CONTINUOUS SAFETY MONITORING OF EXCESS TOXICITY IN SINGLE ARM EARLY PHASE BIOMARKER DRIVEN TRIALS

by

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CERTIFICATE OF APPROVAL

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This is to certify that the Master's thesis of

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ABSTRACT

Early phase oncology trials often require a continuous safety monitoring because of the unexpected toxicity associated with investigational agents. Safety monitoring becomes especially challenging in biomarker driven trials where each patient potentially receives a different treatment according to his/her biomarker profile. We propose to develop and evaluate continuous stopping boundaries for excess toxicity in the context of biomarker driven clinical trials. In this investigation, we intend to extend the Pocock methodology adopted by Ivanova et al. (2005) [1] for safety monitoring of a single agent to biomarker driven clinical trials in which multiple drugs of different toxicity profiles are studied. We will develop drug-specific as well as overall toxicity boundaries. The proposed method will be evaluated by simulation studies. The motivation from this research came from the phase IB trial of the standard chemotherapy plus a targeted agent among newly diagnosed acute myeloid leukemia patients, where the targeted agent is identified using the kinase inhibitor screening assay. The proposed method will be illustrated using the actual clinical trial.

INTRODUCTION

Background Literature

Acute Myeloid Leukemia (AML)

Acute myeloid leukemia (AML), also referred as acute myelogenous leukemia or acute myelocytic leukemia, is the most common type of blood cancer in adults, with more than 50% of cases recorded in individuals over 65. The American's Cancer Society estimates about 20,830 new cases in 2015 in the United States of America. The median age at diagnostic of AML is 67 and it is uncommon before the age of 45. The disease is very aggressive with only 40 to 50% of patients that can be cured [2] [3]. Relapse is nearly always fatal [4].

According the World Health Organization (WHO), Acute myeloid leukemia, along with its genetic abnormalities, is defined based on combination of clinical, morphologic, immunophenotypic and genetic features [5]. One major clinical question in AML is to categorize patients depending on their responses to treatments. Identification of cytogenetic and molecular alterations using diagnostic tests is of significant importance in the aim of stratifying patients into prognostic categories. An international expert panel on behalf of the European LeukemiaNet (ENL) [6] convened in 2010 to develop a genetic risk classification based on cytogenetic and selected molecular abnormalities that correlate strongly with genetic findings and treatment outcomes (Table 1). This classification gives indication on the heterogeneity of AML based on its clinical presentation, response to treatment and overall prognosis. Molecular dysfunctions leading to abnormal kinase activation for AML patients renders the choice of tyrosine kinase inhibitors (TKIs) difficult with existing techniques. TKIs constitute a unique class of therapy that

block the enzyme tyrosine kinase without destroying the healthy cells, compared to standard chemotherapy, which tend to stop cancer cells growth and division.

Table 1: European LeukemiaNet Standardized Reporting System for Correlation of Cytogenetic and Molecular Genetic Data in AML With Clinical Data

Genetic Group	Subsets
Favorable	t(8;21)(q22;q22); RUNX1-RUNX1T1 inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11 Mutated NPM1 without FLT3-ITD* (normal karyotype) Mutated CEBPA (normal karyotype)
Intermediate-I	Mutated NPM1 and FLT3-ITD (normal karyotype) Wild-type NPM1 and FLT3-ITD (normal karyotype) Wild-type NPM1 without FLT3-ITD (normal karyotype)
Intermediate-II	t(9;11)(p22;q23); MLLT3-MLL Cytogenetic abnormalities not classified as favorable or adverse
Adverse	inv(3)(q21q26.2) or t(3;3)(q21;q26.2); RPN1-EVI1 t(6;9)(p23;q34); DEK-NUP214 t(v;11)(v;q23); MLL rearranged –5 or del(5q) –7 abnl(17p) Complex karyotype**

*ITD, internal tandem duplication

**Complex karyotype is defined as three or more chromosome abnormalities in the absence of one of the WHO designated recurring translocations or inversions: t(8;21), inv(16) or t(16;16), t(15;17), t(9;11), t(v;11)(v;q23), t(6;9), inv(3) or t(3;3).

Targeted Therapies in Acute Myeloid Leukemia (AML)

Investigators from the Knight Cancer Institute at Oregon Health and Sciences University tested personalized targeted interventions with a kinase inhibitor rapid screening assay to firstly identify tyrosine kinase signaling pathways that lead to inhibition of myeloid leukemia cell growth, and secondly help finding individualized treatment options in a short timeframe of 3-5 days. Since AML is characterized by constitutive tyrosine kinase activation, treatment

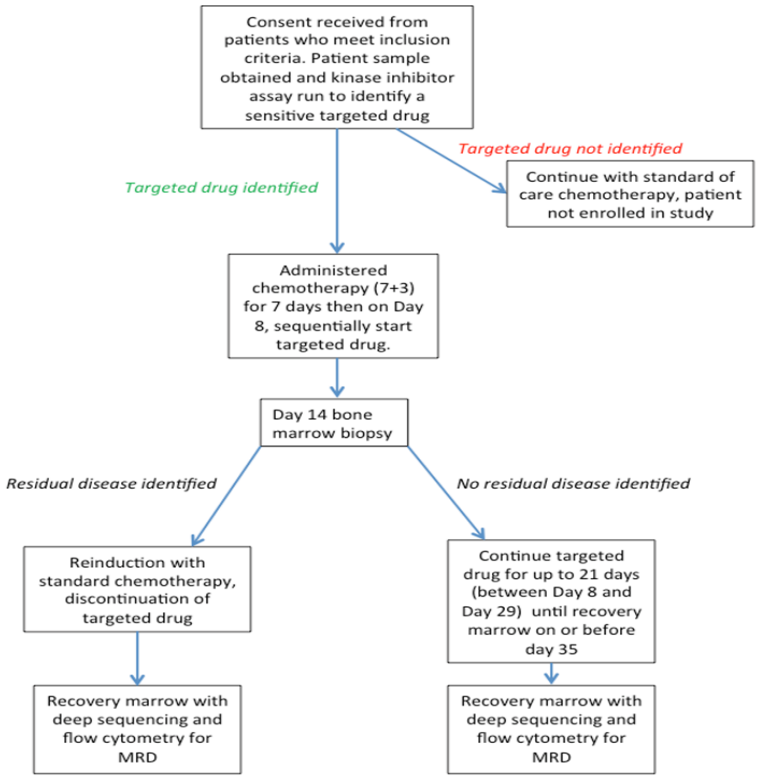
considerations have been recently favoring TKIs. Nevertheless, these latter demonstrate short clinical responses when administered on their own. Targeted TKIs in conjunction with standard chemotherapy can significantly improve clinical outcomes. In this setting, a phase IB trial was initiated to evaluate the safety of the combination of kinase inhibitors and chemotherapy regimen [OHSU eIRB #11766 "A phase IB feasibility study of personalized kinase inhibitor therapy combined with induction chemotherapy in acute myeloid leukemia in patients who exhibit in vitro kinase inhibitor sensitivity." (PI: Stephen Spurgeon, MD)].

After consent is given from patients who meet the inclusion/exclusion criteria, peripheral blood or bone marrow samples are collected and assessed for drug sensitivity through an in-vitro functional kinase inhibitor screen (Figure 1). The kinase inhibitor that kills most leukemic cells at the lowest concentration is considered most effective and designated as a target drug. Once the targeted drug is identified, a subject receives the standard chemotherapy plus the target drug. If multiple kinase inhibitors are identified as sensitive, the kinase inhibitor is chosen using additional sensitivity parameters including additional curve fitting parameters (slope and area under the curve) and consistency among triplicates.

Five FDA approved drugs are currently under study: Dasatinib, Sorafenib, Sunitinib, Ponatinib, and Nilotinib. The assay workflow is set up to identify one target-drug by day 7, which is administered on day 8. Whereas, induction therapy consisted in a combination of standard chemotherapy with 7 days of continuous infusion of cytarabine and 3 days of anthracycline. This therapy was referred to as "7+3" treatment and it shows 70 to 80% complete response in patients, noting that prognosis is poor for 20 to 30% of patients who were refractory to induction (Figure 1). This phase IB trial constituted the beginning of treatment safety assessment where the goal is

to evaluate safety of "7+3" plus target drug treatment, therefore requiring ongoing toxicity monitoring.

Figure 1: Flowchart Combination "7+3" and Targeted Therapy

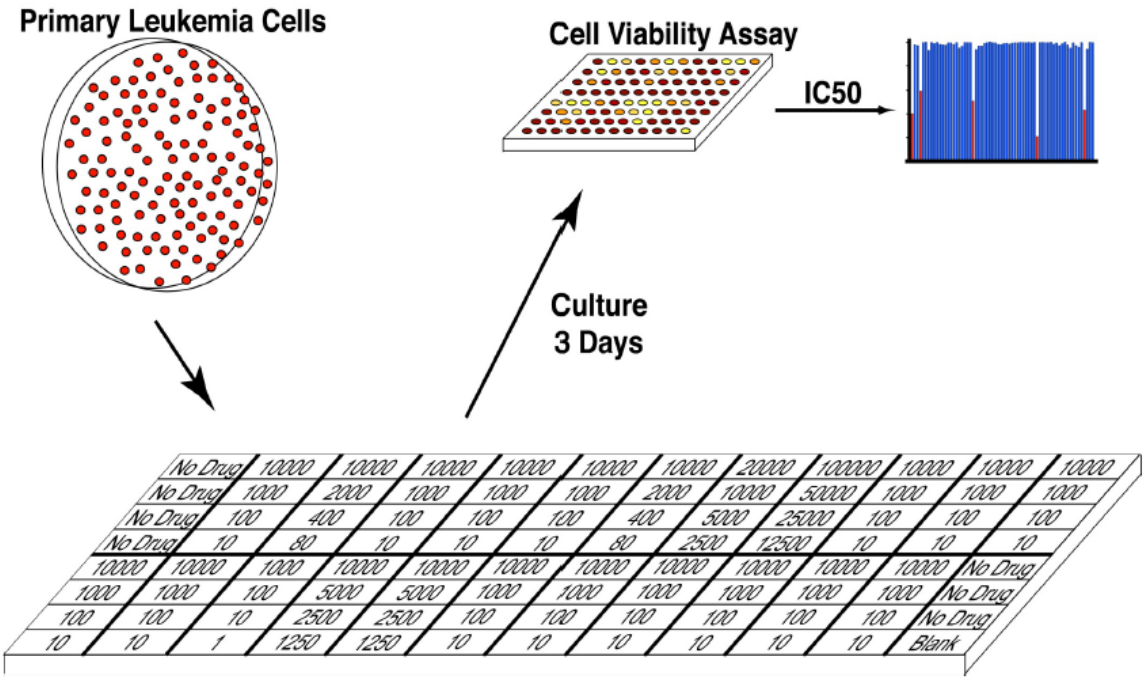


Kinase Inhibitor Screen

The kinase inhibitor screen is a high-throughput assay with 384-well plate format, utilizing 90 small-molecule inhibitor drugs that are FDA approved or in clinical trials. The kinase inhibitor screen was implemented at OHSU in the aim of selecting inhibitors in relapsed refractory AML/ALL patients, by identifying kinase inhibitors to which patient primary leukemia sample was sensitive. In the eIRB 11766 trial, leukemia samples (peripheral blood or bone marrow) from newly diagnosed AML patients, between 21 to 64 years of age, are assessed for in vitro

response/drug sensitivity using a functional kinase inhibitor screen. The best kinase inhibitor is the one that kills most leukemia cells at the lowest concentration. Eight different concentrations are recorded, including the IC50 concentration (Figure 2). Dose-response curve is generated with the response being the percentage of live leukemia cells at each concentration. IC50 ("half maximal inhibitor concentration", concentration leading to 50% decrease in cell viability), the dose that kills 50% of leukemia cells, are computed from the dose-response curve. Values are compared to all samples tested to determine the most effective treatment for the subject regarding the degree of response in vitro. Percentage of the median IC50 is computed by dividing the observed IC50 by the median IC50 of the drug based on all the past samples. A drug with the lowest percentage of the median IC50 is considered as the most sensitive drug, a drug target for the patient. This approved drug, with a clinically achievable IC50, is added to the "7+3" induction therapy.

Figure 2: Kinase Inhibitor Screen



Sequential Methods

In most randomized clinical trials, the subject recruitment and the outcome measurements are done sequentially over a period of time. As data accumulate over time, it is primordial to monitor the data and consider early stopping of the trial in case of safety or efficacy issues. Sequential methods are used to perform interim analysis of accumulating data. Typically the data are monitored at specific intervals; however, in certain instances, the data are monitored continuously, such as toxicity monitoring in very high-risk trials (e.g., gene therapy trials). In this section, sequential methods for interval monitoring are reviewed. Group sequential tests are very useful in clinical trials where the primary endpoint is evaluated at pre-specified time points during the trial. These tests offer an advantageous window for early stopping due to either a lack of efficacy (futility) or overwhelming efficacy. In both cases, such an action is considered ethnical since either the effective drug becomes available to everyone, or the ineffective drug is removed and does not consume additional resource.

Modern sequential methods was first introduced and largely investigated by Abram Wald (1947) [7] with his sequential probability ratio test (SPRT). SPRT methods lay on its selection between two competing hypotheses. It is a sequential hypothesis test, where it is assumed that the observations are from a distribution probability density function given from a parameter θ, testing a null H_0: $\theta = \theta_0$ versus the alternative H_1: $\theta = \theta_1$; with successive observations taken under the condition that the likelihood ratio remains in (a,b) interval. The critical boundary values a and b are chosen based on α and β, which are approximately equal to type I and type II errors. As new data increment, cumulative sum (S_i) of the log-likelihood ratio is calculated. When $a < S_i < b$, monitoring continues. If $S_i \leq a$ and $S_i \leq b$, we accept H_0 and H_1 respectively.

