determine with much accuracy the MTD, especially if the starting dose is at a low dose level. A number such as 4 or 5 would be most common, and there would need to be a strong rationale for deviations from that.

3.2 Target level of dose limiting toxicity

This should be determined by the clinical investigator in discussion with the statistician. The choice will depend on the severity of the disease, the severity of the possible toxicities and the chance of dose limiting toxicity associated with other treatments for this disease. The definition of what constitutes a dose limiting toxicity needs to be very carefully defined. Whether severe, but expected, toxicities are included in the DLT, should be determined. A typical target level of dose limiting toxicity is in the range of 0.20 to 0.35.

3.3 Initial estimate of the probability of dose limiting toxicity at each dose level

This should be determined by the clinical investigator in discussion with the statistician. It will be based on prior knowledge and data. Sometimes limited information is available. We suggest that the target level of dose limiting toxicity be close to the dose limiting toxicity rate at one of the intermediate doses. It is not necessary that the initial estimate at any of the dose levels be exactly equal to the target level. For technical reasons the estimate of the dose limiting toxicity rate at the lowest dose should be strictly positive and the estimate of the toxicity rate at the highest dose should be less than 0.95. The probabilities of dose limiting toxicity must be strictly increasing with dose. We suggest that the probabilities of dose limiting toxicity at neighboring dose levels be reasonably well separated, e.g. it is better to avoid initial estimates such as 0.05, 0.15, 0.25, 0.27, 0.40 for a five level experiment, because the

3rd and 4th dose limiting toxicity rates are too close to each other.

3.4 Starting dose

The starting dose can have a big impact on the properties of the design. After the trial is completed most information about the MTD will be obtained if many patients are treated at or near the MTD, thus the sooner the choice of dose can converge on the MTD the more effective the trial will be. Thus the best design would have the starting dose be the dose level (d_k) that gives an initial estimate of dose limiting toxicity closest to the target rate. Concerns about safety are also important here, and they would favor the most conservative approach of starting at the lowest possible dose just in case the initial estimates of dose limiting toxicity were substantial underestimates. As a compromise we suggest starting at the second lowest does or at one dose level lower than d_k. Starting at the lowest dose can introduce some logistical problems as it does not allow for any dose reduction if the first one or two patients happen to experience a toxicity.

3.5 Admissible Margin - Choosing the next dose

The dose for the next patient is selected so that the estimated probability at that dose is close to the target level. A feature of the dose escalation part of the TITE-CRM program is the flexibility in specifying the margin for the dose selection. This allows the selection of the dose level for the next patient that may have an estimated probability of toxicity larger than the target level but less than the target level plus the margin. It finds the dose closest to the target probability even if it has a higher estimated probability. The selection of the dose involves minimizing the absolute difference between the target and estimated probabilities at each dose level, such that the difference is less than or equal to the margin, it minimizes over k $|\hat{p}_k - p^*|$ such that $\hat{p}_k < p^* + margin$.

This feature aids an investigator who might be interested in looking at doses that are within a range of the target level during the early stages of the trial. Premature stopping of a trial could be averted if the toxicity levels are in the tolerable range. Values like 0, 0.05 or 0.10 could be used. A value of the margin of 0.05 in the presence of a target level of 0.15 would give rise to a new toxicity level of 0.20. In such a

scenario a dose with an estimated probability of 0.16 would be selected over another with a posterior toxicity of 0.12. A value of 0 implies that the margin feature is not in use.

The program also allows the margin to change to a value of 0 after a certain number of patients. The user can specify the number of patients after which the admissible margin feature will be turned off. This feature allows latitude in the selection of doses in the early parts of the trial to facilitate escalation to close to the MTD, but for later patients the selected dose would have a probability of toxicity less than the target, rather than close to the target. If turning off the margin is to be used, we suggest doing so after about ten patients when the probability estimates and choice of dose are beginning to stabilize.

3.6 Escalation restrictions

The dose escalation restrictions can have a big impact on the properties of the design. Since more information about the MTD will be obtained if many patients are treated at or near the MTD, the sooner the choice of dose can converge on the MTD the more effective the trial will be. The best design would have no restrictions at all; however safety must be considered. We recommend not allowing any doses to be skipped in the escalation scheme, and that an increase in the dose level between consecutive patients can only be one level.

How much experience is required at each dose level before escalation is allowed is also important. A conservative approach would be to require three patients to fully complete their evaluation period before any escalation is required. We do not recommend this approach, however, as it will slow down the escalation significantly, leading to less patients being treated at or near the MTD, and a less certain estimate of the MTD. An alternative approach would be to require a cumulative time of exposure among all enrolled subjects to be B units before escalation is allowed. An aggressive approach would be to have $B = 1$; we recommend $B = 2$

The speed of patient accrual can influence the choice of escalation restrictions. If patients are enrolled so rapidly that many patients will still be under evaluation when a new patient is to be enrolled the design will base dose escalation decisions on very little follow-up and some of the benefits of using the TITE-CRM approach may be

lost. In such cases it may be beneficial to limit the rate of accrual into the trial. If a large number of dose levels are being examined, then less restrictions should be placed on escalation rules since the differences between toxicities at each dose are likely to be smaller.

3.7 Prior distribution

The TITE-CRM uses a parametric logistic dose-toxicity model with a single parameter α that is determined using a Bayesian estimation procedure. The parameter α has a $N(1, \sigma^2)$ prior distribution, where the value of σ is specified in advance by the investigators. The default value of $\sigma = 0.3$ works well if the initial estimates of toxicities are not drastically different from the true toxicity rates. A larger value of σ can also be used, somewhere in the range 0.3 to 1.0. A smaller value of σ will be desirable for the first few patients in the study, when there is little data available from the patients.

3.8 Sample size

The sample size in TITE-CRM Phase I studies is fixed in advance. There are no explicit stopping rules built into the approach. Stopping rules can be written into the protocol as deemed necessary for the conduct of the study. The sample size is typically between 20 and 40 patients. One rule of thumb is to set the sample size to be six times the number of dose levels. Usually the primary determinant of sample size is the availability of patients. Twenty patients is usually too small to obtain much assurance that the selected dose at the end of the study will be the correct one. In an"average" TITE-CRM phase I trial the selected dose would tend to hover around the correct MTD after about 10 to 15 patients, but this could vary considerably from one trial to the next. If there is a plan to collect other laboratory correlative data or preliminary efficacy data then a larger sample size is desirable.

3.9 Weight function

The weight function can impact the operating characteristics of the study. The linear weight function is the default. Using a (convex) weight function which is low and only increases to 1 near the end of the evaluation period is a conservative approach. It

would be appropriate to use such a weight function if there is strong prior expectation that the toxicities that are going to occur will be later in the observation period.

For most Phase I trials the period of observation for designating a DLT is the first treatment cycle, and toxicities that occur in later treatment cycles do not count as a DLT. The weight function is a mechanism by which toxicities that occur during later cycles could count as a DLT. For example if the window of observation includes the first two cycles, and it is also thought that most dose limiting toxicity that will occur will happen in the first cycle then a concave weight function such as depicted on the right hand side of Figure 4 can be used. A bent stick weight functions is recommended, which is linear for the first cycle to a value near 1.0, and also linear but with a smaller slope after the first cycle. A rough rule for the choosing the weight function is that W should approximate the expected distribution function of when the toxicities will occur given that they are going to occur during the window of observation. If this distribution function cannot be approximated then a linear weight function is a good choice.

3.10 Simulations

The operating characteristics of the trial can be evaluated and optimized using simulations. It is important that the trial properties be simulated not only under the assumption that the true dose limiting toxicity rates match the initial estimate, but also under scenarios where they differ. Situations in which the initial estimate is both an under-estimate and an over-estimate should be considered.

4 The `titecrm.sas` Program: Single Trial Mode

The titecrm.sas program operates in two ways: single trial mode and simulation mode. Single trial mode is discussed here, while simulation mode is described in Section 5. The SAS code is maintained by the Biostatistics Unit of the University of Michigan Comprehensive Cancer Center and can be downloaded at `http:roadrunner.cancer.med.umich.edu/wiki/index.php/TITE-CRM`.

In single trial mode the program makes all of the calculations necessary to determine dose allocation of a trial in real-time. Two input files must be created prior to running the program: dose level information is contained in the dose data file (*dosefile*), and patient information is contained in the patient data file (*patfile*). Both are tab-delimited text files that must be formatted in a specific manner in order for the program to run properly.

4.1 Dose Data File

The dose data file is a plain-text file that has two columns of information with no header. The dose level descriptions for all of the doses to be considered in the trial are listed in the first column, followed by the corresponding initial estimates of the probability of dose limiting toxicity in the second column.

