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An analysis for establishing a necessary condition for equivalence in active control clinical trials.

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AN ANALYSIS FOR ESTABLISHING A NECESSARY CONDITION FOR EQUIVALENCE IN ACTIVE CONTROL CLINICAL TRIALS

by

CRAIG JEFFERSON

A DISSERTATION

Submitted to the graduate faculty of The University of Alabama at Birmingham,
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ABSTRACT OF DISSERTATION
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Title An Analysis for Establishing a Necessary Condition for Equivalence in Active Control Clinical Trials

The approach is an empirical Bayesian methodology in a survival analysis context with an application to clinical trials. The intent of this proposed methodology is to give individuals in clinical trial equivalency research more flexibility in model selection. The methodology is an extension of Bartolucci and Singh's (1993) work to the Weibull and linear-exponential models that involves testing nonscale parameters by classical methods. For the nonscale parameter, the Thoman and Bain (1969) method is employed for the Weibull, and a nonconventional likelihood ratio test is derived in the linear-exponential case. Pertaining to the scale parameter, the approach defines a general class of discrepancy measures for equivalency, shows specific limiting cases of the general measures, and then applies the Bayesian neighborhood null hypothesis theory to derive posterior credibility regions on the measures for both distributions.

DEDICATION

This document is dedicated to the memory of my paternal grandmother affectionately known as Mama Dear; my maternal grandparents; and my father, mother, brother, and sister.

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I give glory and praise unto my Heavenly Father for His blessings and for constantly reminding me that He is greater. I would like to thank my advisor, Dr. Alfred A. Bartolucci, for his support and for producing an environment conducive to growth. I would like to thank the co-chair of my committee, Dr. Karan P. Singh, for always encouraging me to do good research and often reminding me of the rewards of such. To the other members of my committee, Dr. Edwin Bradley, Dr. Charles Katholi, and Dr. Malcom Turner, I am grateful for your kind doings, service on my committee, and helpful hints. To Dr. George Munchus, I owe many thanks for his constant support of my efforts. I also would like to thank Dr. Colin M. Ramsay and Dr. Mostafa Mashayekhi of the University of Nebraska at Lincoln for providing meaningful feedback regarding ideas I presented to them during the early stages of this dissertation. Finally, I would like to thank my family for their sustainment through this process.

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PREFACE

This dissertation addresses some of the foundational issues in clinical trials research regarding equivalence. There are many unresolved issues pertaining to the determinance of equivalence. Some of those issues are inference, design, analysis, and some are nonstatistical in nature. However, given the information regarding some of the previously mentioned issues, the focus of this dissertation is on the analysis aspect of the determinance of equivalence. The proposed approach is an extension of Bartolucci and Singh's (1993) work. This extension gives researchers more flexibility regarding model selection.

1. INTRODUCTION

1.1 Prologue

Generally speaking, the topic of this discourse is equivalence. Equivalence may be defined as two or more treatments, drugs, or therapies yielding similar desirable results. Research scholars representing the Food and Drug Administration (FDA), medical, and pharmaceutical industries commonly refer to this topic as bio or therapeutic equivalence. However, the concept may be generalized to include the manufacturing industry. From a manufacturing perspective, manufacturers (suppliers and customers) are interested in providing or assuring that products, machines, services, and processes are equivalent in performance with respect to prototypes.

The equivalence problem area is rich with many unresolved issues. A few of those issues are listed below:

Inference Issues:

--Dosage (i.e., fixed dosage versus dose titration)

--Clinical practice versus clinical trials

Design Issues:

--Study biases

--Concomitant medication

Analysis Issues:

--Stopping rule

--Proposed statistical methods are not accepted industry-wide

Nonstatistical Issues:

--Inadequate calibration of measuring instruments

--Lack of documentation during the clinical trial.

However, the emphasis of this writing is on the analysis of bio or therapeutic equivalence data from positive or active control trials.