THEORY

Pocock's Test

As we discussed previously, both subject recruitment and outcome measurements are sequential in randomized clinical trials, leading to a necessity to monitor and assess accumulating data. Repeated testing results in an increase of the null probability of detecting significant difference. The rational for a repeated significance test of observations or matched pair observations relies on a fixed overall significance level α (set to a required level), which is the probability of observing a treatment difference under the null hypothesis.

Pocock's test evaluates accumulated data amending the notion of a repeated significance test [8]. It accounts for sequential design using two treatments, patient recruitment in matched pairs, and instant assessment of patient's normal or binary response. In this test, patient entry is divided into *K* equal-sized groups with *m* subjects in each group. Analysis is performed after accounting for each new group of subjects. One way of illustrating Pocock's test is to display a random assignment to treatment in each group considering that the subjects are administered each treatment. Instead of applying a level-α two sided-test at each step of analysis, which increases type I error, Pocock's test uses a repeatedly applied significance test. It rejects the null hypothesis if the standardized statistic Z_k is large with $Z_k = \frac{1}{\sqrt{(2mk\sigma 2}} (\sum_{i=1}^{mk} X_{Ai} - \sum_{i=1}^{mk} X_{Bi})$, X_{Ai} and X_{Bi} observations for treatment groups A and B:

- After group k =1,…, K-1: if $|Z_k| \geq C_P(K,\alpha)$ then reject H_0 and stop, otherwise continue to group k+1;
- After group K: if $|Z_k| \geq C_P(K,\alpha)$ then reject H_0 and stop, otherwise accept H_0 and stop.

$C_P(K,\alpha)$ are obtained using the joint distribution of the sequence of statistics $Z_1,\ldots, Z_k$, presented in table 2 [7]. At analysis k=1,…,K, H_0 is rejected if the two-sided significance level of a non-sequential test applied to each analysis is inferior to $\alpha'=2[1-\phi\{C_P(K,\alpha)\}]$, the nominal significance level (NB: $\phi\{C_P(K,\alpha)\}$ is the cumulative distribution function of the standard normal). This is a repeated significance test with constant "nominal significance level" α'.

Table 2: Pocock tests: constants $C_P(K,\alpha)$ for two-sided tests with k groups of observations and Type I error probability α R_B

	Cp(K,α)		
K	α = 0.01	α = 0.05	α = 0.10
1	2.576	1.96	1.645
2	2.772	2.178	1.875
3	2.873	2.289	1.992
4	2.939	2.361	2.067
5	2.986	2.413	2.122
6	3.023	2.453	2.164
7	3.053	2.485	2.197
8	3.078	2.512	2.225
9	3.099	2.535	2.249
10	3.117	2.555	2.27
11	3.133	2.572	2.288
12	3.147	2.588	2.304
15	3.182	2.626	2.344
20	3.225	2.672	2.392

O'Brien & Fleming's Test

O'Brien & Fleming's test proposes an alternative to the repeated significance test by allowing the nominal significance α' to increase at each analysis. Hence, rejecting H_0 becomes more challenging in the beginning of the analysis, and easier as the analysis evolves. The test is defined as follows:

i) After group k=1,…, K-1: if $|Z_k| \geq C_B(K,\alpha)\sqrt{(K/k)}$ then reject H_0 and stop, otherwise continue to group k+1;

ii) after group K: if $|Z_k| \geq C_B(K,\alpha)$ then reject H_0 and stop, otherwise accept H_0 and stop.

$C_B(K,\alpha)$ values are presented in table 3 [7]. At each analysis, H_0 is rejected if the two-sided significance level of H_0 is below $\alpha'_k=2[1-\phi\{C_B(K,\alpha)\sqrt{(K/k)}\}]$.

Table 3: O'Brien and Fleming tests: constants $C_B(K,\alpha)$ for two-sided tests with K groups of observations and Type I error probability α.

	CB(K,α)		
K	α = 0.01	α = 0.05	α = 0.10
1	2.576	1.960	1.645
2	2.58	1.977	1.678
3	2.595	2.004	1.71
4	2.609	2.024	1.733
5	2.621	2.04	1.751
6	2.631	2.053	1.765
7	2.640	2.063	1.776
8	2.648	2.072	1.786
9	2.654	2.08	1.794
10	2.660	2.087	1.801
11	2.665	2.092	1.807
12	2.670	2.098	1.813
15	2.681	2.11	1.826
20	2.695	2.126	1.842

Pocock and O'Brien Fleming tests differ qualitatively and quantitatively. Pocock test has narrower boundaries initially, allowing a greater opportunity for very early stopping. O'brien test shows narrower boundaries at later analyses and a smaller maximum sample size. Pocock uses the same boundaries at each look, whereas O'Brien boundaries decrease after each look (Appendix 1).

A Non-Bayesian Method for Identifying Stopping Boundary (Goldman 2001)

Both Pocock test and O'Brien & Fleming test are intended for efficacy evaluation, not safety. Goldman et al (2001) [9] proposed a method to simultaneous evaluation of efficacy and toxicity in small trials. The Goldman's method treats two events, efficacy and toxicity, in a single arm phase II trial setting, with efficacy as primary outcome. Therefore, the maximum sample size

will be determined based on the efficacy outcome. Efficacy will not be evaluated sequentially, as opposed to toxicity, which will ‘be continuously monitored using an upper stopping boundary.

In 1987, Goldman proposed a stopping boundary based on the upper SPRT boundary. In this approach, a maximum sample size is set and a stopping rule is constructed through adjustments of components, until a type I error rate is established. A newer version of this method was implemented in 2001 using a FORTRAN program called SeqOne, which introduced the computation of average sample number (ASN) and expected relative loss (ERL). Goldman illustrated this method with a one-arm bone marrow transplant phase II trial where they evaluated efficacy outcome and severe adverse experiences (toxicity monitoring). Three essential conditions are listed for the technique. Firstly, the maximum sample size (N), is determined by efficacy outcome. Two aspects seem to drive the choice of the sample size: phase II trials are known to assess efficacy; efficacy outcome and adverse events are usually correlated, leading to possible misleading information if both criteria are used to determine the sample size. Second, the trial is monitored continuously with an evaluation when an adverse event occurs. Finally, an upper boundary is used resulting in early termination of the trial if there is excessive number of toxicities. Let consider π the probability of a toxic event in a single patient and $b(e,j)$ the probability of e toxicities happening in j patients:

$$b(e,j) = \binom{j}{e} \pi^{e} (1-\pi)^{j-e}$$

The null hypothesis tests that the probability of observing a toxic event in a single patient is equal to the historical probability of toxicity, while the alternative hypothesis tests that the same probability of a toxic event is equivalent to an unacceptable high probability of toxicity. Toxicity monitoring is obtained by accumulating the number of events (e) and the number of subjects

enrolled at the time of event (n_e). Trial will be stopped if the e^{th} event occurs when n_e or fewer subjects are enrolled.

SPECIFIC AIMS

A phase 1b trial establishes the safety of a new treatment in humans in combination with other drugs or agents. It constitutes the first step before investigating the efficacy of a new treatment. As an early phase trial, unexpected toxicities associated with the treatment are very likely. Therefore a continuous monitoring of toxicity is crucial for insuring safety of human subjects.

Aim 1: Evaluate the operating characteristics of drug-specific toxicity boundaries based on Pocock methodology in a biomarker driven phase IB trial.

We develop and evaluate drug-specific toxicity boundaries for the phase IB trial of target tyrosine kinase inhibitors (TKIs) for newly diagnosed AML patients. TKIs represent individualized therapies of five FDA approved drugs, Dasatinib, Sorafenib, Sunitinib, Ponatinib, and Nilotinib, selected from a sensitivity-screening assay. Individual toxicity boundary will be derived using Pocock methodology and applied to each target drug group.

Aim 2: Evaluate the operating characteristics of overall toxicity boundaries using continuous toxicity stopping boundaries based on Pocock methodology.

We evaluate how to monitor safety when combining targeted TKIs therapy in conjunction with the standard chemotherapy induction. Standard chemotherapy induction refers to a combination of chemotherapy with 7 days of continuous infusion of cytarabine and 3 days of anthracyclin, designated as "7+3". We will implement overall toxicity boundary utilizing Pocock methodology

and evaluate the operating characteristics of the boundaries under different toxicity profiles of five study drugs.

APPROACH

Safety will be evaluated by the incidence of dose-limiting toxicity (DLT) over and above the expected toxicities of induction therapy, i.e. any Grade 3 or higher toxicity event. The trial will stop if the number of DLTs is equal or exceeds the stopping boundary (b_n) out of n patients with completed follow-up. The maximum planned sample size is determined at 40 patients. The desired probability of early stopping can be determined in consultation with the principal investigator. The event probability varies from drug to drug. Therefore one continuous toxicity boundary will be applied to the whole group, while individual toxicity boundary will be applied to each target group, with the option of terminating a particular drug-group in case of excess toxicity.

METHODS

Overall and drug-specific continuous toxicity boundaries will be developed using Pocock sequential boundary methodology. The method generates a Pocock-type boundary for repeated testing for toxicity. Pocock evaluated different group sequential boundaries depending on the number of planned interim analyses (Pocock's boundary is an increasing function of the number of interim analyses). This method has been extensively used focusing on safety monitoring of a single treatment. We will construct drug-specific and overall toxicity boundaries. We will need to specify the stopping boundary for after each patient of the sample size, with toxicity event defined as the dose-limiting toxicity (DLT) and K interim safety analyses after specific numbers

of patients. The boundaries are constant at each stage of those interim analyses, using the same critical values for each interim analysis. The proposed boundaries will be evaluated by simulation studies and will be illustrated using a Phase IB trial of the standard chemotherapy plus a targeted agent among newly diagnosed acute myeloid patients, where the targeted agent is identified using the kinase inhibitor screening assay.

Pocock Basic Model

The boundaries of the basic model will be constructed using toxicity outcome. The trial can stop early or continue until all K patients are treated. The trial stops if upper or lower boundaries are hit. Upper boundary is defined as the maximum number of toxicities that is tolerable during the trial, while lower boundary is the minimum number of toxicities acceptable. We consider that if all K patients are treated without halting the trial (no early stopping), this latter has reached the right boundary.

Let K be the maximum sample size and θ be the true toxicity rate of the dose chosen in the phase IB trial. θ is the mean of outcomes that are independent binary random variables. A treatment is considered safe if the incidence of dose-limiting toxicity (DLT) is less than θ_0. We will define θ_0 as the overall and drug-specific DLT interchangeably. We expect the probability of early stopping Φ to be small if $\theta = \theta_0$. Let $(b_1,...,b_K)$ the set of stopping boundaries for each k=1,…,K. The trial will stop if the number of toxicities for the first k patients is equal to or exceeds b_K. We consider a set of pointwise probabilities $\alpha_1=\alpha_2=\ldots=\alpha_K$ that define each boundary as data accumulate. Pocock boundary stipulates that each α_K is defined such that $\theta = \theta_0$, indicating that the probability of early stopping is as close to Φ as possible, but still below Φ. The estimation of

α in the Pocock boundary method is $\alpha = Pr\{Z>C_P(K, \alpha)\}$. Boundaries b_k are computed as the smallest integer such that $Pr\{Y \geq b_k\} \leq \alpha$, with Y following a binomial with parameters (k,θ_0).

Evaluation of the Proposed Method

We will illustrate the proposed method using an example from Ivanova et al. (2005), proposing a single-arm phase II study. This study included stopping boundaries based on toxicity level, with a maximum sample size of 20. The event probability is set to 0.20, while the desired probability of early stopping is equal to 0.05. The values of α for constructing the Pocock boundaries that yield the probability of stopping of 0.05 are given in table 4 [1]. Sequential boundaries are visited in order to determine boundaries with 20 stages as possible stopping boundaries for toxicity. The trial will stop if the number of dose-limiting toxicities is equal or superior to b_n out of n patients with completed follow-up. The Pocock boundary, that yields to the probability of crossing the boundary at most 0.0481, when the DLT is the acceptable level 0.20, is generated based on probability $\alpha=0.01959$ consistent with $Cp(K,\alpha) = 2.054$ [1]. The stopping boundaries are presented in table 5 [1] [11], along with detailed statistics.

Table 4: Pointwise Probabilities α Values for Constructing Pocock Boundaries for $\phi=0.05$

$\theta_0 = 0.1$		$\theta_0 = 0.2$		$\theta_0 = 0.3$	
K	α	K	α	K	α
15-16	0.02685	15, 18–20	0.01959	15–17	0.0253
17-20	0.02566	16–17	0.02666	18–21	0.02162
21-22	0.02389	21–24	0.01941	22–24	0.02097
23-24	0.02238	25–26	0.01806	25–26	0.01823
25-26	0.01853	27	0.01734	27–29	0.01747
27	0.01822	28–30	0.01696	30–31	0.01694
28-31	0.01791	31	0.01629	32–33	0.01525
32	0.01701	32–34	0.01672	34–36	0.01426
33-37	0.01585	35–36	0.01629	37–40	0.01384
38-39,44	0.01467	37–40	0.01487	41	0.01308
40-43	0.0155	41	0.01442	42–45	0.01215
45	0.01445	42, 44	0.01301	46	0.01166
46, 48-49	0.01403	43	0.01419	47–48	0.01133
47	0.01411	45–47	0.01272	49, 51	0.0113
50-51	0.01315	48	0.01263	50, 52–54	0.01116
52	0.0128	49–51	0.01167	55–56	0.01094
53-57	0.01273	52	0.01166	57–60	0.01073
58-60	0.01258	53–56	0.01161		
		57–59	0.01101		
		60	0.01098		

Table 5: Pocock and O'Brien-Fleming Boundaries

k	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Pocock boundary $\mathbf{b_k}$	-	-	3	4	4	4	5	5	5	6	6	6	7	7	7	8	8	8	9	9
O'Brien-Fleming $\mathbf{b_k}$ boundary	-	-	-	-	-	6	6	6	6	6	6	7	7	7	7	7	7	8	8	8

	Actual probability of early stopping	**Number of Events Expected Values**		**Number of Patients Expected Values**			
θ	**ϕ**	**E[Y]**	**SD[Y]**	**E[N]**	**SD[N]**	**E[Y/N]**	**SD[Y/N]**
0.2	0.0484	3.89	1.65	19.47	2.58	0.21	0.13
0.3	0.2326	5.31	1.6	17.7	4.81	0.34	0.18
0.4	0.5517	5.79	1.58	14.47	6.17	0.48	0.2
0.5	0.8342	5.39	1.64	10.78	5.91	0.6	0.2
0.6	0.9667	4.66	1.43	7.76	4.52	0.7	0.19
0.7	0.9972	4.03	1.05	5.76	3.03	0.78	0.18
0.8	0.9999	3.6	0.72	4.5	1.93	0.86	0.15
0.9	1	3.29	0.49	3.65	1.16	0.93	0.11
1	1	3	0	3	0	1	0

Y = the number of events, random, between 0 and N
N = the number of patients, random, between 1 and K
ϕ^* = the actual probability of early stopping (hitting the boundary)
E[ ] denotes the expected value (mean)
SD[ ] denotes the standard deviation

Extended Pocock-type Continuous Toxicity Boundary by Simulation Studies

We will adapt the Pocock stopping boundaries with K stages for continuous toxicity monitoring in a setting of multiple drugs with different toxicity levels, developed by Ivanova et al. (2005).