The dose levels do not need to be listed in ascending order of initial probability of dose limiting toxicity. If they are listed out of order, the program will automatically consider the dose with the lowest initial probability of dose limiting toxicity to be dose level 1, and the dose with the next highest initial probability of dose limiting toxicity to be level 2, and so on. An example of a dose data file for a trial that is studying six dose levels appears below.

```
25 mg     0.075
40 mg     0.125
55 mg     0.150
70 mg     0.200
85 mg     0.225
95 mg     0.250
```

4.2 Patient Data File

The other input file is the patient data file, which contains the information about all patients that have enrolled in the study in six colums (in this order): patient identification, dose administered, date treatment started, toxicity outcome, date treatment ended and treatment delay. Like the dose data file, it contains no header and is tab-delimited. The patient identification information can be an ID number or name up to 20 characters including spaces. The dose administered to the patient needs to be provided exactly as it appears in the dose data file. All dates must be in `DDMMMYYYY` format.

The dose limiting toxicity response variable takes the value 0 if no toxicity, 1 if toxicity, 2 if the patient has dropped out of the study prior to the end of the fixed observation period without having had a dose limiting toxicity and is not evaluable. Use the value 3 in the event that patient enrolls but is never actually treated. Under the default mode when the dose limiting toxicity response variable is set to 2 or 3 the patient's data will be ignored. There are advance settings that will allow the contribution of patients with dose limiting toxicity response of 2 to be partially weighted consistent with their time observed. For each study there is a maximum follow up period for observation of possible toxicities. Sometimes patients have a delay in their treatment resulting in the need for a prolonged observation period. The delay column accounts for the additional needed days on the study. Valid values include any non-negative number including zero which signifies absence of any delay. An example of a patient data file for an ongoing trial for which 19 patients have been enrolled appears below.

```
51113     25 mg     06JUL2007     0     31AUG2007     0
51125     25 mg     22JUL2007     0     16SEP2007     0
51147     25 mg     26JUL2007     0     20SEP2007     15
51152     25 mg     30AUG2007     0     25OCT2007     0
51178     40 mg     07SEP2007     0     02NOV2007     0
51179     40 mg     18OCT2007     2     06NOV2007     0
51203     40 mg     25OCT2007     0     20DEC2007     0
51220     40 mg     08NOV2007     0     03JAN2008     6
51246     40 mg     22NOV2007     0     18JAN2008     0
51283     40 mg     06DEC2007     1     19JAN2008     0
51287     40 mg     08DEC2007     0     02FEB2008     0
51299     55 mg     20DEC2007     1     05FEB2008     0
51374     55 mg     03JAN2008     0     28FEB2008     0
51388     55 mg     17JAN2008     0     15MAR2008     0
51442     55 mg     07FEB2008     0     03APR2008     0
51443     55 mg     07FEB2008     0     03APR2008     0
51508     70 mg     14FEB2008     0     10APR2008     0
51526     70 mg     01MAR2008     0     20NOV2008     10
51597     70 mg     07MAR2008     0     30OCT2008     10
```

Unlike the dose data file, which does not need to be modified once it is created, the patient data file needs to be updated upon the enrollment of each new patient so that the assigned dose can be determined. Note that the end date of the observation period can be left blank for patients still under observation. By default, the dose allocation calculation is based on the partial follow-up for patients that have not completed the observation period and is calculated as of the day the program is executed. The formatting rules for the two input files are summarized in Table 3.

4.3 Running the Program

The `titecrm.sas` program operates via a series of SAS macros. The portion of the code that requires user input is at the very end of the program syntax. The code works by calling five macro modules (in this order): `%defaults`, `%dday`, `%defdose`, `%patdata`, and `%simtite`. These macro modules automatically import the information from the dose data file and patient data file, perform the TITE-CRM calculations, and prepare the output.

In addition to the five macro modules, six variables that have no predefined de-

Table 3: Formatting the Input Files

File	Column	Variable	Formatting Description
Dose file	1	Dose Description	Any label up to 20 characters
	2	Initial Toxicity Estimates	Must be numerical
Patient file	1	Patient ID	ID number or name up to 20 characters
	2	Dose Administered	Dose description (as it appears in *dosefile*)
	3	Date Treatment Started	Dates must be in `DDMMMYYYY` format
	4	Toxicity Outcome	0 = No toxicity 1 = Toxicity 2 = Patient drops-out without toxicity 3 = Patient enrolls but is never treated
	5	Date Treatment Ended	Dates must be in `DDMMMYYYY` format
	6	Delay in Observation	Days must be ≥ 0

fault values need to be specified: `dosefile`, `patfile`, `outdir`, `simflag`, `obsdays`, and `target`. A description of each appears below in Table 4. A complete list of all modifiable macro variables and the values each are allowed to take appears at the beginning of the program code and has been reproduced in the appendix to this document as a reference. Any of the default values can be modified using the standard SAS syntax for defining macro variables (`%let` *variable_name* = *value*;).

When running the program in SAS for the Windows operating system if a desired output directory is not specified using the `outdir` variable the output will likely be saved to a root directory that may not be accessible to all users (such as

`C:\Windows\System32`). For this reason, users are advised to avoid running the code without first specifying an output directory.

By default, the program uses many of the aspects of the TITE-CRM design previously described. In particular, notable program defaults include:

- The logistic dose-toxicity model
- Normal prior distribution for α, with prior standard deviation $\sigma = 0.3$
- Weights as described above
- Dose level increases between consecutive patients limited to one level at a time
- Dose escalation not permitted until one patient completes observation period without experiencing a DLT
- Admissible margin = 0
- Excess = 0.20

4.4 Example Program Set-up

Suppose a TITE-CRM trial is in progress and the dose level and patient information are exactly those provided in the example *dosefile* and *patfile* shown earlier in this section. These files have been named `dosefile1.txt` and `patfile1.txt`, respectively. The study has six dose levels of interest and 19 patients have enrolled as of March 7, 2008. Participants are observed for dose limiting toxicity over eight weeks (56 days), and the target probability of dose limiting toxicity for the MTD is $p^* = 0.20$.

On April 12, 2009 the 20-th patient becomes available to be enrolled. The following program code is executed to determine the dose that the new participant should be assigned to.

```
⋮
/* All of the titecrm.sas code is above this line */


%defaults

   %let dosefile = %str(C:\MyDir\dosefile1.txt);
   %let patfile = %str(C:\MyDir\patfile1.txt);

   %let outdir = %str(C:\MyDir);

   %let simflag = 0;

   %let obsdays = 56;
   %let target = 0.20;
   %let dateflag=2;
   %let somedate=29OCT2009;

%dday

%defdose

%patdata

%simtite
```

The program output is a two-page pdf file that provides a summary of the number of patients treated at each dose so far, along with the number of DLTs that have occurred. Also included is the calculated posterior probability of dose limiting toxicity for each dose level, 95% credible intervals of this posterior distribution and the posterior probability mass greater than $p^* + E$ where E is the excess. The output provided by the example program appears as Figures 5 and 6.

According to the model, dose level 5 has an estimated dose limiting toxicity rate closest to the target rate without going over, unless the admissible margin has been set. Thus, as noted on the bottom of the first page of the output file, the patient that is ready to enroll in the study will be assigned dose level 5 (85 mg). The second page

Example Trial
Estimated Toxicities Based on Data Set C:\temp\patients_manual.txt

Level	Dose	Posterior P(DLT)	# DLTs	# Treated	Prior P(DLT)	Lower CI	Upper CI	P(p>target+ excess)
1	25 mg	0.058	0	4	0.075	0.011	0.194	0.001
2	40 mg	0.100	1	6	0.125	0.023	0.275	0.006
3	55 mg	0.122	1	5	0.150	0.031	0.310	0.010
4	70 mg	0.167	0	3	0.200	0.048	0.373	0.028
5	85 mg	0.190	0	0	0.225	0.058	0.401	0.043
6	90 mg	0.214	0	0	0.250	0.070	0.428	0.063

Target Rate is 0.2
Estimated alpha is 1.050 with SD = 0.143
Next Assigned Dose is 85 mg

Source: titecrm.sas 10DEC2008

Figure 5: Program output page 1

Example Trial
Data Set C:\temp\patients_manual.txt

Reg #	On Study	Dose	Level	Response Date	Response	Weight	Delay
51113	06JUL2007	25 mg	1	31AUG2007	0=No DLT	1.00	0
51125	22JUL2007	25 mg	1	16SEP2007	0=No DLT	1.00	0
51147	26JUL2007	25 mg	1	20SEP2007	0=No DLT	1.00	0
51152	30AUG2007	25 mg	1	25OCT2007	0=No DLT	1.00	0
51178	07SEP2007	40 mg	2	02NOV2007	0=No DLT	1.00	0
51179	18OCT2007	40 mg	2	06NOV2007	2=NE	0.00	0
51203	25OCT2007	40 mg	2	20DEC2007	0=No DLT	1.00	0
51220	08NOV2007	40 mg	2	03JAN2008	0=No DLT	1.00	0
51246	22NOV2007	40 mg	2	18JAN2008	0=No DLT	1.00	0
51283	06DEC2007	40 mg	2	19JAN2007	1=DLT	1.00	0
51287	08DEC2007	40 mg	2	02FEB2008	0=No DLT	1.00	0
51299	20DEC2007	55 mg	3	05FEB2008	1=DLT	1.00	0
51374	03JAN2008	55 mg	3	28FEB2008	0=No DLT	1.00	0
51388	17JAN2008	55 mg	3	15MAR2008	0=No DLT	1.00	0
51442	07FEB2008	55 mg	3	03APR2008	0=No DLT	1.00	0
51443	07FEB2008	55 mg	3	03APR2008	0=No DLT	1.00	0
51508	14FEB2008	70 mg	4	10APR2008	0=No DLT	1.00	0
51526	01MAR2008	70 mg	4	.	0=No DLT	0.75	0
51597	07MAR2008	70 mg	4	.	0=No DLT	0.64	0

Source: titecrm.sas 10DEC2008

Figure 6: Program output page 2

summarizes the patient level information in order of entry into the trial, including the weight assigned to patients that remain under observation.