The total sample size is K=40. An overall toxicity boundary will be defined considering the whole sample size, as well a drug-specific boundary applied to each target drug. We will construct the boundaries (b_n) using different parameter setting by simulation of 1000 trials.

Several profiles based on the drug toxicity rates will be built around the drug assignments to construct the stopping rules (Figure 3). We will simulate various scenarios using 5 drugs in a first setting (Table 6) and 10 drugs (Table 7-11) in a second situation. In the first setting, we will determine the expectations of the drug assignment probabilities (p_i) of each drug as realistic as possible in conjunction with the investigator in newly diagnosed AML patients. Pocock-type boundaries that yield probability of early stopping of 0.05 and 0.10, as well as event probability of 0.20 and 0.10 respectively are used in the 5-drug setting to construct the termination rules.

According to the second setting, various drug assignment probabilities will be developed arbitrarily following certain distributions. An imbalance factor based on the probability of specific drug assignment will then be estimated as follows: $ImF = \frac{max(pi)}{min(pi)}$. The drug toxicity rates will be represented by θ_{ij} (with i drug and j scenarios).

The overall toxicity is a weighted average of the frequency probabilities and the toxicity probabilities, $\theta = \sum_{i=1}^{5} pi * \theta ij$ or $\theta = \sum_{i=1}^{10} pi * \theta ij$, depending on the setting of 5 or 10 drugs.

With regard to the scenarios, a maximum frequency probability will be set at 0.4 and the minimum at 0.025. The maximum and minimum toxicity rates will be fixed at respectively 0.8 and 0.1. The drug or trial should be stopped when the toxicity rate exceeds 0.20.

Figure 3: Drug Profiles for Boundary Construction

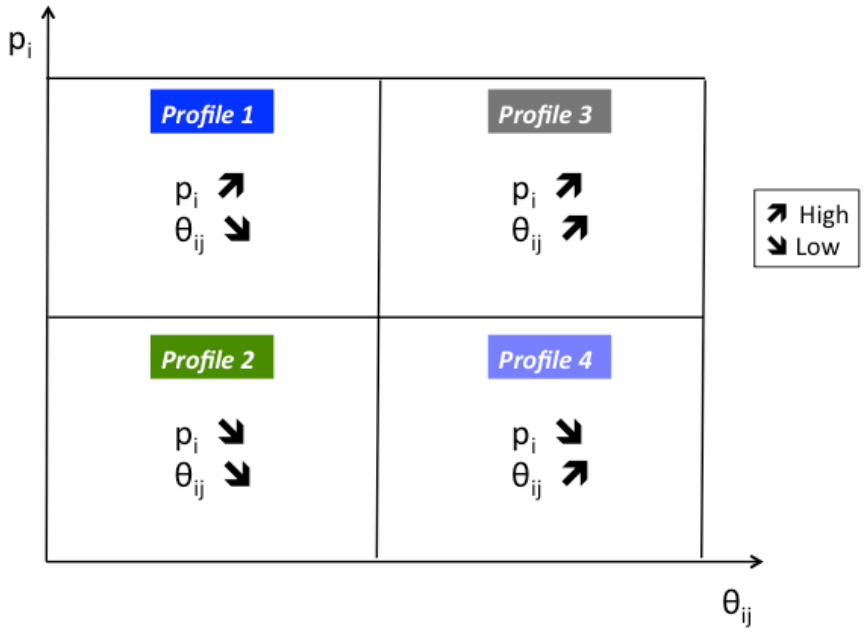


Table 6: Drug Assignment Probabilities with Various Toxicity Rates with 5 Drug-Simulation Setting

Drugs	p_i	θ_{i1}	θ_{i2}	θ_{i3}	θ_{i4}	θ_{i5}	θ_{i6}	θ_{i7}	θ_{i8}	θ_{i9}	θ_{i10}	θ_{i11}
Drug A	0.30	0.10	0.30	0.60	0.80	0.80	0.35	0.40	0.10	0.10	0.50	0.80
Drug B	0.29	0.10	0.30	0.10	0.10	0.60	0.35	0.40	0.10	0.10	0.50	0.70
Drug C	0.14	0.10	0.30	0.10	0.10	0.10	0.10	0.40	0.10	0.70	0.60	0.80
Drug D	0.24	0.10	0.30	0.10	0.10	0.20	0.10	0.40	0.10	0.10	0.50	0.80
Drug E	0.03	0.10	0.30	0.10	0.10	0.10	0.10	0.10	0.80	0.80	0.60	0.70
Overall	1	0.10	0.30	0.25	0.31	0.48	0.25	0.39	0.12	0.21	0.52	0.77

Table 7---11: Drug Assignment Probabilities with Various Toxicity Rates with 10 Drug-Simulation Setting

Drugs	p_i	θ_{i1}	θ_{i2}	θ_{i3}	θ_{i4}	θ_{i5}

Scenario 1 (pi are uniformely distributed)							
Drug A	0.10	0.30	0.80	0.80	0.80	0.60	ImF=1
Drug B	0.10	0.30	0.30	0.70	0.60	0.50	
Drug C	0.10	0.30	0.30	0.60	0.60	0.60	
Drug D	0.10	0.30	0.30	0.30	0.50	0.60	
Drug E	0.10	0.30	0.20	0.30	0.50	0.50	
Drug F	0.10	0.30	0.20	0.20	0.60	0.60	
Drug G	0.10	0.30	0.20	0.20	0.30	0.60	
Drug H	0.10	0.30	0.10	0.20	0.20	0.50	
Drug I	0.10	0.30	0.10	0.10	0.20	0.60	
Drug J	0.10	0.30	0.10	0.10	0.10	0.60	
Overall		0.30	0.26	0.35	0.44	0.57	

Drugs	p_i	θ_{i1}	θ_{i2}	θ_{i3}	θ_{i4}	θ_{i5}	
Scenario 2 (pi are exponentially distributed)							
Drug A	0.25	0.30	0.80	0.60	0.20	0.10	ImF=10
Drug B	0.2	0.30	0.30	0.50	0.20	0.10	
Drug C	0.175	0.30	0.30	0.60	0.10	0.20	
Drug D	0.125	0.30	0.30	0.50	0.30	0.30	
Drug E	0.075	0.30	0.20	0.60	0.30	0.30	
Drug F	0.05	0.30	0.20	0.20	0.20	0.60	
Drug G	0.025	0.30	0.20	0.20	0.20	0.50	
Drug H	0.025	0.30	0.10	0.20	0.30	0.60	
Drug I	0.025	0.30	0.10	0.10	0.30	0.70	
Drug J	0.025	0.30	0.10	0.10	0.80	0.80	
Overall		0.30	0.39	0.54	0.22	0.24	

Drugs	p_i	θ_{i1}	θ_{i2}	θ_{i3}	θ_{i4}	θ_{i5}	
Scenario 3 (pi are normally distributed)							
Drug A	0.025	0.30	0.10	0.80	0.80	0.10	ImF=9
Drug B	0.05	0.30	0.20	0.60	0.70	0.30	
Drug C	0.1	0.30	0.30	0.40	0.60	0.20	
Drug D	0.15	0.30	0.50	0.30	0.30	0.20	
Drug E	0.225	0.30	0.80	0.20	0.20	0.80	
Drug F	0.175	0.30	0.70	0.10	0.10	0.70	
Drug G	0.125	0.30	0.40	0.30	0.20	0.50	
Drug H	0.075	0.30	0.30	0.40	0.10	0.50	
Drug I	0.05	0.30	0.20	0.50	0.20	0.60	
Drug J	0.025	0.30	0.10	0.60	0.10	0.50	

Overall		0.30	0.49	0.31	0.27	0.51

Drugs	p_i	θ_{i1}	θ_{i2}	θ_{i3}	
Scenario 4 (pi are Beta distributed)					
Drug A	0.25	0.30	0.80	0.10	ImF=5
Drug B	0.1	0.30	0.40	0.30	
Drug C	0.05	0.30	0.10	0.50	
Drug D	0.05	0.30	0.10	0.60	
Drug E	0.05	0.30	0.10	0.60	
Drug F	0.05	0.30	0.10	0.50	
Drug G	0.05	0.30	0.10	0.50	
Drug H	0.05	0.30	0.10	0.60	
Drug I	0.1	0.30	0.40	0.30	
Drug J	0.25	0.30	0.60	0.20	
Overall		0.30	0.46	0.30	

Drugs	p_i	θ_{i1}	θ_{i2}	θ_{i3}	
Scenario 5 (pi are Gamma distributed)					
Drug A	0.075	0.30	0.30	0.60	ImF=10
Drug B	0.25	0.30	0.60	0.10	
Drug C	0.225	0.30	0.50	0.20	
Drug D	0.15	0.30	0.60	0.30	
Drug E	0.1	0.30	0.40	0.40	
Drug F	0.075	0.30	0.30	0.50	
Drug G	0.05	0.30	0.20	0.60	
Drug H	0.025	0.30	0.20	0.60	
Drug I	0.025	0.30	0.10	0.60	
Drug J	0.025	0.30	0.10	0.50	
Overall		0.30	0.46	0.31	

RESULTS

Pocock-type Stopping Boundaries

As mentioned in the methods section sequential boundaries are used to monitor dose-limiting toxicity rate. The accrual will be halted if excessive numbers of dose-limiting toxicities are seen,

that is, if the number of dose-limiting toxicities is equal to or exceeds b_k out of K patients with full follow-up. Tables 12 and 13 present the Pocock-type stopping boundary that yields the probability of crossing the boundary at most 0.05 or 0.10 when the rate of dose-limiting toxicity is equal to the acceptable event probability of 0.20 or 0.30, respectively.

When θ_{ij}=0.20 the probability of early stopping is Φ=0.0495. Early stopping consideration starts at 3 three patients with complete follow-up. After three patients with complete follow-up, the trial will stop if the number of toxicities is equal to 3. The trial will stop if we find 15 or more toxicity events after forty patients with complete follow-up. The expected number of toxicities is estimated at 8 (SD=2.4).

Similarly when θ_{ij}=0.30 the probability of early stopping is Φ=0.0967. The trial will stop if we record more than 19 toxicities for 40 patients with complete follow-up. The expected number of toxicities is 11 (SD=3.04).

Table 12: Pocock-type Boundary for K=40 that yields Probability of Early Stopping of 0.05 and Event Probability of 0.20.

k	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Pocock boundary $\mathbf{b_k}$	-	-	3	4	4	5	5	5	6	6	6	7	7	7	8	8	8	9	9	9
k	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
Pocock boundary $\mathbf{b_k}$	9	10	10	10	11	11	11	11	12	12	12	13	13	13	13	14	14	14	15	15

This boundary is equivalent to testing the null hypothesis, after each patient, that the event rate is equal to 0.2, using a one-sided level 0.015124 test.

	Actual probability of early stopping	Number of Events Expected Values		Number of Patients Expected Values			
θ	ϕ	E[Y]	SD[Y]	E[N]	SD[N]	E[Y/N]	SD[Y/N]
0.2	0.0495	7.76	2.4	38.8	5.77	0.21	0.11
0.3	0.3521	9.83	2.74	32.77	11.7	0.35	0.17
0.4	0.7992	8.82	3.31	22.06	12.8	0.49	0.19
0.5	0.9789	6.72	2.78	13.43	9.03	0.61	0.19
0.6	0.9995	5.25	1.91	8.75	5.54	0.7	0.19
0.7	1	4.38	1.34	6.25	3.5	0.79	0.17
0.8	1	3.79	0.96	4.74	2.26	0.87	0.15
0.9	1	3.35	0.63	3.72	1.33	0.94	0.11
1	1	3	0	3	0	1	0

Y = the number of events, random, between 0 and N
N = the number of patients, random, between 1 and K
ϕ^* = the actual probability of early stopping (hitting the boundary)
E[ ] denotes the expected value (mean)
SD[ ] denotes the standard deviation

Table 13: Pocock-type Boundary for K=40 that yields Probability of Early Stopping of 0.10 and Event Probability of 0.30.

k	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Pocock boundary $\mathbf{b_k}$	-	-	3	4	5	5	6	6	6	7	7	8	8	9	9	9	10	10	11	11
k	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
Pocock boundary $\mathbf{b_k}$	11	12	12	13	13	13	14	14	15	15	15	16	16	16	17	17	18	18	18	19

This boundary is equivalent to testing the null hypothesis, after each patient, that the event rate is equal to 0.3, using a one-sided level 0.027898 test.

	Actual probability of early stopping	Number of Events Expected Values		Number of Patients Expected Values			
θ	ϕ	E[Y]	SD[Y]	E[N]	SD[N]	E[Y/N]	SD[Y/N]
0.3	0.0967	11.25	3.04	37.49	8.37	0.33	0.15
0.4	0.4135	12.33	4.11	30.81	13.1	0.47	0.19
0.5	0.8229	10.21	4.74	20.4	13.1	0.61	0.19
0.6	0.9831	7.35	3.68	12.25	8.83	0.71	0.18
0.7	0.9997	5.5	2.4	7.85	5.18	0.8	0.17
0.8	1	4.41	1.63	5.52	3.15	0.88	0.14
0.9	1	3.64	1.1	4.05	1.86	0.94	0.1
1	1	3	0	3	0	1	0

Y = the number of events, random, between 0 and N
N = the number of patients, random, between 1 and K
ϕ^* = the actual probability of early stopping (hitting the boundary)
E[ ] denotes the expected value (mean)
SD[ ] denotes the standard deviation

Simulations using Five Drug Setting

Tables 14 and 15 showcase overall and drug-specific probabilities of early termination, at event probability of respectively 0.20 and 0.30, in a setting of 5 drugs with diverse toxicity level profiles.

When the drug frequency is high and the toxicity is low, the results show that the probability of early termination is quite low, or even inexistent. Similarly the probability of early termination is low for low drug toxicity and low drug frequency combination. When both drug toxicity and drug frequency are high, the probability of early stopping is very large. Low drug-frequency combined with high drug-toxicity leads to a low likelihood of early termination.

The results of the combination of high/low drug-frequency and high/low drug-toxicity show meaningful variances in the detection of excess toxicity. Considering a realistic heterogeneity among drug groups, in the case where the drug toxicity is uniform among all drugs and considered low, the drug-specific and overall probability of early termination remains very low ($0 <= P(ET) <= 0.001$ where $\theta=0.20$ and $\theta=0.30$). On the assumption of heterogeneous drug groups and marginally high toxicity ($pi=0.30$), the probability of drug-specific early termination remains low ($0 <= P(ET) <= 0.033$ where $\theta=0.20$; $0 <= P(ET) <= 0.006$ where $\theta=0.30$), while the overall early termination probability is quite high ($P(ET)=0.34$ where $\theta=0.20$; $P(ET)=0.09$ where $\theta=0.30$). The probability of early sopping on any boundaries is also prominent ($P(ET)=0.35$ and $P(ET)=0.09$). Given a very high toxicity on heterogeneous drug groups, the drug-specific and overall early termination probability is very elevated, almost equal to 1 (Figure 5 and 7).

In the scenarios where we combine high-frequency drugs with elevated toxicities, and low frequency drugs with low toxicity levels the overall probability of early termination is quite high, as well as that same probability of early stopping at any boundaries. When only one drug group with high frequency is toxic (θ_{12}=0.6), overall early stopping likelihood is higher in the case where the event probability is equal to 0.20 (P(ET)=0.14)), compared to when the event probability is 0.30 (P(ET)=0.03). In the event where we apply a stronger toxicity to only one drug group (θ_{13}=0.80), the overall early termination probability is even higher, yet smaller when the event probability is set to 0.30 (P(ET)=0.40 vs. P(ET)=0.14). When toxicity is applied to two high frequency drug groups the overall and any boundaries early termination probabilities are very close or even equal to 1 (Figure 4 and 6). In the event where two of the higher frequency drug groups are fairly toxic (θ_{i2}=0.35) and the event probability set at 0.30, the overall probability of early stopping is slightly low (P(ET)=0.03), compared to when the event probability is set to 0.20 (P(ET)=0.16). When higher frequency drug groups are slightly toxic (θ_{ij}=0.40), drug-specific early stopping probabilities hardly reach the boundary, however the overall probability of early termination is 0.77 for event probability of 0.20 in contrast to 0.40 for event probability of 0.30.

Note that when strong toxicity is present in low frequency drug groups and low toxicity to high frequency drug groups, the overall probability of early termination is far lesser than the case where the opposite is the case, yet weak in some instances (weak especially when the event probability is set to 0.30).

Table 14: Probabilities of Early Termination after Simulation of a 1000 Trials using Pocock-type Boundary that yields Probability of Early Stopping of 0.05 and Event Probability of 0.20.

Drugs	p_i	θ_{i1}	θ_{i2}	θ_{i3}	θ_{i4}	θ_{i5}	θ_{i6}	θ_{i7}	θ_{i8}	θ_{i9}	θ_{i10}	θ_{i11}

Drug A	0.30	0.10	0.30	0.60	0.80	0.80	0.35	0.40	0.10	0.10	0.50	0.80
Drug B	0.29	0.10	0.30	0.10	0.10	0.60	0.35	0.40	0.10	0.10	0.50	0.70
Drug C	0.14	0.10	0.30	0.10	0.10	0.10	0.10	0.40	0.10	0.70	0.60	0.80
Drug D	0.24	0.10	0.30	0.10	0.10	0.20	0.10	0.40	0.10	0.10	0.50	0.80
Drug E	0.03	0.10	0.30	0.10	0.10	0.10	0.10	0.10	0.80	0.80	0.60	0.70
Overall		0.10	0.30	0.25	0.31	0.48	0.25	0.39	0.12	0.21	0.52	0.77
	E(N)					**P(ET)**						
Drug A	12	0.000	0.019	0.545	0.901	0.926	0.070	0.111	0.000	0.000	0.303	0.904
Drug B	11	0.000	0.033	0.000	0.000	0.505	0.070	0.118	0.000	0.000	0.286	0.747
Drug C	6	0.000	0.005	0.000	0.000	0.000	0.000	0.025	0.000	0.237	0.106	0.358
Drug D	10	0.000	0.005	0.000	0.000	0.001	0.000	0.076	0.000	0.000	0.202	0.779
Drug E	1	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.001	0.004	0.000	0.000
Overall		0.001	0.337	0.142	0.398	0.973	0.158	0.773	0.003	0.054	0.990	1.000
Any Boundaries		0.001	0.349	0.251	0.578	1	0.186	0.839	0.003	0.102	1.169	1.000
						Proportion (ET)						
% Overall Only		1.000	0.832	0.022	0.003	0.019	0.373	0.620	0.600	0.080	0.329	0.000
% Drug Only		0.000	0.040	0.745	0.558	0.013	0.255	0.010	0.400	0.793	0.000	0.000
% Both		0.000	0.128	0.233	0.438	0.968	0.373	0.370	0.000	0.126	0.671	1.000

Figure 4: Probability of Early Termination using Pocock-type Boundary that yields Probability of Early Stopping of 0.05 and Event Probability of 0.20, with two Toxic Drug Groups in the High Frequency or Low Frequency Groups.

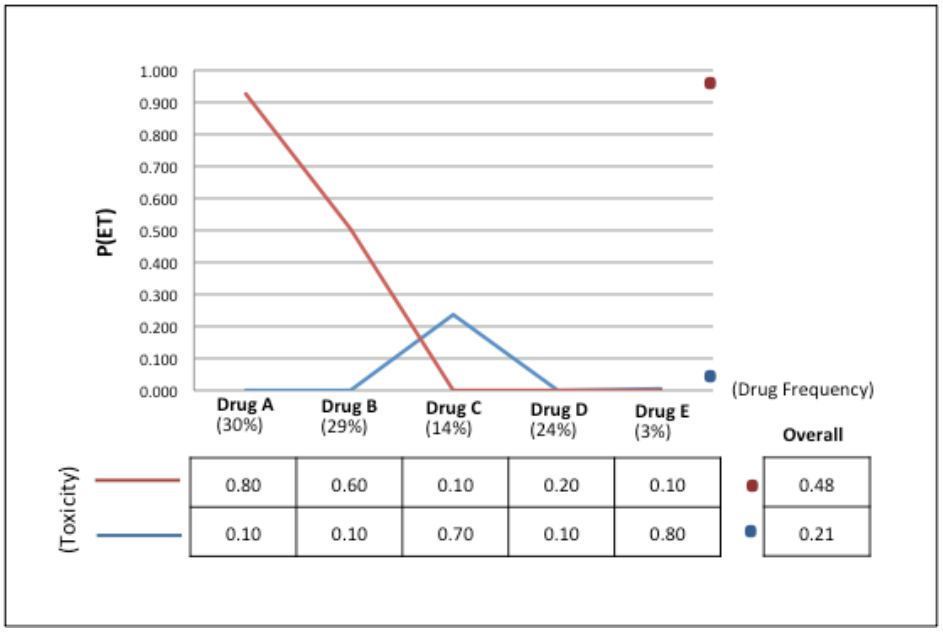


Figure 5: Probability of Early Termination using Pocock-type Boundary that yields Probability of Early Stopping of 0.05 and Event Probability of 0.20, with only very Toxic Drugs or non-toxic Drugs.

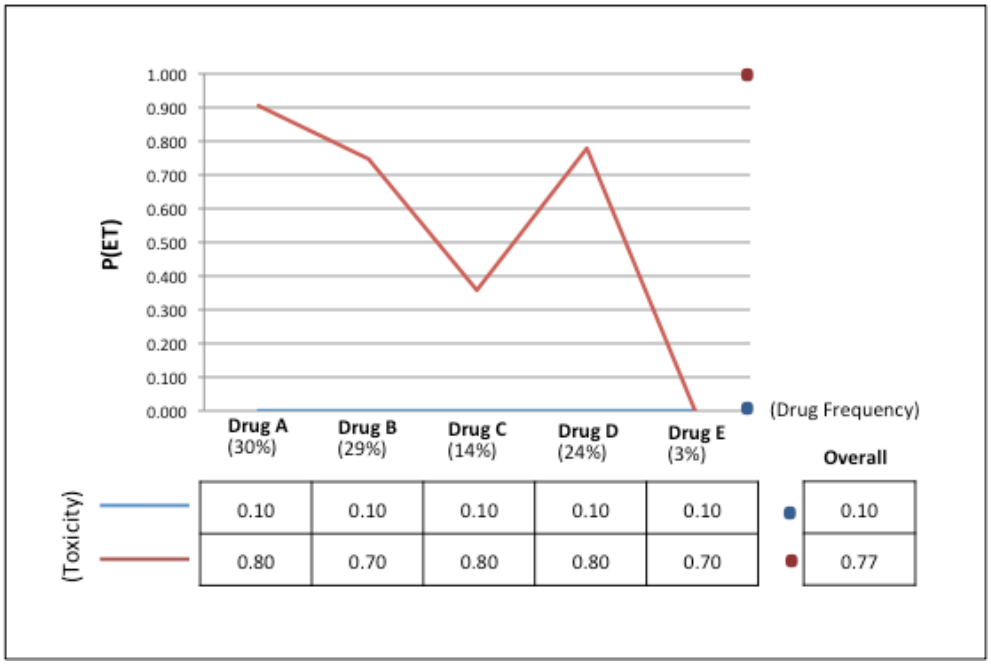


Table 15: Probabilities of Early Termination after Simulation of a 1000 Trials using Pocock-type Boundary that yields Probability of Early Stopping of 0.10 and Event Probability of 0.30.

Drugs	p_i	θ_{i1}	θ_{i2}	θ_{i3}	θ_{i4}	θ_{i5}	θ_{i6}	θ_{i7}	θ_{i8}	θ_{i9}	θ_{i10}	θ_{i11}
Drug A	0.30	0.10	0.30	0.60	0.80	0.80	0.35	0.40	0.10	0.10	0.50	0.80
Drug B	0.29	0.10	0.30	0.10	0.10	0.60	0.35	0.40	0.10	0.10	0.50	0.70
Drug C	0.14	0.10	0.30	0.10	0.10	0.10	0.10	0.40	0.10	0.70	0.60	0.80
Drug D	0.24	0.10	0.30	0.10	0.10	0.20	0.10	0.40	0.10	0.10	0.50	0.80
Drug E	0.03	0.10	0.30	0.10	0.10	0.10	0.10	0.10	0.80	0.80	0.60	0.70
Overall		0.10	0.30	0.25	0.31	0.48	0.25	0.39	0.12	0.21	0.52	0.77
	E(N)						**P(ET)**					
Drug A	12	0.000	0.003	0.371	0.782	0.832	0.016	0.043	0.000	0.000	0.142	0.823
Drug B	11	0.000	0.006	0.000	0.000	0.310	0.013	0.032	0.000	0.000	0.146	0.547
Drug C	6	0.000	0.004	0.000	0.000	0.000	0.000	0.005	0.000	0.112	0.048	0.208
Drug D	10	0.000	0.005	0.000	0.000	0.000	0.000	0.023	0.000	0.000	0.098	0.632
Drug E	1	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.001	0.001	0.001	0.000
Overall		0.001	0.088	0.029	0.139	0.753	0.030	0.400	0.001	0.010	0.867	1.000
Any Boundaries		0.001	0.092	0.103	0.295	1	0.036	0.421	0.001	0.033	0.954	1.000
							Proportion (ET)					

% Overall Only	1.000	0.806	0.013	0.005	0.031	0.442	0.765	1.000	0.050	0.564	0.018
% Drug Only	0.000	0.054	0.923	0.823	0.176	0.423	0.050	0.000	0.916	0.003	0.000
% Both	0.000	0.140	0.064	0.172	0.793	0.135	0.185	0.000	0.034	0.432	0.982

Figure 6: Probability of Early Termination using Pocock-type Boundary that yields Probability of Early Stopping of 0.10 and Event Probability of 0.30, with two Toxic Drug Groups in the High Frequency or Low Frequency Groups.