Table 4: There are six variables that have no default values and need to be specified in order for the program to run

Variable	Description
`dosefile`	File name of the dose data file
`patfile`	File name of the patient data file
`outdir`	Path name to save output file
`simflag`	0 for single trial mode, 1 for simulation mode
`obsdays`	Maximum time T (in days) a patient will be observed for dose limiting toxicity
`target`	The target probability of dose limiting toxicity $p^* \in (0, 1)$ for MTD

4.5 Admissible Margin - dose escalation

The admissible margin feature can be set via the `adm_dose` and `adm_marg` parameters in the macro. Setting `adm_dose` = 1 selects the largest dose with posterior probability less than or equal to the target probability while setting `adm_dose` = 2 selects the dose closest to the target probability. In conjunction to setting `adm_dose` = 2 we also need to specify `adm_margin,` the allowable excess in estimated probabilities over the desired value of the target probability. For `adm_dose` = 2 we also need to specify the patient number (`off_adm_margin`) after which the admissible margin will be set to zero. The default value for `off_adm_margin` is 10.

4.6 Dose Escalation Restrictions

By default, the `titecrm.sas` program does not allow dose levels to be skipped and will not increase the dose level until one patient has been completely observed at the given dose level. Although it is common to prefer that dose levels not be skipped, it is certainly possible to relax this restraint. Any restrictions that are implemented, however, will apply throughout the course of the entire study. Presently, the program

does not allow different sets of restrictions to apply to different periods of the study. The dose escalation restrictions can be customized using the `rscheme` variable to:

- Permit a certain number of dose level jumps between consecutive patients
- Require a certain number of patients with completed observations periods prior to allowing dose escalation
- Require a certain amount of cumulative time on a dose before allowing dose escalation

Table 5: Consider a clinical trial with a 30 day observation window, target toxicity probability of 0.30, and three participants all assigned to dose level 1. For each restriction scheme the next assigned dose level is given for each combination of the `nproceed` and `dosejump` variables.

Patient No.	1	2	3
Assigned Dose Level	1	1	1
Follow-up (days)	30	15	5
Toxicity	0	1	0

Dose Level	1	2	3	4	5	6
Estimated Prob. of Tox.	0.14	0.19	0.24	0.29	0.38	0.42

`rscheme` = 0

		nproceed				
		1	2	3	...	n
dosejump	1	4	4	4		4
	2	4	4	4		4
	3	4	4	4		4
	4	4	4	4		4
	5	4	4	4		4

`rscheme` = 1

		nproceed				
		1	2	3	...	n
dosejump	1	2	2	2		2
	2	3	3	3		3
	3	4	4	4		4
	4	4	4	4		4
	5	4	4	4		4

`rscheme` = 2

		nproceed				
		1	2	3	...	n
dosejump	1	4	4	1		1
	2	4	4	1		1
	3	4	4	1		1
	4	4	4	1		1
	5	4	4	1		1

`rscheme` = 3

		nproceed				
		1	2	3	...	n
dosejump	1	4	1	1		1
	2	4	1	1		1
	3	4	1	1		1
	4	4	1	1		1
	5	4	1	1		1

`rscheme` = 12

		nproceed				
		1	2	3	...	n
dosejump	1	2	2	1		1
	2	3	3	1		1
	3	4	4	1		1
	4	4	4	1		1
	5	4	4	1		1

`rscheme` = 13

		nproceed				
		1	2	3	...	n
dosejump	1	2	1	1		1
	2	3	1	1		1
	3	4	1	1		1
	4	4	1	1		1
	5	4	1	1		1

4.7 Restriction Schemes

When some escalation restrictions are desired, the `rscheme` variable is used in conjunction with either the `dosejump` and/or `nproceed` variables. To permit a certain number of dose level jumps between consecutive patients, set `rscheme` = 1 and specify the number of levels that can be skipped using the `dosejump` variable (e.g., `rscheme` = 1 with `dosejump` = 2). Here, consecutive dose levels are considered one jump apart. That is, `dosejump` = 2 means that the dose level is allowed to go from level 1 to at

most level 3.

To require a certain number of patients with completed observations periods prior to allowing dose escalation set `rscheme` = 2 and specify the number of completed patients before proceeding to a higher dose using the `nproceed` variable (e.g., `rscheme` = 1 with `nproceed` = 4). To require a certain amount of time on a dose before allowing a dose level increase, set `rscheme` = 3 and express the amount of time as a multiple of the fixed observation window (`obsdays`). For a clinical trial with a 56 day observation window for DLTs, $56 \times 2 = 112$ days of cumulative experience on a dose before allowing a dose level escalation by setting `rscheme` = 3 and `nproceed` = 2. It should be clear from the usage that fractional values are permitted for `nproceed` (e.g., `nproceed` = 1.5 or `nproceed` = 0.75) when `rscheme` = 3, but not when `rscheme` = 2.

Table 6: Summary of the restriction scheme options

`rscheme`	`dosejump`	`nproceed`
0	Not applicable	Not applicable
1	Number of levels that can be skipped	Not applicable
2	Not applicable	Number of complete patients
3	Not applicable	Number of observation periods
12	Number of levels that can be skipped	Number of complete patients
13	Number of levels that can be skipped	Number of observation periods

Two combined options are also possible. It is possible to use `rscheme` = 1 in conjuction with `rscheme` = 2, by setting `rscheme` = 12. Similarly, it is possible to use `rshceme` = 1 in conjunction with `rscheme` = 3, by setting `rscheme` = 13. Note, however, that it is not possible to use both `rscheme` = 2 and `rscheme` = 3 simultaneously. Table 6 summarizes the variables that need to be specified for each dose level escalation restriction scheme.

Table 5 provides an example of how the dose escalation restrictions work. For this example, three participants have been enrolled in a study that has a 30 day observation window and target toxicity probability of 0.30. Each of the three previous participants has been assigned to the lowest dose level. A fourth participant is ready to enroll, and based on the estimated probabilities of toxicities at each dose level, the dose level will be escalated. Patients 1 has completed the 30-day follow-up period. Patient 2 is also finished with follow-up since s/he experienced a dose limiting toxicity (on day 15). Patient 3 has been in the study for 5 days and is still under observation. Table 5 shows which dose level the fourth patient would be assigned to for various settings of the dose escalation restriction schemes.

With no restrictions (`rscheme` $= 0$) the fourth participant will be assigned to dose level 4 since it has estimated probability of dose limiting toxicity that is closest to (without going over) the target probability. As shown in the other configurations displayed in Table 5, restrictions can be applied to avoid this jump (`dosejump` $= 1$ only permit the assigned dose level to go from level 1 to level 2, `dosejump` $= 2$ will permit the assigned dose level to go from level 1 to level 3, etc.).

Say that there was a desire to wait for three participants to complete follow-up before allowing dose escalation (so that `rscheme` $= 2$ with `nproceed` $= 3$). Since only two participants have completed follow-up in this example, the dose level would not be permitted to increase and would stay at dose level 1 for the participant that is ready to enroll. Alternatively, say that there was a desire to wait for 60 days of cumulative experience at dose level (two complete observation periods) before allowing dose escalation (so that `rscheme` $= 3$ with `nproceed` $= 2$). Since only $30 + 15 + 5 = 55$ days of experience at dose level 1 has accumulated in this example, the dose level would not be permitted to increase and would stay at dose level 1 for the participant that is ready to enroll.

4.8 Early Stopping Rules

If the $\hat{p}_{Jk}$ at the lowest dose is too high, greater than a threshold value then the trial should stop. If this happens the program points that it is not possible to assign a dose. The threshold for determining that $\hat{p}_{Jk}$ is too high is controlled by the `target, nrunin, adm_dose, adm_marg and off_adm_marg`. For the first `nrunin` patients the

threshold is 1 so that there is no early stopping. If `adm_dose` flag has been set to 2 then for patient numbered $nrunin + 1$ until patient numbered `off_adm_margin` the threshold is set to $target + adm\_marg$ and after patient numbered `off_adm_marg` the threshold is the target(p^*). If `adm_dose` has been flagged to 1 then for all patients after `nrunin` the threshold is set to `target(`p^*`)`.