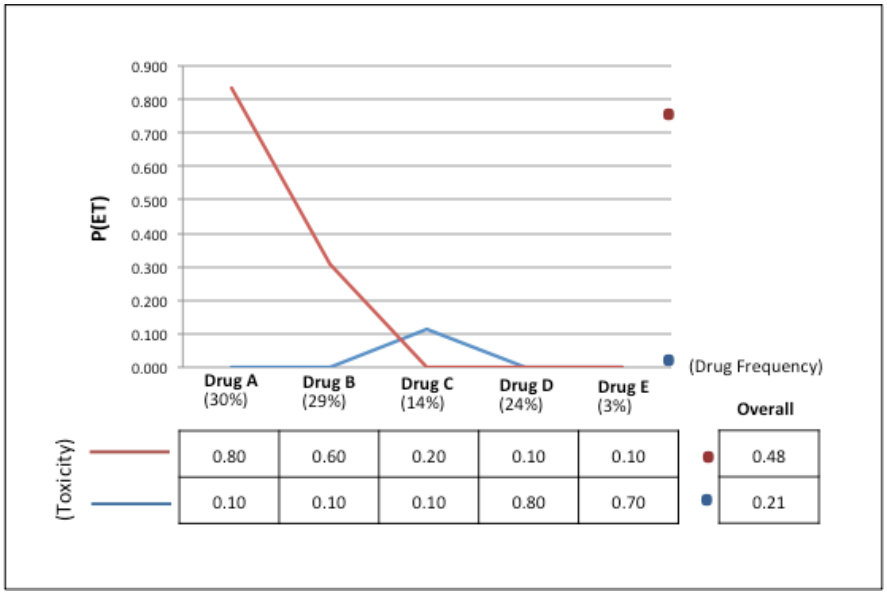
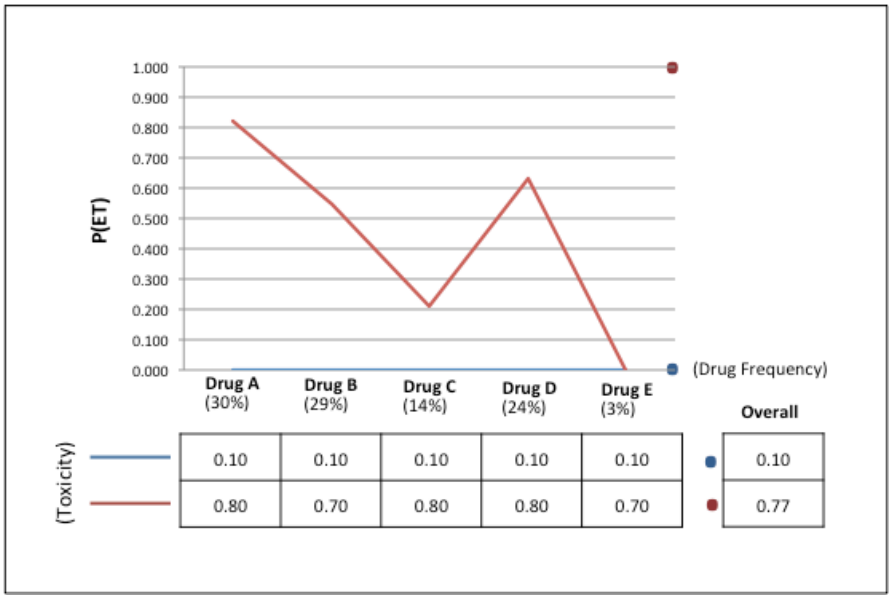


Figure 7: Probability of Early Termination using Pocock-type Boundary that yields Probability of Early Stopping of 0.10 and Event Probability of 0.30, with only very Toxic Drugs or non-toxic Drugs.



Simulations using Ten Drug Setting

In this simulation using 10 drugs, (Table 16 – 20) we consider a scenario when the probability of early termination is 0.05 when the incidence of unacceptable toxicity is 0.20. When the drug groups are uniformly distributed as well as slightly high in toxicity, the probability of early stopping is high overall and at any boundaries, but fairly low when considered individual drug groups (Figure 8). When the incidence of unacceptable toxicity is high among one or more drug groups, overall probability of stopping the trial and drug-specific early termination probabilities that were mostly low, especially when the toxicity was below 0.70.

The overall and any boundaries probability of early termination are high for all scenarios chosen. Exponential, normal, beta and gamma distributions of the drug group frequencies show the same pattern of high overall and any boundaries early termination probabilities for any combination of high/low toxicity (Figure 9 – 11). Drug-specific early stopping probability is high when the toxicity of the drug group and the drug-frequency group are high. Drug-specific early

termination probability remains low if the drug group shows low frequency with any toxicity (high or low).

Table 16: Probabilities of Early Termination after Simulation of a 1000 Trials using Pocock-type Boundary that yields Probability of Early Stopping of 0.05 and Event Probability of 0.20 where Drug Assignment Probabilities are Uniformly Distributed.

pi are Uniformly Distributed (ImF=1)						
Drugs	p_i	θ_{i1}	θ_{i2}	θ_{i3}	θ_{i4}	θ_{i5}
Drug A	0.10	0.30	0.80	0.80	0.80	0.60
Drug B	0.10	0.30	0.30	0.70	0.60	0.50
Drug C	0.10	0.30	0.30	0.60	0.60	0.60
Drug D	0.10	0.30	0.30	0.30	0.50	0.60
Drug E	0.10	0.30	0.20	0.30	0.50	0.50
Drug F	0.10	0.30	0.20	0.20	0.60	0.60
Drug G	0.10	0.30	0.20	0.20	0.30	0.60
Drug H	0.10	0.30	0.10	0.20	0.20	0.50
Drug I	0.10	0.30	0.10	0.10	0.20	0.60
Drug J	0.10	0.30	0.10	0.10	0.10	0.60
Overall		0.30	0.26	0.35	0.44	0.57
	E(N)			**P(ET)**		
Drug A	4	0.000	0.156	0.164	0.144	0.045
Drug B	4	0.002	0.001	0.087	0.040	0.016
Drug C	4	0.002	0.003	0.043	0.053	0.046
Drug D	4	0.002	0.000	0.001	0.018	0.049
Drug E	4	0.003	0.000	0.002	0.020	0.017
Drug F	4	0.001	0.000	0.000	0.047	0.044
Drug G	4	0.002	0.001	0.000	0.000	0.036
Drug H	4	0.000	0.000	0.000	0.000	0.000
Drug I	4	0.001	0.000	0.000	0.000	0.042
Drug J	4	0.002	0.000	0.000	0.000	0.055
Overall		0.314	0.197	0.610	0.908	0.999
Any Boundaries		0.317	0.229	0.669	0.972	1
				Proportion (ET)		
% Overall Only		0.953	0.437	0.569	0.675	0.703
% Drug Only		0.006	0.311	0.070	0.004	0.000
% Both		0.041	0.252	0.361	0.320	0.297

Figure 8: Probabilities of Early Termination with Drug Assignment Probabilities Uniformly Distributed

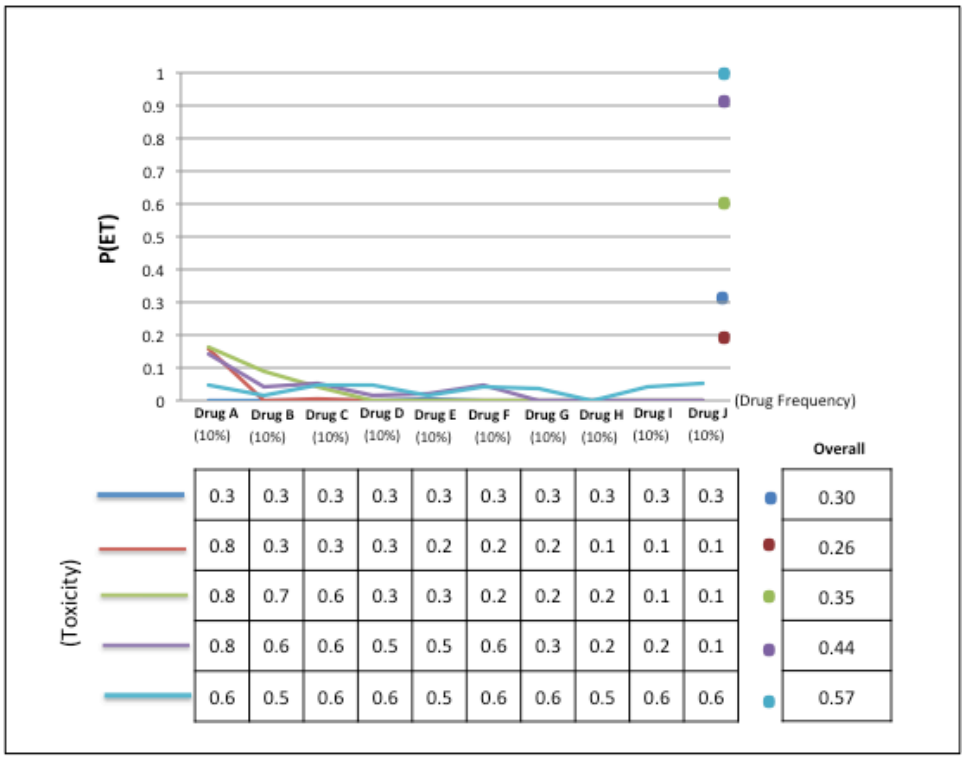


Table 17: Probabilities of Early Termination after Simulation of a 1000 Trials using Pocock-type Boundary that yields Probability of Early Stopping of 0.05 and Event Probability of 0.20 where Drug Assignment Probabilities are Exponentially Distributed

pi are Exponentially Distributed (ImF=10)						
Drugs	p_i	θ_{i1}	θ_{i2}	θ_{i3}	θ_{i4}	θ_{i5}
Drug A	0.3	0.30	0.80	0.60	0.20	0.10
Drug B	0.2	0.30	0.30	0.50	0.20	0.10
Drug C	0.2	0.30	0.30	0.60	0.10	0.20
Drug D	0.125	0.30	0.30	0.50	0.30	0.30
Drug E	0.1	0.30	0.20	0.60	0.30	0.30
Drug F	0.05	0.30	0.20	0.20	0.20	0.60
Drug G	0.025	0.30	0.20	0.20	0.20	0.50
Drug H	0.025	0.30	0.10	0.20	0.30	0.60
Drug I	0.025	0.30	0.10	0.10	0.30	0.70
Drug J	0.025	0.30	0.10	0.10	0.80	0.80
Overall		0.30	0.39	0.54	0.22	0.24
	E(N)			**P(ET)**		

Drug A	10	0.025	0.825	0.416	0.001	0.000
Drug B	8	0.011	0.007	0.141	0.004	0.000
Drug C	7	0.006	0.007	0.222	0.000	0.000
Drug D	5	0.003	0.001	0.046	0.002	0.005
Drug E	3	0.001	0.001	0.018	0.002	0.000
Drug F	2	0.000	0.000	0.000	0.000	0.006
Drug G	1	0.000	0.000	0.000	0.000	0.000
Drug H	1	0.000	0.000	0.000	0.000	0.000
Drug I	1	0.000	0.000	0.000	0.000	0.001
Drug J	2	0.000	0.000	0.000	0.014	0.017
Overall		0.354	0.770	0.976	0.123	0.186
Any Boundaries		0.363	0.938	1.145	0.128	0.192
		Proportion (ET)				
% Overall Only		0.874	0.077	0.324	0.831	0.850
% Drug Only		0.008	0.144	0.004	0.096	0.036
% Both		0.118	0.779	0.671	0.074	0.114

Figure 9: Probabilities of Early Termination with Drug Assignment Probabilities Exponentially Distributed

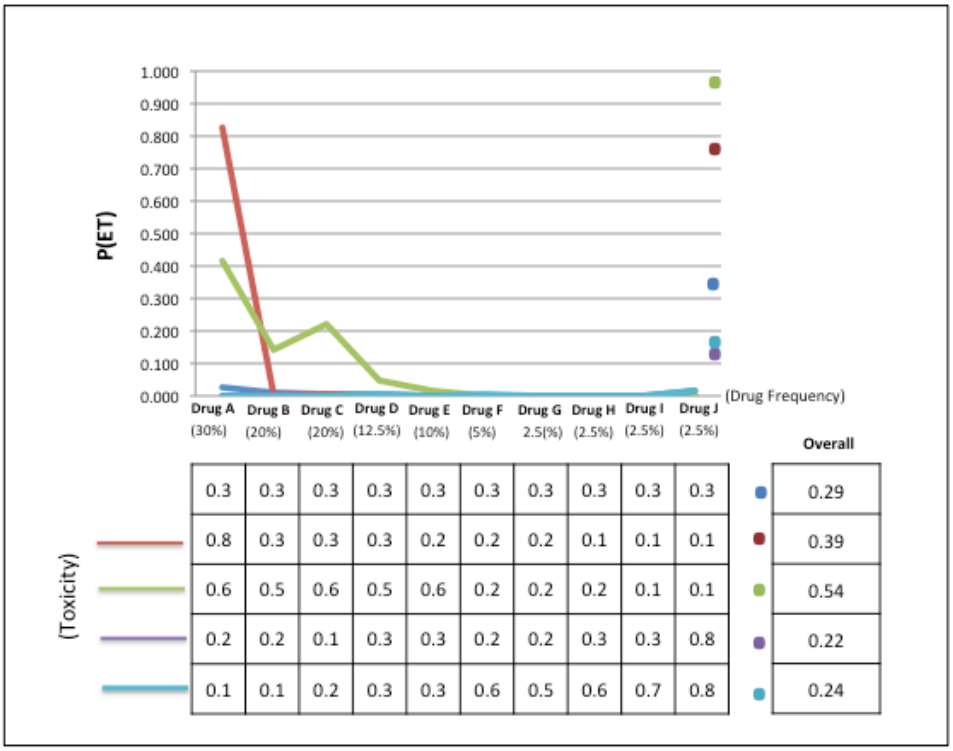


Table 18: Probabilities of Early Termination after Simulation of a 1000 Trials using Pocock-type Boundary that yields Probability of Early Stopping of 0.05 and Event Probability of 0.20 where Drug Assignment Probabilities are Normally Distributed

pi are Normally Distributed (ImF=9)						
Drugs	p_i	θ_{i1}	θ_{i2}	θ_{i3}	θ_{i4}	θ_{i5}
Drug A	0.03	0.30	0.10	0.80	0.80	0.10
Drug B	0.05	0.30	0.20	0.60	0.70	0.30
Drug C	0.1	0.30	0.30	0.40	0.60	0.20
Drug D	0.15	0.30	0.50	0.30	0.30	0.20
Drug E	0.2	0.30	0.80	0.20	0.20	0.80
Drug F	0.175	0.30	0.70	0.10	0.10	0.70
Drug G	0.1	0.30	0.40	0.30	0.20	0.50
Drug H	0.075	0.30	0.30	0.40	0.10	0.50
Drug I	0.05	0.30	0.20	0.50	0.20	0.60
Drug J	0.025	0.30	0.10	0.60	0.10	0.50
Overall		0.30	0.49	0.31	0.27	0.51
	E(N)			**P(ET)**		
Drug A	1	0.000	0.000	0.002	0.000	0.000
Drug B	2	0.000	0.000	0.003	0.011	0.000
Drug C	4	0.003	0.003	0.003	0.053	0.000
Drug D	6	0.003	0.068	0.004	0.009	0.000
Drug E	9	0.026	0.736	0.004	0.002	0.736
Drug F	7	0.007	0.377	0.000	0.000	0.351
Drug G	5	0.005	0.014	0.005	0.000	0.042
Drug H	3	0.000	0.000	0.000	0.000	0.000
Drug I	2	0.000	0.000	0.001	0.000	0.005
Drug J	1	0.000	0.000	0.000	0.000	0.000
Overall		0.380	0.980	0.384	0.204	0.986
Any Boundaries		0.389	1	0.388	0.219	1
				Proportion (ET)		
% Overall Only		0.888	0.120	0.943	0.682	0.142
% Drug Only		0.013	0.005	0.005	0.124	0.003
% Both		0.099	0.875	0.052	0.193	0.855