4.9 Starting Dose

Furthermore, for safety considerations, many investigators would prefer to take the conservative approach of starting the trial at the lowest dose (instead of, say, the dose level with initial dose limiting toxicity estimate closest to the target rate). The dose assigned to the very first patient in the trial can be altered using the `level1` option. By setting `level1` = 1, the first patient is assigned to the lowest dose.

4.10 Example Program Syntax

In the example SAS program code below, which continues the previous example, the trial will start at the lowest dose, will not skip dose levels (by default, `dosejump` = 1) and will require that three patients be completely observed on a dose before any dose level increases are permitted (i.e., `nproceed` = 3).

```
⋮
/* All of the titecrm.sas code is above this line */


%defaults

   %let dosefile = %str(C:\MyDir\dosefile1.txt);
   %let patfile = %str(C:\MyDir\patfile1.txt);

   %let outdir = %str(C:\MyDir);

   %let simflag = 0;

   %let obsdays = 56;
   %let target = 0.20;

   %level1 = 1;

   %rscheme = 2;
   %nproceed = 3;

%dday

%defdose

%patdata

%simtite
```

4.11 Run Date References

Typically, the program is executed at the time a new patient is prepared to enter the trial. Using the most up-to-date information, the program identifies the dose level assignment for this patient. By default, all follow-up time and weighting is automatically calculated with respect to the date that the SAS code is executed. If it is desired to consider what the dose assignment would be for a date different than the date the program is run, the `somedate` variable can be used to specify a reference date in `DDMMMYYYY` format. Note that in order to use the `somedate` variable it is also necessary to set `dateflag` = 2.

The `dateflag` variable itself has another use at the conclusion of the study. Once the clinical trial has ended, final calculations should be based on the end of the ob-

servation period of the final participant, irrespective of the date the program is run. Setting `dateflag` = 1 will accomplish this.

4.12 Variable Weighting

The variable weighting feature of the `titecrm.sas` program allows investigators to customize the distribution of weights appropriate for any clinical trial. While the plots in Figure 4 consist of two line segments, variable weight schemes can be constructed from any number of continuous, non-decreasing line segments. Set `vwflag` = 1 to identify that variable weighting will be used, and list the specific coordinates of the points that define the line segments by using the `vwdays` and `vwwts` variables. For example, to have weights increase linearly from 0 to 0.2 over the first three-quarters of a 56 day observartion period, then increase linearly from 0.2 to 1.0 over the final quarter of a 56 day observation period, set `vwdays` $= 0, 42, 56$ and `vwwts` $= 0.0, 0.2, 1.0$.

4.13 Traditional CRM Functionality

The `titecrm.sas` program can also be used for the administration of traditional CRM trials. The CRM gives full weight to completed participants, but ignores the partial follow-up time contributed by those participants still being observed for dose limiting toxicity. Use `titeflag` = 0 to run the trial using the traditional CRM design.

5 The `titecrm.sas` Program: Simulation Mode

A useful feature of the `titecrm.sas` program is the ability to simulate complete trials in order to understand the operating characteristics of a design. The enrollment dates are simulated based on user-specifed mean patient interarrival times, and incidence of DLTs are simulated based on the true probability of dose limiting toxicity for the assigned dose level. Participant enrollment into the study is simulated as if the arrival times follow an approximate Poisson process. Setting `simflag` = 1 indicates that the program is in simulation mode.

5.1 Simulation Dose File

Since all of the patient-level information is simulated by the computer, there is no need to supply a *patfile* input file. A *dosefile*, however, is required, and is slightly different from the *dosefile* used in real-time single trial mode. In simulation mode, the *dosefile* contains the same first two columns of data as used in the single trial mode (dose labels and initial dose limiting toxicity estimates), but now contains a third column that provides the true probability of dose limiting toxicity for each dose level. In practice, the true underlying probabilities of toxicity are never known. For simulations, however, the "truth" is controlled by the user. An example *dosefile* suitable for simulation mode appears below.

```
25 mg     0.075     0.067
40 mg     0.125     0.095
55 mg     0.150     0.100
70 mg     0.200     0.170
85 mg     0.225     0.210
95 mg     0.250     0.350
```

5.2 Running the Program

The `titecrm.sas` program can be switched to simulating mode by simply setting `simflag` = 1. Most of the essential variables from the real-time single trial mode can be used in simulation mode. At the very least, `obsdays` and `target` must be provided

in order for the program to run. Note that to use variable weighting in simulation mode use the variable `urflag`, `urwts`, and `urdays` instead of `vwflag`, `vwwts`, and `vwdays`.

In order to reproduce a simulated dataset at a later time, it is useful to specify the seed for the random number generator used for creating the simulated data. The seed can be set using the `seed1` variable. One may wish to simulate a series (perhaps thousands) of completed trials. Use the `nsim` variable to specify the desired number of simulated trials.

The number of study participants can be the same in each of the simulated trials, or can differ from trial to trial subject to user-specified recruitment parameters. The variable recruitment option (`varcruit`) is used to make this distinction. To have the same number of study participants in each simulated trial use `varcruit` = 0, then set `maxsub` to be the number of subjects per trial and `rectime` to be the mean interarrival time between patients. When `varcruit` = 0 the interarrival times are randomly drawn from a Uniform (0, 2*rectime) distribution.

To allow the number of study participants in each simulated trial to vary set `varcruit` = 1. The variable `periods` can be used to specify a factor that multiplies the mean interarrival time between patients in order to arrive at the full length of the simulated trial. When using `periods`, the variable `rectimes` provides the mean interarrival time between patients. Note that `rectime` and `rectimes` are different variable names.

The number of patients to be enrolled in the study before checking the stopping rule can be controlled through `nrunin`. This variable provides the means to avoid premature termination of the trial in event of a surprisingly large number of toxicities in the first few subjects of the simulated study. The default value for `nrunin` is 3. After the run-in period the simulated trial will stop if the estimated probability of toxicity at the lowest dose is greater than the target plus admissible margin. All these variables have been summarized in Table 7.

Table 7: Variables for simulation mode

Variable	Description
`nsim`	Number of complete trials to simulate
`seed1`	Seed for random number generator
`varcruit`	Variable recruitment indicator
`maxsub`	Number of patients per trial (with `varcruit` = 0)
`nrunin`	Number of patients to be enrolled before checking the stopping rule
`rectime`	Mean interarrival time between patients (with `varcruit` = 0)
`periods`	Trial length as multiple of mean interarrival time (with `varcruit` = 1)
`rectimes`	Mean interarrival time between patients (with `varcruit` = 1)
`urflag`	Analogous to `vwflag` in single trial mode
`urwts`	Analogous to `vwwts` in single trial mode
`urdays`	Analogous to `vwdays` in single trial mode

5.3 Simulation Output

Upon executing the program in simulation mode, two SAS data files are generated (saved to the path given in `outdir`) named *trial.sas7bdat* and *patients.sas7bdat*. The *trial.sas7bdat* dataset contains counts of DLTs for each dose level, the number treated at each dose level, as well as the final dose-toxicity model parameter estimate and final estimates for the probability of toxicity at each dose level. Each row of this file represents a separate complete simulation. The *patients.sas7bdat* dataset contains the start and end dates for each simulated patient, along with their assigned dose level and dose limiting toxicity outcome. The dose-toxicity model parameter estimate at the time of the enrollment of each participant is also given.

From a set of simulated clinical trials, it is possible to understand the operating characteristics of a design by considering some relevant statistics such as:

- The frequency of patients assigned to each dose level
- The average number of toxicities observed at each dose level
- The average estimated probability of dose limiting toxicity at each dose level

- The number of times each dose level has been declared the MTD

Since the simulation output files are SAS datasets, these summaries can be calculated using any of the usual SAS procedures. A simple example of SAS code that prints the two simulation output files and calculates the average number of patients treated at each dose level appears below.

```
libname outdir 'C:\MyDir';


/* Produce a printout of the data sets */

proc print data = outdir.patient;
run;

proc print data = outdir.trial;
run;


/* Calculate the average number of patients treated at each dose level */

proc means data = outdir.trial;
   var n1 n2 n3 n4 n5 n6;
run;
```

5.4 Example Simulation Program

In the example program below, 1000 complete trials are simulated each with 30 participants. An input *dosefile*, similar to the example provided at the beginning of Section 5, has been created and saved to the directory identified in the code. Each trial starts at the lowest dose and patients are observed for DLTs over 56 days and are assumed to arrive, on average, 15 days apart (`rectime` = 15). The target dose limiting toxicity rate is 0.20. There is a dose escalation restriction is place; the dose can only increase after three patients have completed their observation periods at an administered dose (`rscheme` = 2 with `nproceed` = 3).

```
⋮
/* All of the titecrm.sas code is above this line */


%defaults

  %let dosefile = %str(C:\MyDir\sim_dosefile1.txt);

  %let outdir = %str(C:\MyDir);

  %let simflag = 1;

  %let seed1 = 1928048;

  %let nsim = 1000;

  %let maxsub = 30;
  %let rectime = 15;

  %let obsdays = 56;
  %let target = 0.20;

  %level1 = 1;

  %rscheme = 2;
  %nproceed = 3;

%dday

%defdose

%patdata

%simtite
```

6 Program Validation

In order to validate the `titecrm.sas` code its output was compared to that of a separate TITE-CRM program. Ken Cheung has written a TITE-CRM program for the R statistical environment. The program is available as part of the titecrm package that can be downloaded from the Comprehensive R Archive Network (`http://www.cran.r-project.com`). To compare the two programs, the *titecrm* R function was first modified so that it incorporated the same set of dose escalation restrictions and logistic dose-toxicity model that are part of the SAS program.