Figure 10: Probabilities of Early Termination with Drug Assignment Probabilities Normally Distributed

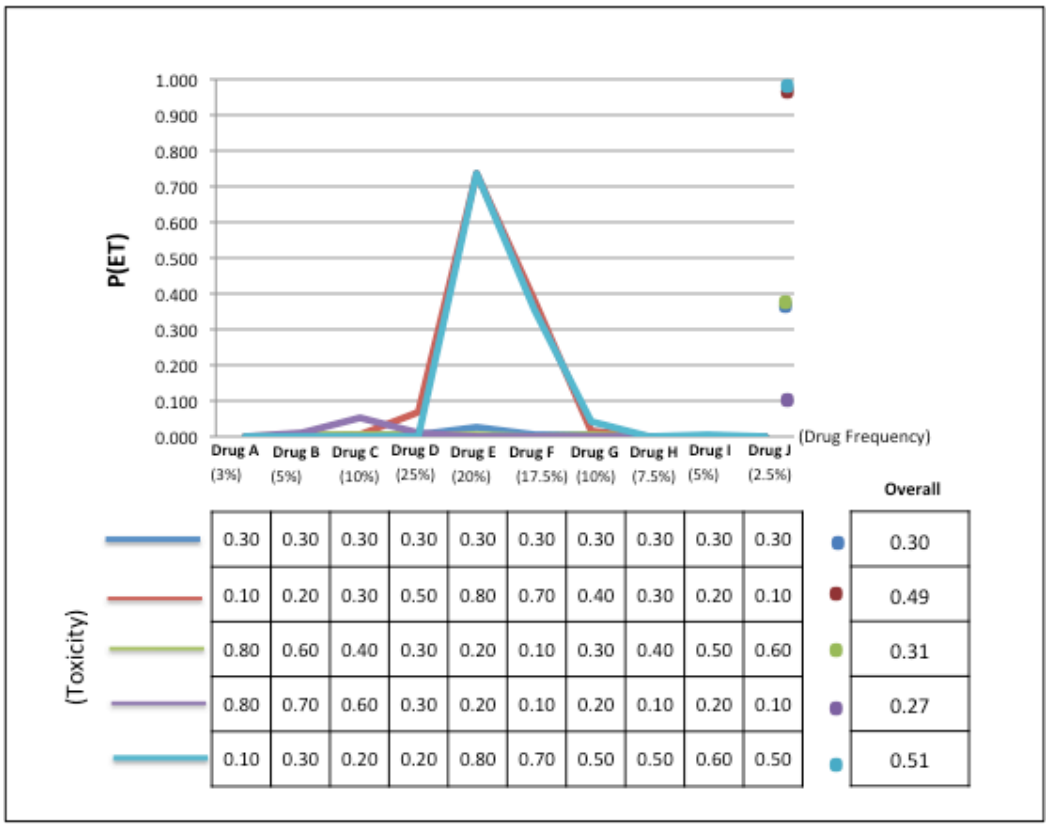


Table 19: Probabilities of Early Termination after Simulation of a 1000 Trials using Pocock-type Boundary that yields Probability of Early Stopping of 0.05 and Event Probability of 0.20 where Drug Assignment Probabilities are Beta Distributed

pi are Beta Distributed (ImF=5)				
Drugs	p_i	θ_{i1}	θ_{i2}	θ_{i3}
Drug A	0.25	0.30	0.80	0.10
Drug B	0.1	0.30	0.40	0.30
Drug C	0.05	0.30	0.10	0.50
Drug D	0.05	0.30	0.10	0.60
Drug E	0.05	0.30	0.10	0.60
Drug F	0.05	0.30	0.10	0.50
Drug G	0.05	0.30	0.10	0.50
Drug H	0.05	0.30	0.10	0.60
Drug I	0.1	0.30	0.40	0.30
Drug J	0.25	0.30	0.60	0.20
Overall		0.30	0.46	0.30

	E(N)	P(ET)		
Drug A	10	0.019	0.828	0.000
Drug B	4	0.004	0.004	0.002
Drug C	2	0.000	0.000	0.004
Drug D	2	0.000	0.000	0.001
Drug E	2	0.000	0.000	0.002
Drug F	2	0.000	0.000	0.002
Drug G	2	0.000	0.000	0.003
Drug H	2	0.000	0.000	0.000
Drug I	4	0.000	0.006	0.004
Drug J	10	0.019	0.419	0.001
Overall		0.322	0.950	0.332
Any Boundaries		0.330	1	0.336
		Proportion (ET)		
% Overall Only		0.875	0.055	0.943
% Drug Only		0.015	0.028	0.012
% Both		0.110	0.917	0.045

Figure 11: Probabilities of Early Termination with Drug Assignment Probabilities Beta Distributed

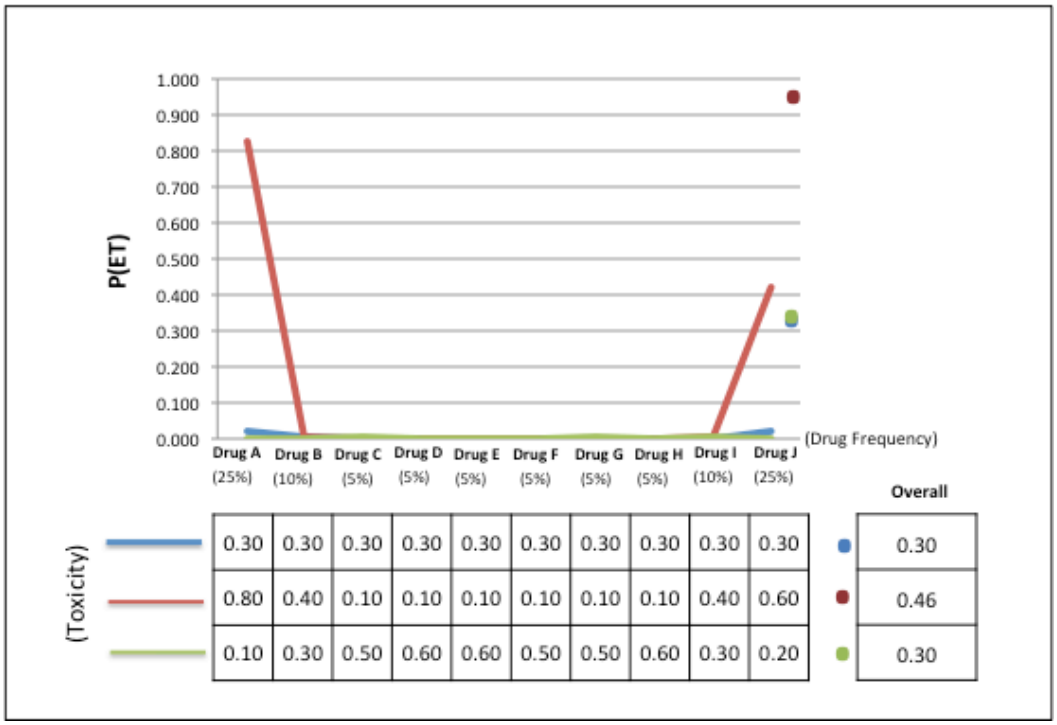
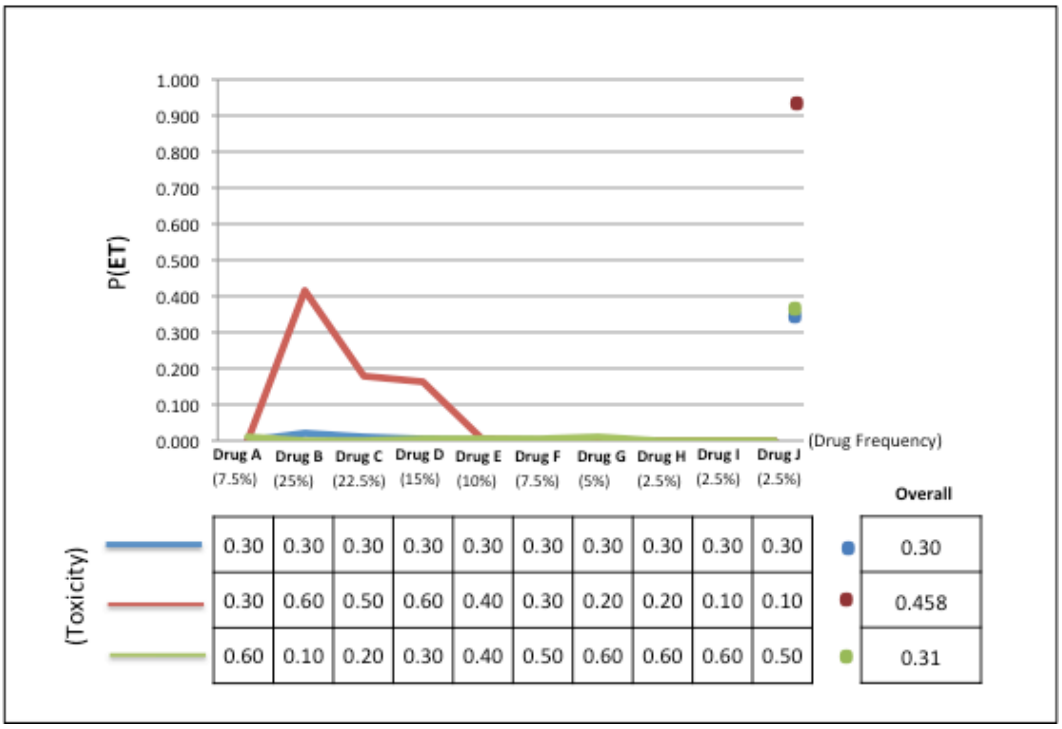


Table 20: Probabilities of Early Termination after Simulation of a 1000 Trials using Pocock-type Boundary that yields Probability of Early Stopping of 0.05 and Event Probability of 0.20 where Drug Assignment Probabilities are Gamma Distributed

pi are Gamma Distributed (ImF=10)				
Drugs	p_i	θ_{i1}	θ_{i2}	θ_{i3}
Drug A	0.075	0.30	0.30	0.60
Drug B	0.25	0.30	0.60	0.10
Drug C	0.225	0.30	0.50	0.20
Drug D	0.15	0.30	0.60	0.30
Drug E	0.1	0.30	0.40	0.40
Drug F	0.075	0.30	0.30	0.50
Drug G	0.05	0.30	0.20	0.60
Drug H	0.025	0.30	0.20	0.60
Drug I	0.025	0.30	0.10	0.60
Drug J	0.025	0.30	0.10	0.50
Overall	1	0.30	0.4575	0.31
	E(N)		**P(ET)**	
Drug A	3	0.000	0.000	0.012
Drug B	10	0.021	0.418	0.000
Drug C	9	0.013	0.181	0.001
Drug D	6	0.004	0.162	0.004
Drug E	4	0.000	0.007	0.003
Drug F	3	0.000	0.001	0.005
Drug G	2	0.000	0.000	0.008
Drug H	1	0.000	0.000	0.000
Drug I	1	0.000	0.000	0.000
Drug J	1	0.000	0.000	0.000
Overall		0.346	0.936	0.374
Any Boundaries		0.354	1	0.381
		Proportion (ET)		
% Overall Only		0.892	0.346	0.916
% Drug Only		0.020	0.008	0.013
% Both		0.088	0.645	0.071

Figure 12: Probabilities of Early Termination with Drug Assignment Probabilities Gamma Distributed



DISCUSSION

Common safety monitoring often focused on one single drug. The current biomarker-driven trial emphases multiple agents with different toxicity profiles, rendering safety monitoring complex and challenging. After extending Pocock methodology we are able to evaluate overall and drug-specific toxicity boundaries by simulation studies.

Overall toxicity is important to introduce in order to firstly evaluate the safety of the personalized medicine strategy as a whole. Secondly, overall toxicity allows an earlier termination where it may be impossible to detect a highly toxic drug with a low frequency. In fact, it is demonstrated that in those cases, it is impossible to detect any toxicity; with the overall

toxicity we are at least able to pool the data across other drug groups with similar toxicity incidence.