6.1 R Program Comparison

Several example trials were executed from start to finish using both `titecrm.sas` and the *titecrm* program for R (version 2.6) concurrently, and the output was compared for each step of the calculation process. The patient start dates, end dates, and dose limiting toxicity outcomes were simulated based on given dose levels with known probabilities of dose limiting toxicity as they would be for a simulated trial generated using the simulation mode of the `titecrm.sas` program. Table 8 provides an example of a set of six dose levels with initial estimates and assumed true probabilities of dose limiting toxicity (unobserved) that are used in several of the scenarios that follow.

Table 8: Simulation Parameters for Example Validation Datasets

Dose Level	Initial Estimate Probability of Toxicity	True Probability of Toxicity
1	0.050	0.075
2	0.100	0.098
3	0.150	0.127
4	0.200	0.165
5	0.250	0.214
6	0.300	0.278

The process was repeated for several different trial configurations (i.e., unrestricted

escalation, forbidding dose skipping, starting the trial at the dose closest to initial MTD estimate, starting the trial at the lowest dose). For all these examples the admissible margin is 0 and the nrunin is 0. For each scenario that was tested, the dose-toxicity parameter estimate, posterior probabilities of toxicity for each dose, and the dose allocation recommendations were found to match.

The tables that follow provide two examples of validation datasets that were independently run using `titecrm.sas` and the *titecrm* program for R. In the first example (Table 9), the dose level escalation is unrestricted. The second example (Table 10) uses the same simulated start dates, end dates, and dose limiting toxicity outcomes as the first example, but dose skipping is prohibited (i.e., `rscheme` = 0 and `dosejump` = 1). The initial estimates and given true values for the probability of dose limiting toxicity for each of the six dose levels is shown with each example dataset. As indicated in the tables, the dose-toxicity model parameter estimates were consistent to at least five decimal places and the next assigned dose level always matched.

Table 9: Example validation dataset 1

Patient Number	Start Date	End Date	Toxicity	Program	Parameter Estimate	Next Dose Level
1	1-Jan-2008	21-Mar-2008	0	SAS	1.0116217410	3
				R	1.0116217376	3
2	22-Jan-2008	11-Apr-2008	0	SAS	1.0297414854	3
				R	1.0297414831	3
3	6-Feb-2008	26-Apr-2008	0	SAS	1.0476329058	3
				R	1.0476329042	3
4	16-Feb-2008	6-May-2008	0	SAS	1.1084231237	4
				R	1.1084231236	4
5	16-Mar-2008	4-Jun-2008	0	SAS	1.1361277998	4
				R	1.1361277998	4
6	30-Mar-2008	18-Jun-2008	0	SAS	1.1728294367	5
				R	1.1728294367	5
7	19-Apr-2008	8-Jul-2008	0	SAS	1.1880621031	5
				R	1.1880621031	5
8	28-Apr-2008	17-Jul-2008	0	SAS	1.2094462140	5
				R	1.2094462140	5
9	12-May-2008	31-Jul-2008	0	SAS	1.2190904453	5
				R	1.2190904453	5
10	18-May-2008	6-Aug-2008	0	SAS	1.2464028552	6
				R	1.2464028589	6
11	2-Jun-2008	21-Aug-2008	0	SAS	1.2807729109	6
				R	1.2807729109	6
12	23-Jun-2008	11-Sep-2008	0	SAS	1.3142477113	6
				R	1.3142477113	6
13	16-Jul-2008	13-Aug-2008	1	SAS	1.3420490293	6
				R	1.3420490293	6
14	12-Aug-2008	31-Oct-2008	0	SAS	1.2145309753	5
				R	1.2145309753	5
15	14-Aug-2008	4-Sep-2008	1	SAS	1.2285984261	5
				R	1.2285984261	5
16	1-Sep-2008	20-Nov-2008	0	SAS	1.1287860752	4
				R	1.1287857661	4
17	4-Sep-2008	23-Nov-2008	0	SAS	1.1392946276	4
				R	1.1392946264	4
18	19-Sep-2008	8-Dec-2008	0	SAS	1.1537471391	4
				R	1.1537471373	4
19	9-Oct-2008	28-Dec-2008	0	SAS	1.1669710425	5
				R	1.1669710400	5
20	24-Oct-2008	10-Jan-2009	1	SAS	1.1796093182	5
				R	1.1796093148	5
21	7-Nov-2008	29-Jan-2009	0	SAS	1.1832503429	5
				R	1.1832503392	5
22	11-Nov-2008	30-Jan-2009	0	SAS	1.1979760807	5
				R	1.1979760813	5
23	27-Nov-2008	15-Feb-2009	0	SAS	1.2046124334	5
				R	1.2046120358	5
24	5-Dec-2008	23-Feb-2009	0	SAS	1.2252794438	5
				R	1.2252796079	5
25	30-Dec-2008	20-Mar-2009	0	SAS	1.1564733540	5
				R	1.1564733716	5

Table 10: Example validation dataset 2

Patient Number	Start Date	End Date	Toxicity	Program	Parameter Estimate	Next Dose Level
1	1-Jan-2008	21-Mar-2008	0	SAS	1.0116217410	2
				R	1.0116217376	2
2	22-Jan-2008	11-Apr-2008	0	SAS	1.0286120947	3
				R	1.0286120923	3
3	6-Feb-2008	26-Apr-2008	0	SAS	1.0456103807	3
				R	1.0456103792	3
4	16-Feb-2008	6-May-2008	0	SAS	1.1035418998	4
				R	1.1035418996	4
5	16-Mar-2008	4-Jun-2008	0	SAS	1.1299520834	4
				R	1.1299520834	4
6	30-Mar-2008	18-Jun-2008	0	SAS	1.1661176772	5
				R	1.1661176772	5
7	19-Apr-2008	8-Jul-2008	0	SAS	1.1818010300	5
				R	1.1818010300	5
8	28-Apr-2008	17-Jul-2008	0	SAS	1.2037452991	5
				R	1.2037452991	5
9	12-May-2008	31-Jul-2008	0	SAS	1.2136253942	5
				R	1.2136253942	5
10	18-May-2008	6-Aug-2008	0	SAS	1.2415890232	6
				R	1.2415890232	6
11	2-Jun-2008	21-Aug-2008	0	SAS	1.2766920331	6
				R	1.2766920331	6
12	23-Jun-2008	11-Sep-2008	0	SAS	1.3107998244	6
				R	1.3107998244	6
13	16-Jul-2008	13-Aug-2008	1	SAS	1.3390548499	6
				R	1.3390548499	6
14	12-Aug-2008	31-Oct-2008	0	SAS	1.2111833797	6
				R	1.2111833797	6
15	14-Aug-2008	4-Sep-2008	1	SAS	1.2254421087	5
				R	1.2254421087	5
16	1-Sep-2008	20-Nov-2008	0	SAS	1.1255081653	4
				R	1.1255078620	4
17	4-Sep-2008	23-Nov-2008	0	SAS	1.1361390596	4
				R	1.1361387457	4
18	19-Sep-2008	8-Dec-2008	0	SAS	1.1507619890	4
				R	1.1507619873	4
19	9-Oct-2008	28-Dec-2008	0	SAS	1.1641486165	5
				R	1.1641486142	5
20	24-Oct-2008	10-Jan-2009	1	SAS	1.1769395563	5
				R	1.1769395531	5
21	7-Nov-2008	29-Jan-2009	0	SAS	1.1806229924	5
				R	1.1806229889	5
22	11-Nov-2008	30-Jan-2009	0	SAS	1.1955134337	5
				R	1.1955134340	5
23	27-Nov-2008	15-Feb-2009	0	SAS	1.2022191853	5
				R	1.2022187879	5
24	5-Dec-2008	23-Feb-2009	0	SAS	1.2230930592	5
				R	1.2230932159	5
25	30-Dec-2008	20-Mar-2009	0	SAS	1.1542684269	4
				R	1.1542683949	4

6.2 Restriction Scheme Confirmation

Table 11 shows the results of a simulated trial with `level1` = 1, `rshceme` = 12, `dosejump` = 1, and `nproceed` = 3. The target probability of dose limiting toxicity is 0.15. Escalation to dose level 2 from dose level 1 was not permitted until three participants have completed their observation period on dose level 1. The third participant assigned to dose level 1 completed observation on April 26, 2008, and since no toxicities had occurred the participant that enrolled two days later on April 28, 2008 was assigned to dose level 2.

Likewise, the third participant assigned to dose level 2 completed the observation period toxicity-free on August 6, 2008, and so the participant that enrolled on August 12, 2009 was assigned to dose level 3. Also note that because `dosejump` = 1, dose levels are not skipped. Of course, for escalation to take place when the restriction rules are satisfied the estimated probability of dose limiting toxicity must be closest to (without going over) a dose level greater than dose level 1 (not shown).

In the next example, escalation does not occur until three completed observation periods. The `titecrm.sas` program parameters are `level1` = 1, `rshceme` = 13, `dosejump` = 1 and `nproceed` = 3 (Table 12). The target probability of dose limiting toxicity is also 0.15. Patient 18 enrolls in the clinical trial on September 19, 2008. Patient 12 has completed the 80 day observation window on dose level 3. Patients 13, 14, 15, 16, and 17 are still under observation on September 19, 2008 and on this day have been observed for 65, 38, 46, 18, and 15 days, respectively. Thus, when Patient 18 is ready to join the study there has been $65 + 38 + 46 + 18 + 15 = 252$ days of cumulative experience on dose level 3. Patient 18 was the first participant to enroll after three observation periods of combined experience ($80 \times 3 = 240$ days) on dose level 3 and was permitted to receive the next highest dose.

Table 13 shows an example trial with `level1` = 1, `rshceme` = 2, and `nproceed` = 11. Escalation is not permitted to occur until after 11 patients have completed the observation period. The eleventh participant finished the follow-up window on August 21, 2008. The next patient to enter the study after this date was Patient 16 (started on September 4, 2008). This patient was allowed to be assigned a dose level other than level 1. Note that by this time the dose-toxicity model recommended that the dose level closest to the target toxicity probability without going over was level 5.

Table 14 shows a simulated trial with `level1` = 3 and `rshceme` = 0. Again, the target probability of dose limiting toxicity is 0.15. In this situation the initial dose limiting toxicity estimates remain the same as in the previous examples, but the true probabilities of toxicity are now assumed to exceed these initial estimates. Since the simulated toxicity outcomes are based on the assumed true probabilities, there are now more observed toxicities. For this particular clinical trial the first participant is assigned to dose level 3, which is initially presumed to be closest to the target probability of dose limiting toxicity. No escalation schemes are used.

Table 11: Example validation dataset 3: target = 0.15, `level1` = 1, `rshceme` = 12, `dosejump` = 1, `nproceed` = 3

Dose Level	Initial Estimate Probability of Toxicity	True Probability of Toxicity
1	0.050	0.075
2	0.100	0.098
3	0.150	0.127
4	0.200	0.165
5	0.250	0.214
6	0.300	0.278

Patient Number	Start Date	End Date	Toxicity	Assigned Level
1	1-Jan-2008	21-Mar-2008	0	1
2	22-Jan-2008	11-Apr-2008	0	1
3	6-Feb-2008	26-Apr-2008	0	1
4	16-Feb-2008	6-May-2008	0	1
5	16-Mar-2008	4-Jun-2008	0	1
6	30-Mar-2008	18-Jun-2008	0	1
7	19-Apr-2008	8-Jul-2008	0	1
8	28-Apr-2008	17-Jul-2008	0	2
9	12-May-2008	31-Jul-2008	0	2
10	18-May-2008	6-Aug-2008	0	2
11	2-Jun-2008	21-Aug-2008	0	2
12	23-Jun-2008	11-Sep-2008	0	2
13	16-Jul-2008	13-Aug-2008	0	2
14	12-Aug-2008	31-Oct-2008	0	3
15	14-Aug-2008	2-Nov-2008	0	3
16	1-Sep-2008	20-Nov-2008	0	3
17	4-Sep-2008	23-Nov-2008	0	3
18	19-Sep-2008	17-Oct-2008	1	3
19	9-Oct-2008	28-Dec-2008	0	3
20	24-Oct-2008	14-Nov-2008	1	3
21	7-Nov-2008	29-Jan-2009	0	4
22	11-Nov-2008	30-Jan-2009	0	4
23	27-Nov-2008	15-Feb-2009	0	3
24	5-Dec-2008	23-Feb-2009	0	3
25	30-Dec-2008	18-Mar-2009	1	3

Table 12: Example validation dataset 4: target = 0.15, `level1` = 1, `rshceme` = 13, `dosejump` = 1, `nproceed` = 3

Dose Level	Initial Estimate Probability of Toxicity	True Probability of Toxicity
1	0.050	0.075
2	0.100	0.098
3	0.150	0.127
4	0.200	0.165
5	0.250	0.214
6	0.300	0.278

Patient Number	Start Date	End Date	Toxicity	Assigned Level
1	1-Jan-2008	21-Mar-2008	0	1
2	22-Jan-2008	11-Apr-2008	0	1
3	6-Feb-2008	26-Apr-2008	0	1
4	16-Feb-2008	6-May-2008	0	1
5	16-Mar-2008	4-Jun-2008	0	1
6	30-Mar-2008	18-Jun-2008	0	2
7	19-Apr-2008	8-Jul-2008	0	2
8	28-Apr-2008	17-Jul-2008	0	2
9	12-May-2008	31-Jul-2008	0	2
10	18-May-2008	6-Aug-2008	0	2
11	2-Jun-2008	21-Aug-2008	0	2
12	23-Jun-2008	11-Sep-2008	0	3
13	16-Jul-2008	13-Aug-2008	0	3
14	12-Aug-2008	31-Oct-2008	0	3
15	14-Aug-2008	2-Nov-2008	0	3
16	1-Sep-2008	20-Nov-2008	0	3
17	4-Sep-2008	23-Nov-2008	0	3
18	19-Sep-2008	17-Oct-2008	1	4
19	9-Oct-2008	28-Dec-2008	0	4
20	24-Oct-2008	14-Nov-2008	1	4
21	7-Nov-2008	26-Jan-2009	0	4
22	11-Nov-2008	30-Jan-2009	0	4
23	27-Nov-2008	15-Feb-2009	0	3
24	5-Dec-2008	23-Feb-2009	0	4
25	30-Dec-2008	18-Mar-2009	1	4

Table 13: Example validation dataset 5: target = 0.15, `level1` = 1, `rshceme` = 2, `nproceed` = 11

Dose Level	Initial Estimate Probability of Toxicity	True Probability of Toxicity
1	0.050	0.075
2	0.100	0.098
3	0.150	0.127
4	0.200	0.165
5	0.250	0.214
6	0.300	0.278

Patient Number	Start Date	End Date	Toxicity	Assigned Level
1	1-Jan-2008	21-Mar-2008	0	1
2	22-Jan-2008	11-Apr-2008	0	1
3	6-Feb-2008	26-Apr-2008	0	1
4	16-Feb-2008	6-May-2008	0	1
5	16-Mar-2008	4-Jun-2008	0	1
6	30-Mar-2008	18-Jun-2008	0	1
7	19-Apr-2008	8-Jul-2008	0	1
8	28-Apr-2008	17-Jul-2008	0	1
9	12-May-2008	31-Jul-2008	0	1
10	18-May-2008	6-Aug-2008	0	1
11	2-Jun-2008	21-Aug-2008	0	1
12	23-Jun-2008	11-Sep-2008	0	1
13	16-Jul-2008	13-Aug-2008	0	1
14	12-Aug-2008	31-Oct-2008	0	1
15	14-Aug-2008	2-Nov-2008	0	1
16	1-Sep-2008	20-Nov-2008	0	5
17	4-Sep-2008	23-Nov-2008	0	5
18	19-Sep-2008	17-Oct-2008	1	5
19	9-Oct-2008	28-Dec-2008	0	5
20	24-Oct-2008	14-Nov-2008	1	4
21	7-Nov-2008	26-Jan-2009	0	4
22	11-Nov-2008	30-Jan-2009	0	4
23	27-Nov-2008	15-Feb-2009	0	3
24	5-Dec-2008	23-Feb-2009	0	3
25	30-Dec-2008	18-Mar-2009	1	3

Table 14: Example validation dataset 6: target = 0.15, `level1` = 3, `rshceme` = 0

Dose Level	Initial Estimate Probability of Toxicity	True Probability of Toxicity
1	0.050	0.300
2	0.100	0.400
3	0.150	0.500
4	0.200	0.600
5	0.250	0.700
6	0.300	0.800