The conclusions of the simulation study are uniform across all the profiles (five drug and 10 drug setting) and scenarios (combination of high/low toxicities) considered. The results demonstrate that individual stopping rule is an important tool in continuous monitoring of excess toxicity in biomarker driven trials. In fact, there is a remarkable benefit in introducing drug-specific continuous stopping boundaries as it improves the probability of early termination when an excess toxicity is detected in some of the drugs. Nevertheless, the magnitude of improvement depends strongly on the prevalence of drug groups. Considering drug-specific early termination, excess risk is poorly detectable when the number of subjects in the drug group is small. The results revealed that, although the overall early termination probability is high, it is nearly impossible to observe an early termination for excess toxicity for one drug group when the frequency of that group is low, regardless of the toxicity level. Additionally, when toxicity is elevated for low frequency drug groups and weak for high frequency drug groups, the overall excess toxicity is hardly detectable. Overall excess toxicity is higher when toxicity is elevated for high frequency drug groups and weak for low frequency drug groups. The likelihood of drug-specific early termination is detectable when the drug frequency and the toxicity are both prominent.

Regardless of drug frequency, the objective of adding an early stopping boundary is to be able to stop the trial in the presence of toxicity, but this task is difficult to operate when the drug frequency is low. In fact, detecting toxicity, even if it is high, is very challenging whenever the drug frequency is low.

This situation of addressing toxicity would probably improve if we had a much larger sample size. However, in this study we are focusing on typical early phase trials, where it is unlikely that the total sample size will exceed 40 patients. Additionally, continuous monitoring might not be feasible for a large number of subjects. Continuous real time monitoring may only be conducted for clinical trials involving 30-40 patients. . In summary this study is focusing on early phase trials. Mathematically it would make sense to increase the sample size or look at big portions of subjects in order to ameliorate the excess toxicity determination, but realistically it is not typical of classical phase II trial where it is desirable to use small sample size.

With the risk and apprehension of missing potentially harmful events, controlling Type I error resumes best with the issue of assessing efficacy, and less with the question of evaluating toxicity. In this logic, the perspective of evaluating more intervals can be raised. In fact, practical intervals might be valid to gauge, but we would worry about the drugs high toxicity.

One limitation of this study resides in the absence of correction for multiple testing. The Pocock methodology used is solely based on early single arm phase trial controlling therefore for Type I error for individual treatment, while the research focused on multiple drugs and different toxicity profiles setting. Correction for multiple testing could have been used in order to control for the Type I error for multiple treatments.

SUMMARY AND CONCLUSIONS

Safety monitoring in clinical trials is a critical element in a drug-development phase [10]. Monitoring becomes particularly challenging in trials where each patient is administered a different drug giving his/her biomarker profile. In order to monitor excess toxicity in a Phase IB

trial of a standard chemotherapy plus a targeted agent among newly diagnosed acute myeloid patients, continuous overall and drug-specific stopping boundaries are developed and implemented by extending the Pocock approach to multiple drugs of different toxicity profiles.

The simulation study shows that in a biomarker multiple agent trial the proportion of subjects needs to be sufficiently large in order to detect an excess toxicity. Excess toxicity is practically undetectable in case of low frequency in drug groups.

The overall excess toxicity is difficult to assess, especially when heterogeneity exists among the subject drug groups. Therefore, there is a huge benefit in including individual drug stopping rule.

Model-based approach can be useful in developing of continuous toxicity boundaries as well as simultaneous estimation of target drug frequencies and drug-specific DLT probabilities.

REFERENCES

[1] Anastasia Ivanova, Bahjat F. Qaqish, and Michael J. Schell. Continuous Toxicity Monitoring in Phase II Trials in Oncology. Biometrics 61, 540–545 (June 2005).

[2] Ahmedin Jemal, Andrea Thomas, Taylor Murray and Michael Thun. Cancer Statistics, 2002. CA Cancer J Clin, 2002. **52**(1): p. 23-47.

[3] Saiko Kurosawa, Takuhiro Yamaguchi, Shuichi Miyawaki, Naoyuki Uchida, Toru Sakura, Heiwa Kanamori, Kensuke Usuki, Takuya Yamashita, Yasushi Okoshi, Hirohiko Shibayama, Hirohisa Nakamae, Momoko Mawatari, Kazuo Hatanaka, Kazutaka Sunami, Manabu Shimoyama, Naohito Fujishima, Yoshinobu Maeda, Ikuo Miura, Yoichi Takaue, and Takahiro Fukuda. Prognostic index for adult patients with acute myeloid leukemia in first relapse. J Clin Oncol, 2005. **23**(9): p. 1969-78.

[4] Francis Giles, Susan O'Brien, Jorge Cortes, Srdan Verstovsek, Carlos Bueso-Ramos, Jianqin Shan, Sherry Pierce, Guillermo Garcia-Manero, Michael Keating, Hagop Kantarjian. Outcome of patients with acute myelogenous leukemia after second salvage therapy. Cancer, 2005. **104**(3): p. 547-54.

[5] Michael Andreeff . Targeted therapy of acute Myeloid Leukemia. Current Cancer research, Springer.

[6] Tapan M. Kadia, MD, Farhad Ravandi, MD, Jorge Cortes, MD Hagop Kantarjian, MD. Toward Individualized Therapy in Acute Myeloid Leukemia, JAMA Oncol. 2015; 1(6): 820-828. doi:10.1001/jamaoncol.2015.0617.

[7] Christopher Jennison and Bruce W. Turnbull. Group Sequential Methods, Applications to Clinical Trials. Chapman & Hall / CRC.

[8] Group Sequential Methods in the Design and Analysis of Clinical Trials, Stuart J. Pocock, Biometrika, Vol 64, No. 2 (Aug. 1977), 191-199.

[9] Anne I. Goldman and Peter J. Hannan. Optimal continuous sequential boundaries for monitoring toxicity in clinical trials: a restricted search algorithm. Statist. Med. 2001; 20:1575–1589 (DOI: 10.1002/sim.713)

[10] Bin Yao, Li Zhu, Qi Jiang, and H. Amy Xia, Safety Monitoring in Clinical Trials, Pharmaceutics 2013, 5, 94-106.

[11] http://cancer.unc.edu/biostatistics/program/ivanova/ContinuosMonitoringForToxicity.aspx

APPENDIX

<u>Appendix 1:</u> List of Z and p-values used at different interim analyses, with overall p-value 0.05.

No. of Looks	Look	Pocock		O'Brien-Fleming	
		Z	P	Z	P
2	1	2.178	0.029	2.797	0.005
	2	2.178	0.029	1.977	0.048
3	1	2.289	0.022	3.471	0.0005
	2	2.289	0.022	2.454	0.014
	3	2.289	0.022	2.004	0.045
4	1	2.361	0.018	4.049	0.0001
	2	2.361	0.018	2.863	0.004
	3	2.361	0.018	2.338	0.019
	4	2.361	0.018	2.024	0.043
5	1	2.413	0.016	4.562	0.00001
	2	2.413	0.016	3.226	0.0013
	3	2.413	0.016	2.634	0.008
	4	2.413	0.016	2.281	0.023
	5	2.413	0.016	2.04	0.041

<u>Appendix 2:</u> Simulations using scenarios yielding to approximately the same overall toxicity rates

Drugs	p_i	θ_{i1}	θ_{i2}	θ_{i3}	θ_{i4}	θ_{i5}	θ_{i6}	θ_{i7}
Drug A	0.30	0.30	0.40	0.60	0.80	0.50	0.10	0.10
Drug B	0.29	0.30	0.30	0.20	0.10	0.40	0.10	0.40
Drug C	0.14	0.30	0.20	0.10	0.10	0.10	0.80	0.40
Drug D	0.24	0.30	0.30	0.20	0.10	0.10	0.50	0.40
Drug E	0.03	0.30	0.20	0.10	0.10	0.10	0.70	0.40
Overall		0.30	0.31	0.30	0.31	0.31	0.31	0.31
	E(N)				**P(ET)**			
Drug A	12	0.019	0.120	0.519	0.903	0.291	0.000	0.000
Drug B	11	0.033	0.021	0.005	0.000	0.125	0.000	0.128
Drug C	6	0.005	0.000	0.000	0.000	0.000	0.386	0.031
Drug D	10	0.005	0.016	0.003	0.000	0.000	0.181	0.089
Drug E	1	0.000	0.000	0.000	0.000	0.000	0.002	0.000
Overall		0.337	0.389	0.370	0.391	0.404	0.418	0.402
Any Boundaries		0.349	0.420	0.475	0.572	0.487	0.532	0.452

	Proportion (ET)						
% Overall Only	0.022	0.637	0.120	0.003	0.231	0.169	0.490
% Drug Only	0.745	0.072	0.377	0.568	0.195	0.308	0.093
% Both	0.233	0.291	0.503	0.428	0.574	0.523	0.418

Scenarios yielding roughly the same overall toxicity rates gave probabilities of early termination that were high. Scenarios considered toxicity rates that were uniformly distributed, or a mixture of high (or slightly high)/low toxicity rates for low frequency drugs or high frequency drugs. In these cases drug-specific probabilities of early stopping were representative of the toxicity rates, while the overall probability of early termination remained roughly the same for all combinations of high/low drug frequencies and high/low toxicity rates.

Appendix 3: SAS Program

```
/*This program simulates a phase IB clinical trial of target and DLT*/

**********************************************************************************************
5 Drugs Simulation (Specify probability of each target drug and the each toxicity rate for each scenario)
**********************************************************************************************;

data s.simulationI_1;

 /*specify theta1, theta2, theta3, theta4, theta5 = probability of a target drug*/
 p1=.30; p2=.29; p3=.14; p4=.24; p5=.03;

 /*theta1, theta2, theta3, theta4, theta5 = DLT probability*/
 theta1=.30; theta2=.30; theta3=.30; theta4=.30; theta5=.30;

 /*specify the total sample size*/
 n=40;

 do s=1 to 1000;

 /*initial parameter settings**/
 DLTsum=0; DLT1sum=0; DLT2sum=0; DLT3sum=0; DLT4sum=0; DLT5sum=0;
 stp=0; stp1=0; stp2=0; stp3=0; stp4=0; stp5=0;
 boundary=99; b1=0; b2=0; b3=0; b4=0; b5=0;
 et=0; et1=0; et2=0; et3=0; et4=0; et5=0;
 n1=0; n2=0; n3=0; n4=0; n5=0;
```

```
DLT1=0; DLT2=0; DLT3=0; DLT4=0; DLT5=0;
i=1;

do i=1 to n;
  /*specifying boundaries*/
  if i<=3 then boundary=3;
        if (3<i<=5) then boundary=4;
        if (5<i<=8) then boundary=5;
        if (8<i<=11) then boundary=6;
        if (11<i<=14) then boundary=7;
        if (14<i<=17) then boundary=8;
        if (17<i<=21) then boundary=9;
        if (21<i<=24) then boundary=10;
        if (24<i<=28) then boundary=11;
        if (28<i<=31) then boundary=12;
        if (31<i<=35) then boundary=13;
        if (35<i<=38) then boundary=14;
        if (38<i<=40) then boundary=15;

  cutp1=uniform(0);
        target=5;
        if cutp1<p1 then target=1;
          else if cutp1<(p1+p2)then target=2;
          else if cutp1<(p1+p2+p3) then target=3;
          else if cutp1<(p1+p2+p3+p4) then target=4;
  cutp2=uniform(0);
        DLT1=0; DLT2=0; DLT3=0; DLT4=0; DLT5=0;
        if target=1 then do;
    DLT1=(cutp2<theta1); n1=n1+1; DLT1sum=DLT1sum+DLT1;
          if n1<=3 then b1=3;
          if (3<n1<=5) then b1=4;
          if (5<n1<=8) then b1=5;
          if (8<n1<=11) then b1=6;
          if (11<n1<=14) then b1=7;
          if (14<n1<=17) then b1=8;
          if (17<n1<=21) then b1=9;
          if (21<n1<=24) then b1=10;
          if (24<n1<=28) then b1=11;
          if (28<n1<=31) then b1=12;
          if (31<n1<=36) then b1=13;
          if (36<n1<=38) then b1=14;
          if (38<n1<=40) then b1=15;
    stp1=(DLT1sum>b1);
          if (stp1=1) then et1=1;
        end;
        if target=2 then do;
```

```
  DLT2=(cutp2<theta2); n2=n2+1; DLT2sum=DLT2sum+DLT2;
        if n2<=3 then b2=3;
        if (3<n2<=5) then b2=4;
        if (5<n2<=8) then b2=5;
        if (8<n2<=11) then b2=6;
        if (11<n2<=14) then b2=7;
        if (14<n2<=17) then b2=8;
        if (17<n2<=21) then b2=9;
        if (21<n2<=24) then b2=10;
        if (24<n2<=28) then b2=11;
        if (28<n2<=31) then b2=12;
        if (31<n2<=36) then b2=13;
        if (36<n2<=38) then b2=14;
        if (38<n2<=40) then b2=15;
  stp2=(DLT2sum>b2);
        if (stp2=1) then et2=1;
      end;
if target=3 then do;
  DLT3=(cutp2<theta3); n3=n3+1; DLT3sum=DLT3sum+DLT3;
        if n3<=3 then b3=3;
        if (3<n3<=5) then b3=4;
        if (5<n3<=8) then b3=5;
        if (8<n3<=11) then b3=6;
        if (11<n3<=14) then b3=7;
        if (14<n3<=17) then b3=8;
        if (17<n3<=21) then b3=9;
        if (21<n3<=24) then b3=10;
        if (24<n3<=28) then b3=11;
        if (28<n3<=31) then b3=12;
        if (31<n3<=36) then b3=13;
        if (36<n3<=38) then b3=14;
        if (38<n3<=40) then b3=15;
  stp3=(DLT3sum>b3);
        if (stp3=1) then et3=1;
      end;
if target=4 then do;
  DLT4=(cutp2<theta4); n4=n4+1; DLT4sum=DLT4sum+DLT4;
  if n4<=3 then b4=3;
        if (3<n4<=5) then b4=4;
        if (5<n4<=8) then b4=5;
        if (8<n4<=11) then b4=6;
        if (11<n4<=14) then b4=7;
        if (14<n4<=17) then b4=8;
        if (17<n4<=21) then b4=9;
        if (21<n4<=24) then b4=10;
        if (24<n4<=28) then b4=11;
```

```
            if (28<n4<=31) then b4=12;
            if (31<n4<=36) then b4=13;
            if (36<n4<=38) then b4=14;
            if (38<n4<=40) then b4=15;
      stp4=(DLT4sum>b4);
            if (stp4=1) then et4=1;
          end;
    if target=5 then do;
      DLT5=(cutp2<theta5); n5=n5+1; DLT5sum=DLT5sum+DLT5;
            if n5<=3 then b5=3;
            if (3<n5<=5) then b5=4;
            if (5<n5<=8) then b5=5;
            if (8<n5<=11) then b5=6;
            if (11<n5<=14) then b5=7;
            if (14<n5<=17) then b5=8;
            if (17<n5<=21) then b5=9;
            if (21<n5<=24) then b5=10;
            if (24<n5<=28) then b5=11;
            if (28<n5<=31) then b5=12;
            if (31<n5<=36) then b5=13;
            if (36<n5<=38) then b5=14;
            if (38<n5<=40) then b5=15;
      stp5=(DLT5sum>b5);
            if (stp5=1) then et5=1;
          end;

    DLTsum=DLTsum+(DLT1+DLT2+DLT3+DLT4+DLT5);
          stp=(DLTsum>=boundary);
          if (stp=1) then et=1;
  end;

  output;
  end;

run;

data s.simulationI_1;
  set s.simulationI_1;
  type=4;
  etsum=et1+et2+et3+et4+et5;
  if (et=0 and etsum=0) then type=1;
  if (et=1 and etsum=0) then type=2;
  if (et=0 and etsum>=1) then type=3;
  *drop DLT1 DLT2 DLT3 DLT4 DLT5 cutp1 cutp2 target boundary b1 b2 b3 b4 b5
      stp stp1 stp2 stp3 stp4 stp5;
run;
```

```
proc freq data=s.simulationI_1;
  tables et et1 et2 et3 et4 et5 type;
run;

proc means data=s.simulationI_1;
  var n1 n2 n3 n4 n5;
run;


*************************************************************************************
***************
10 Drugs Simulation (Specify probability of each target drug and the each toxicity rate for each
scenario)
*************************************************************************************
***************;
data s.simulationII_1;

  /*specify probability of a target drug*/
  p1=.10; p2=.10; p3=.10; p4=.10; p5=.10; p6=0.10; p7=0.10; p8=0.10; p9=0.10; p10=0.10;

  /*theta1, theta2, theta3, theta4, theta5 = DLT probability*/
  theta1=.30; theta2=.30; theta3=.30; theta4=.30; theta5=.30; theta6=.30; theta7=.30; theta8=.30;
theta9=.30; theta10=.30;

  /*specify the total sample size*/
  n=40;

  do s=1 to 1000;

  /*initial parameter settings**/
  DLTsum=0; DLT1sum=0; DLT2sum=0; DLT3sum=0; DLT4sum=0; DLT5sum=0;
DLT5sum=0; DLT6sum=0; DLT7sum=0; DLT8sum=0; DLT9sum=0; DLT10sum=0;
  stp=0; stp1=0; stp2=0; stp3=0; stp4=0; stp5=0; stp6=0; stp7=0; stp8=0; stp9=0; stp10=0;
  boundary=99; b1=0; b2=0; b3=0; b4=0; b5=0; b6=0; b7=0; b8=0; b9=0; b10=0;
  et=0; et1=0; et2=0; et3=0; et4=0; et5=0; et6=0; et7=0; et8=0; et9=0; et10=0;
  n1=0; n2=0; n3=0; n4=0; n5=0; n6=0; n7=0; n8=0; n9=0; n10=0;
  DLT1=0; DLT2=0; DLT3=0; DLT4=0; DLT5=0; DLT6=0; DLT7=0; DLT8=0; DLT9=0;
DLT10=0;
  i=1;

  do i=1 to n;
    /*specifying boundaries*/
    if i<=3 then boundary=3;
          if (3<i<=5) then boundary=4;
          if (5<i<=8) then boundary=5;
```

```
        if (8<i<=11) then boundary=6;
        if (11<i<=14) then boundary=7;
        if (14<i<=17) then boundary=8;
        if (17<i<=21) then boundary=9;
        if (21<i<=24) then boundary=10;
        if (24<i<=28) then boundary=11;
        if (28<i<=31) then boundary=12;
        if (31<i<=35) then boundary=13;
        if (35<i<=38) then boundary=14;
        if (38<i<=40) then boundary=15;

   cutp1=uniform(0);
        target=10;
        if cutp1<p1 then target=1;
          else if cutp1<(p1+p2)then target=2;
          else if cutp1<(p1+p2+p3) then target=3;
          else if cutp1<(p1+p2+p3+p4) then target=4;
          else if cutp1<(p1+p2+p3+p4+p5) then target=5;
          else if cutp1<(p1+p2+p3+p4+p5+p6) then target=6;
          else if cutp1<(p1+p2+p3+p4+p5+p6+p7) then target=7;
          else if cutp1<(p1+p2+p3+p4+p5+p6+p7+p8) then target=8;
          else if cutp1<(p1+p2+p3+p4+p5+p6+p7+p8+p9) then target=9;

        cutp2=uniform(0);
        DLT1=0; DLT2=0; DLT3=0; DLT4=0; DLT5=0; DLT6=0; DLT7=0; DLT8=0;
DLT9=0; DLT10=0;
        if target=1 then do;
     DLT1=(cutp2<theta1); n1=n1+1; DLT1sum=DLT1sum+DLT1;
          if n1<=3 then b1=3;
          if (3<n1<=5) then b1=4;
          if (5<n1<=8) then b1=5;
          if (8<n1<=11) then b1=6;
          if (11<n1<=14) then b1=7;
          if (14<n1<=17) then b1=8;
          if (17<n1<=21) then b1=9;
          if (21<n1<=24) then b1=10;
          if (24<n1<=28) then b1=11;
          if (28<n1<=31) then b1=12;
          if (31<n1<=36) then b1=13;
          if (36<n1<=38) then b1=14;
          if (38<n1<=40) then b1=15;
     stp1=(DLT1sum>b1);
          if (stp1=1) then et1=1;
        end;
        if target=2 then do;
     DLT2=(cutp2<theta2); n2=n2+1; DLT2sum=DLT2sum+DLT2;
```

```
        if n2<=3 then b2=3;
        if (3<n2<=5) then b2=4;
        if (5<n2<=8) then b2=5;
        if (8<n2<=11) then b2=6;
        if (11<n2<=14) then b2=7;
        if (14<n2<=17) then b2=8;
        if (17<n2<=21) then b2=9;
        if (21<n2<=24) then b2=10;
        if (24<n2<=28) then b2=11;
        if (28<n2<=31) then b2=12;
        if (31<n2<=36) then b2=13;
        if (36<n2<=38) then b2=14;
        if (38<n2<=40) then b2=15;
  stp2=(DLT2sum>b2);
        if (stp2=1) then et2=1;
      end;
if target=3 then do;
  DLT3=(cutp2<theta3); n3=n3+1; DLT3sum=DLT3sum+DLT3;
        if n3<=3 then b3=3;
        if (3<n3<=5) then b3=4;
        if (5<n3<=8) then b3=5;
        if (8<n3<=11) then b3=6;
        if (11<n3<=14) then b3=7;
        if (14<n3<=17) then b3=8;
        if (17<n3<=21) then b3=9;
        if (21<n3<=24) then b3=10;
        if (24<n3<=28) then b3=11;
        if (28<n3<=31) then b3=12;
        if (31<n3<=36) then b3=13;
        if (36<n3<=38) then b3=14;
        if (38<n3<=40) then b3=15;
  stp3=(DLT3sum>b3);
        if (stp3=1) then et3=1;
      end;
if target=4 then do;
  DLT4=(cutp2<theta4); n4=n4+1; DLT4sum=DLT4sum+DLT4;
  if n4<=3 then b4=3;
        if (3<n4<=5) then b4=4;
        if (5<n4<=8) then b4=5;
        if (8<n4<=11) then b4=6;
        if (11<n4<=14) then b4=7;
        if (14<n4<=17) then b4=8;
        if (17<n4<=21) then b4=9;
        if (21<n4<=24) then b4=10;
        if (24<n4<=28) then b4=11;
        if (28<n4<=31) then b4=12;
```

```
        if (31<n4<=36) then b4=13;
        if (36<n4<=38) then b4=14;
        if (38<n4<=40) then b4=15;
  stp4=(DLT4sum>b4);
        if (stp4=1) then et4=1;
      end;
if target=5 then do;
  DLT5=(cutp2<theta5); n5=n5+1; DLT5sum=DLT5sum+DLT5;
        if n5<=3 then b5=3;
        if (3<n5<=5) then b5=4;
        if (5<n5<=8) then b5=5;
        if (8<n5<=11) then b5=6;
        if (11<n5<=14) then b5=7;
        if (14<n5<=17) then b5=8;
        if (17<n5<=21) then b5=9;
        if (21<n5<=24) then b5=10;
        if (24<n5<=28) then b5=11;
        if (28<n5<=31) then b5=12;
        if (31<n5<=36) then b5=13;
        if (36<n5<=38) then b5=14;
        if (38<n5<=40) then b5=15;
  stp5=(DLT5sum>b5);
        if (stp5=1) then et5=1;
      end;
      if target=6 then do;
  DLT6=(cutp2<theta6); n6=n6+1; DLT6sum=DLT6sum+DLT6;
        if n6<=3 then b6=3;
        if (3<n6<=5) then b6=4;
        if (5<n6<=8) then b6=5;
        if (8<n6<=11) then b6=6;
        if (11<n6<=14) then b6=7;
        if (14<n6<=17) then b6=8;
        if (17<n6<=21) then b6=9;
        if (21<n6<=24) then b6=10;
        if (24<n6<=28) then b6=11;
        if (28<n6<=31) then b6=12;
        if (31<n6<=36) then b6=13;
        if (36<n6<=38) then b6=14;
        if (38<n6<=40) then b6=15;
  stp6=(DLT6sum>b6);
        if (stp6=1) then et6=1;
      end;
      if target=7 then do;
  DLT7=(cutp2<theta7); n7=n7+1; DLT7sum=DLT7sum+DLT7;
        if n7<=3 then b7=3;
        if (3<n7<=5) then b7=4;
```

```
        if (5<n7<=8) then b7=5;
        if (8<n7<=11) then b7=6;
        if (11<n7<=14) then b7=7;
        if (14<n7<=17) then b7=8;
        if (17<n7<=21) then b7=9;
        if (21<n7<=24) then b7=10;
        if (24<n7<=28) then b7=11;
        if (28<n7<=31) then b7=12;
        if (31<n7<=36) then b7=13;
        if (36<n7<=38) then b7=14;
        if (38<n7<=40) then b7=15;
stp7=(DLT7sum>b7);
        if (stp7=1) then et7=1;
    end;
    if target=8 then do;
DLT8=(cutp2<theta8); n8=n8+1; DLTs8um=DLT8sum+DLT8;
        if n8<=3 then b8=3;
        if (3<n8<=5) then b8=4;
        if (5<n8<=8) then b8=5;
        if (8<n8<=11) then b8=6;
        if (11<n8<=14) then b8=7;
        if (14<n8<=17) then b8=8;
        if (17<n8<=21) then b8=9;
        if (21<n8<=24) then b8=10;
        if (24<n8<=28) then b8=11;
        if (28<n8<=31) then b8=12;
        if (31<n8<=36) then b8=13;
        if (36<n8<=38) then b8=14;
        if (38<n8<=40) then b8=15;
stp8=(DLT8sum>b8);
        if (stp8=1) then et8=1;
    end;
    if target=9 then do;
DLT9=(cutp2<theta9); n9=n9+1; DLT9sum=DLT9sum+DLT9;
        if n9<=3 then b9=3;
        if (3<n9<=5) then b9=4;
        if (5<n9<=8) then b9=5;
        if (8<n9<=11) then b9=6;
        if (11<n9<=14) then b9=7;
        if (14<n9<=17) then b9=8;
        if (17<n9<=21) then b9=9;
        if (21<n9<=24) then b9=10;
        if (24<n9<=28) then b9=11;
        if (28<n9<=31) then b9=12;
        if (31<n9<=36) then b9=13;
        if (36<n9<=38) then b9=14;
```

```
        if (38<n9<=40) then b9=15;
    stp9=(DLT9sum>b9);
        if (stp9=1) then et9=1;
       end;
       if target=10 then do;
    DLT10=(cutp2<theta10); n10=n10+1; DLT10sum=DLT10sum+DLT10;
        if n10<=3 then b10=3;
        if (3<n10<=5) then b10=4;
        if (5<n10<=8) then b10=5;
        if (8<n10<=11) then b10=6;
        if (11<n10<=14) then b10=7;
        if (14<n10<=17) then b10=8;
        if (17<n10<=21) then b10=9;
        if (21<n10<=24) then b10=10;
        if (24<n10<=28) then b10=11;
        if (28<n10<=31) then b10=12;
        if (31<n10<=36) then b10=13;
        if (36<n10<=38) then b10=14;
        if (38<n10<=40) then b10=15;
    stp10=(DLT10sum>b10);
        if (stp10=1) then et10=1;
       end;


DLTsum=DLTsum+(DLT1+DLT2+DLT3+DLT4+DLT5+DLT6+DLT7+DLT8+DLT9+DLT10
);
        stp=(DLTsum>=boundary);
        if (stp=1) then et=1;
 end;

 output;
 end;

run;

data s.simulationII_1;
 set s.simulationII_1;
 type=4;
 etsum=et1+et2+et3+et4+et5+et6+et7+et8+et9+et10;
 if (et=0 and etsum=0) then type=1;
 if (et=1 and etsum=0) then type=2;
 if (et=0 and etsum>=1) then type=3;
run;

proc freq data=s.simulationII_1;
 tables et et1 et2 et3 et4 et5 et6 et7 et8 et9 et10 type;
```

```
run;

proc means data=s.simulationII_1;
  var n1 n2 n3 n4 n5 n6 n7 n8 n9 n10;
run;
```