Patient Number	Start Date	End Date	Toxicity	Assigned Level
1	1-Jan-2008	18-Feb-2008	1	3
2	22-Jan-2008	11-Apr-2008	0	3
3	6-Feb-2008	26-Apr-2008	0	3
4	16-Feb-2008	6-May-2008	0	3
5	16-Mar-2008	4-Jun-2008	0	1
6	30-Mar-2008	18-Jun-2008	0	1
7	19-Apr-2008	8-Jul-2008	0	2
8	28-Apr-2008	4-May-2008	1	2
9	12-May-2008	7-Jul-2008	1	1
10	18-May-2008	6-Aug-2008	0	1
11	2-Jun-2008	1-Aug-2008	1	1
12	23-Jun-2008	11-Sep-2008	0	1
13	16-Jul-2008	4-Oct-2008	0	1
14	12-Aug-2008	9-Sep-2008	1	1
15	14-Aug-2008	2-Nov-2008	0	1
16	1-Sep-2008	22-Sep-2008	1	1
17	4-Sep-2008	23-Nov-2008	0	1
18	19-Sep-2008	8-Dec-2008	0	1
19	9-Oct-2008	28-Dec-2008	0	1
20	24-Oct-2008	12-Jan-2009	0	1
21	7-Nov-2008	24-Jan-2009	1	1
22	11-Nov-2008	30-Jan-2009	0	1
23	27-Nov-2008	15-Feb-2009	0	1
24	5-Dec-2008	23-Feb-2009	0	1
25	30-Dec-2008	20-Mar-2009	0	1

6.3 Validation of Variable Weighting and Delay Options

6.3.1 Effect of Weights without Delay

The outputs of the `titecrm.sas` program are validated for variable weighting by comparing the results of uniform weighting versus the results of variable weighting. The patient data file has five subjects with study dates as shown in Table 15. The total observation period for toxicity is 126 days.

Table 15: Patient data and weighting with uniform weighting

Reg Number	Dose	Study date	Response	Response date	Delay	Weight
DEF	24 mg	30JUN2009	0	05SEP2009	0	0.96
GHI	24 mg	03JUL2009	0	09OCT2009	0	0.94
ABC	24 mg	17JUL2009	0	20SEP2009	0	0.83
JKL	26 mg	02AUG2009	0	08OCT2009	0	0.70
MNO	26 mg	15AUG2009	1	21OCT2009	0	1.00

Table 16: The output from the `titecrm.sas` program for estimated toxicities using uniform weighting

Level	Dose	Posterior P	DLTs	Num treated	Prior P	Lower CI	Upper CI	P$>target+E$
1	24 mg	0.066	0	3	0.01	0.003	0.442	0.075
2	26 mg	0.106	1	2	0.02	0.007	0.517	0.119

alpha 0.744 SD alpha 0.186

Consider patient DEF, the number of days on study w.r.t. the current date 29OCT2009 is 121 days and hence the weight is correctly calculated as $121/126 = 0.96$. The weights for other subjects are correctly calculated in a similar manner. It should be noted that patients who have experienced a DLT are given a weight of 1.

Now consider the results in the presence of variable weighting. The weight was linear up to 0.9 at day 63 then linear to a value of 1 from this change point for the remaining 63 days. The output is presented in Table 17 and Table 18 presents the posterior probability distribution in the presence of variable weighting.

Consider subject DEF again, who was on study for 121 days. As per the variable weighting scheme his weight is calculated by interpolating 121 between 63 and 126 days. Using the slope formula we have the weight as $0.9+(1-0.9)*(121-63)/(126-$

Table 17: Patient data and weighting with variable weighting

Reg Number	Dose	Study date	Response	Response date	Delay	Weight
DEF	24 mg	30JUN2009	0	05SEP2009	0	0.99
GHI	24 mg	03JUL2009	0	09OCT2009	0	0.99
ABC	24 mg	17JUL2009	0	20SEP2009	0	0.97
JKL	26 mg	02AUG2009	0	08OCT2009	0	0.94
MNO	26 mg	15AUG2009	1	21OCT2009	0	1.00

Table 18: The output from the `titecrm.sas` program for estimated toxicities using variable weighting

Level	Dose	Posterior P	DLTs	Num treated	Prior P	Lower CI	Upper CI	P$> target + E$
1	24 mg	0.059	0	3	0.01	0.003	0.405	0.060
2	26 mg	0.097	1	2	0.02	0.007	0.482	0.099

alpha 0.759 SD alpha 0.182

63) $= 0.9 + 0.092 = 0.992$ The slopes for the other subject GHI with 118 days on study and subject ABC with 104 days is calculated in a similar manner.

Another fact to be noted is that posterior probabilities are lower in the case of variable weighting as compared to uniform weighting. This is because the four patients who do not have a DLT are given a greater weight as compared to the case of uniform weighting which causes the estimate of alpha to be higher and thus the net effect is a decrease in the estimated toxicity levels.

6.3.2 Effect of Weights with Delay

The `titecrm.sas` program has the option of incorporating delay in the trial. The output in the presence of delay is validated by comparing the output with and without delay. The `titecrm.sas` program is executed by adding delays for some of the subjects on study in the presence of uniform weighting. Table 19 shows the patient profile in the absence of delay.

The input dataset has two subjects ABC and GHI with a delay of 30 and 20 days respectively. The corresponding days on study for these subjects as of 29OCT2009 is 104 and 118 respectively and each have a corresponding weight of $104/(126 + 30) = 0.67$ and $118/(126 + 20) = 0.81$ Since the other subjects do not have any delay their

Table 19: Patient data and weighting with uniform weighting and absence of delay

Reg Number	Dose	Study date	Response	Response date	Delay	Weight
DEF	24 mg	30JUN2009	0	05SEP2009	0	0.96
GHI	24 mg	03JUL2009	0	09OCT2009	0	0.94
ABC	24 mg	17JUL2009	0	20SEP2009	0	0.83
JKL	26 mg	02AUG2009	0	08OCT2009	0	0.70
MNO	26 mg	15AUG2009	1	21OCT2009	0	1.00

Table 20: Patient data and weighting with uniform weighting and delay

Reg Number	Dose	Study date	Response	Response date	Delay	Weight
DEF	24 mg	30JUN2009	0	05SEP2009	0	0.96
GHI	24 mg	03JUL2009	0	09OCT2009	20	0.81
ABC	24 mg	17JUL2009	0	20SEP2009	30	0.67
JKL	26 mg	02AUG2009	0	08OCT2009	0	0.70
MNO	26 mg	15AUG2009	1	21OCT2009	0	1.00

Table 21: The output from the `titecrm.sas` program for uniform weighting in the presence of delay

Level	Dose	Posterior P	DLTs	Num treated	Prior P	Lower CI	Upper CI	P$>target+E$
1	24 mg	0.070	0	3	0.01	0.003	0.477	0.085
2	26 mg	0.112	1	2	0.02	0.007	0.548	0.132

alpha 0.736 SD alpha 0.189

weight is calculated by using 126 as the study day period.

In the presence of variable weighting that assigns a weight of 0.9 at 63 days and a weight of 1 at 126 days, the weight for ABC is calculated as $0.9+(1-0.9)*(104-63*factor)/(factor*(126-63)) = 0.9+0.0356 = 0.93$ where $factor = (126+30)/126$ The results are as presented in Table 22 and Table 23

Table 22: Patient data and weighting with variable weighting in presence of delay

Reg Number	Dose	Study date	Response	Response date	Delay	Weight
DEF	24 mg	30JUN2009	0	05SEP2009	0	0.99
GHI	24 mg	03JUL2009	0	09OCT2009	20	0.96
ABC	24 mg	17JUL2009	0	20SEP2009	30	0.93
JKL	26 mg	02AUG2009	0	08OCT2009	0	0.94
MNO	26 mg	15AUG2009	1	21OCT2009	0	1.00

Table 23: The output from the `titecrm.sas` program for variable weighting in the presence of delay

Level	Dose	Posterior P	DLTs	Num treated	Prior P	Lower CI	Upper CI	P$>target+E$
1	24 mg	0.060	0	3	0.01	0.003	0.410	0.062
2	26 mg	0.098	1	2	0.02	0.007	0.487	0.101

alpha 0.757 SD alpha 0.182

These results also conform to the fact that as delay increases, the weight will decrease and hence the estimated probability of toxicity increases.

6.4 Posterior Intervals

The accuracy of the posterior intervals was evaluated by comparing the results with the results from simulations in WinBUGS using the same data, model and prior distributions. WinBUGS uses Markov Chain Monte Carlo simulations to generate posterior distributions. The simulations cannot incorporate incomplete data and hence all patients on the study are assumed to have experienced an event, either no DLT or a DLT by the end of the observation period T. This is the CRM scenario, a special case of the TITE-CRM algorithm.

The input to the `titecrm.sas` program was tested using the patient profile data shown in Table 24.

Table 24: Profile of patient data for validation of posterior distribution

Level	Dose	DLTs	Num treated
1	24 mg	0	4
2	26 mg	0	3
3	28 mg	1	1

Table 25: Output of posterior probability distribution from the `titecrm.sas` program

Level	Dose	Posterior P	DLTs	Num treated	Prior P	Lower CI	Upper CI	P$>target+E$
1	24 mg	0.030	0	4	0.01	0.001	0.235	0.017
2	26 mg	0.053	0	3	0.02	0.004	0.312	0.033
2	28 mg	0.111	1	1	0.05	0.012	0.433	0.085

alpha 0.854 SD alpha 0.179

For the simulations in WinBUGS, a burn-in period of 1000 was used after 10000 iterations in WinBUGS. Table 26 shows the output of the simulations from Winbugs.

On comparing the outputs from the `titecrm.sas` program and the WinBUGS simulation we find that the value of alpha and its SD matches in both the cases. The median values of the posterior probabilities from WinBUGS are a closer match to the posterior probabilities of the `titecrm.sas` program as compared to the mean

Table 26: Posterior distribution based on simulation in WinBUGS

Parameter	Mean	Median	SD	2.5% cred.int	97.5% cred.int
Alpha	0.855	0.837	0.1804	0.5522	1.25
$\hat{p}_{24}$	0.055	0.034	0.0633	0.0015	0.232
$\hat{p}_{26}$	0.085	0.059	0.0829	0.0036	0.309
$\hat{p}_{28}$	0.149	0.122	0.1137	0.0117	0.430

values. This suggests that the posterior distributions are highly skewed. The credible intervals for the posterior probabilities from the `titecrm.sas` program are a reasonable accurate approximation to those from WinBUGS. For datasets with larger number of patients the correspondence between the two intervals becomes even closer.

6.5 Robustness of Numerical Methods

In order to test the robustness of the numerical integration employed as part of the TITE-CRM program, a fabricated example that forced the dose-toxicity model parameter to take on extreme values was devised. A total of 32 enrolled patients with start and end dates provided in Table 27, all assigned to dose level 1. It should be noted that this example is unrealistic since the adaptive design would have recommended that the dose level be increased.

The initial estimate of the probability of dose limiting toxicity for dose level 1 (π_1) is manipulated to force the dose-toxicity parameter α to become extremely large (Table 28). This scenario was performed using both the `titecrm.sas` and the modified R function. For instance, when the initial estimate of the probability of dose limiting toxicity for dose level 1 is 0.94, the SAS and R programs give similar estimates (25.70912 and 25.70966, respectively). At larger values of π_1, however, the R program cannot accurately estimate the model parameter, while `titecrm.sas` continues to provide reasonable estimates.

Table 27: Numerical Methods Dataset

Patient Number	Start Date	End Date	Toxicity	Assigned Level	Patient Number	Start Date	End Date	Toxicity	Assigned Level
1	1-Jan-2008	5-Sep-2008	0	1	17	3-Feb-2008	20-Sep-2008	0	1
2	1-Jan-2008	6-Sep-2008	0	1	18	3-Feb-2008	9-Sep-2008	0	1
3	2-Jan-2008	12-Sep-2008	0	1	19	3-Feb-2008	9-Sep-2008	0	1
4	2-Jan-2008	5-Sep-2008	0	1	20	16-Feb-2008	20-Sep-2008	0	1
5	2-Jan-2008	9-Sep-2008	0	1	21	16-Feb-2008	19-Aug-2008	0	1
6	2-Jan-2008	8-Sep-2008	0	1	22	17-Feb-2008	20-Sep-2008	0	1
7	2-Jan-2008	5-Sep-2008	0	1	23	17-Feb-2008	20-Sep-2008	0	1
8	3-Jan-2008	9-Sep-2008	0	1	24	1-Mar-2008	12-Sep-2008	0	1
9	16-Jan-2008	19-Aug-2008	0	1	25	1-Mar-2008	9-Aug-2008	0	1
10	17-Jan-2008	20-Sep-2008	0	1	26	1-Mar-2008	12-Sep-2008	0	1
11	1-Feb-2008	6-Aug-2008	0	1	27	3-Mar-2008	20-Sep-2008	0	1
12	1-Feb-2008	6-Aug-2008	0	1	28	1-Apr-2008	9-Aug-2008	0	1
13	2-Feb-2008	8-Sep-2008	0	1	29	2-Apr-2008	5-Sep-2008	0	1
14	2-Feb-2008	8-Sep-2008	0	1	30	17-Apr-2008	20-Sep-2008	0	1
15	2-Feb-2008	5-Sep-2008	0	1	31	16-May-2008	20-Aug-2008	0	1
16	2-Feb-2008	8-Sep-2008	0	1	32	2-Aug-2008	12-Sep-2008	0	1

Table 28: Numerical Methods Results

Dose Level	Number Treated	Number of Toxicities	Prior Estimate
1	32	0	π_1
2	0	0	0.991
3	0	0	0.992
4	0	0	0.993
5	0	0	0.994
6	0	0	0.995

π_1	$\hat{\alpha}_{\text{SAS}}$	$\hat{\alpha}_{\text{R}}$	$\hat{\alpha}_{\text{R}} - \hat{\alpha}_{\text{SAS}}$
0.8000	10.52382	10.52388	0.00006
0.9000	13.45700	13.45714	0.00014
0.9400	25.70912	25.70966	0.00054
0.9460	36.97769	36.97883	0.00114
0.9461	37.28700	168.71860	131.43160
0.9462	37.60400	202.85570	165.25170

7 Appendix

Macro Variables – All Runs:

`adm_dose`	Method for setting admissible dose 1=Dose limiting toxicity is less than Target 2=Dose limiting toxicity closest to the Target Default value = 1
`adm_marg`	Allowable excess of dose limiting toxicity over the Target A value in the range [0,1] Default value = 0.05
`dateflag`	Method for setting `today`: 0 = Current system date (i.e., right now) 1 = Last date relevant to trial (i.e., at end of trial) 2 = Value in `somedate` Default value = 0
`debug`	Debug flag, ON = 1 Default value = 1
`dosefile`	Dose descriptor file name
`dosejump`	Number of dose level increases allowed between consecutive patients Default value = 1
`dtmodel`	Dose-toxicity model, logistic or Lyman Default value = Logistic
`excess`	Unacceptable excess over the Target dose limiting toxicity Any value in the range of [0,1] Default value = 0.2
`gamma`	Gamma parameter for Lyman model
`iflag`	0 = Patients who do not complete observation period become unevaluable 1 = Patients who do not complete observation period are evaluable and downweighted (if response = 2)
`level1`	First dose level for trial
`nproceed`	Number of patients needed to complete before dose escalation Default value = 1
`obsdays`	Number of days patient is followed for toxicity
`off_adm_marg`	Number of patient after which admissible margin becomes zero Default value = 10
`prior`	Prior distribution, normal, beta or exp

Default value = normal

`priora` α of beta prior

`priorb` β of beta prior

`priorstd` Standard deviation of normal prior
Default value = 0.3

`rscheme` 0 = No restriction, use target dose
1 = Allow only `dosejump` levels between patients
2 = Require `nproceed` complete patients before escalation
3 = Require `nproceed` observation periods before escalation
12 = 1 + 2
13 = 1 + 3
Default value = 12

`simflag` 0 = Single trial, 1 = Simulate

`somedate` Fixed date (since 01JAN1960)

`target` Target dose limiting toxicity probability

`td50` TD50 parameter for Lyman model

`titeflag` 0 = CRM, 1 = TITE-CRM
Default value = 1

`vwdays` $\{\delta_1, \ldots, \delta_k\}$ obsdays for variable weighting

`vwflag` 0 = constant weighting throughout trial
1 = variable weighting
Default value = 0

`vwwts` $\{w_1, \ldots, w_{k-1}, 1\}$ for variable weighting

Macro Variables – Simulations Only:

`clearsim` Clear previous simulations:
0 = No
1 = Yes
Default value = 1

`maxsub`	Total number of subjects recruited if `varcruit`=0 Default value = 0
`nsim`	Number of simulated trials
`nrunin`	Number of patients needed before checking the stopping rule Default value = 3
`outdir`	Directory for output SAS Data Files PATIENT and TRIAL
`periods`	Periods (in days) for rectimes if `varcruit`=1
`rectime`	Mean interarrival time between patients if `varcruit`=0
`rectimes`	Mean interarrival times between patients if `varcruit`=1
`seed1`	Random number seed for simulations
`simtag`	ID tag for simulation runs
`urdays`	$\{\delta_1, \ldots, \delta_k\}$ obsdays for variable weighting
`urflag`	Variable (non-uniform) hazard 0 = No, use uniform hazard 1 = Yes, use non-uniform hazard Default value = 0
`urwts`	$\{w_1, \ldots, w_{k-1}, 1\}$ for variable weighting
`varcruit`	Variable recruitment 0 = No, use macro variables `maxsub` and `rectime` 1 = Yes, use macro variables `periods` and `rectimes` Default value = 0

Macro Variables – Single Trial Runs Only:

`patfile`	Patient data full file name
`patform`	Format type of patient data: 1 = Dose levels (e.g., $1, 2, 3, \ldots$) are specified 2 = Dose names (e.g., 25 mg/m^2) are specified Default value = 2
`title1`	Top level title for printouts Default value = Example Trial

Macro Variables – Internally Set:

`nlevel`	Number of dose levels
`readerr`	Patient data read error flag: 0 = No Error 1 = Error
`today`	Date of calculation