1.2 Statement of the Problem

Imagine a statistician who received a data set one particular day from a superior. The characteristics of the data set were as follows: two treatments were applied at random to two different groups of samples, but the samples within each group were from the same homogeneous population; and the random variable of interest was survival times. Imagine also that there was ancillary information available to the statistician that the superior had knowledge of and that was pertinent to the analysis. Finally, imagine that the superior requested that the statistician test the hypothesis of equivalence regarding the two treatments.

The above scenario describes very generally the point at which this dissertation begins. This dissertation focuses on the analysis aspect of equivalence only. It assumes that the design aspects of the study were carried out such that all parties of concern agree with the method. As a result, a formal statement of the following is

> Given a data set of two drug formulations, one as an experimental formulation and the other as the standard formulation, with the objective of demonstrating equivalence of survival times in an active control clinical trial, how does one analyze the data set, assuming that the underlying distributions are either a Weibull

density or a linear-exponential density and that prior information about the parameters of these distributions is available? Furthermore, what is the correct inference?

1.3 Research Objectives

There are several important objectives of this research. One important objective of this research is to extend the methodology of Bartolucci and Singh (1993) to include other survival distributions such as the Weibull and linear-exponential. The purpose of this objective is to give researchers greater flexibility in the modeling and analysis of the data. The Bartolucci and Singh (1993) methodology is also taken a step further to derive the asymptotic joint distribution of the credibility limits so that probabilistic statements can be made about the credibility limits being a subset of the specified interval or any other interval. Finally, the approach taken in this dissertation differs from the Bartolucci and Singh method in terms of calculating the test statistic and the credibility region.

Another objective of this research is to present an integration technique that can be used in integrating posterior distributions derived when using this methodology. This objective is crucial because the posterior distributions derived when using this methodology are usually such that analytical methods are not applicable.

Finally, a further important objective of this research is to provide an argument for the correct inference when the desire of the study is to demonstrate equivalence. The imperativeness of this objective stems from the need to correctly interpret the statistical results of an active control clinical trial.

1.4 An Overview of Other Approaches

Current approaches regarding analysis are referred to as statistical salvage procedures (Pledger and Hall 1983). According to Pledger and Hall, researchers have concentrated on statistical calculations aimed at assuring power with adequate sample sizes and new statistical methods, rather than rethinking the whole experimental inference framework. Pledger and Hall further state, "if there is any discussion at all of inferential problems in connection with positive control trials it is generally a somewhat superficial consideration of the ability of the study to distinguish between A and B" (p. 3), where A is a test drug and B is an active drug. The basis of Pledger and Hall's previous statement is with repect to the use of statistical power and its relationship to efficacy. Continuing, Pledger and Hall state, "sufficient statistical power is taken as grounds for concluding that a nonsignificant difference between A and B implies efficacy of A" (p. 3). Pledger and Hall state three reasons why the power approach is inadequate:

1. It encourages limiting study size, using insensitive measures of response, and allowing study characteristics which needlessly increase variation or obscure the test therapy versus the reference therapy.

2. The power approach makes little use of the observed results of the study.

3. The power approach depends on a quantity D (difference) that can not be empirically validated.

Note: The choice of an important difference in a clinical trial should be based not on what would be considered important in clinical practice but on what has been observed previously in similar controlled studies (Pledger and Hall 1983, p. 3).

Pledger and Hall are correct in regarding the need to rethink the whole experimental inference framework. Actually, what is needed is an experimental inference framework that establishes a sufficient condition for equivalence. A general definition of a

sufficient condition was given by Capaldi (1975) as a condition (state of affairs, thing, process, etc.) that automatically leads to the production of another event. Some academicians embrace the thoughts of Aristotle's "the fallacy of the universal negative," that is, the establishing of such a condition is impossible. As a result, this remains a challenge, and it is a different issue from the context of this dissertation.

However, regarding Pledger and Hall's correctness and my statements of what is needed, the power approach should not be regarded as an approach without merit. On the contrary, the power approach should be recognized for its value, that is, the establishing of a necessary condition. Generally, a necessary condition has been defined by Capaldi (1975) as a condition (state of affairs, thing, process, etc.) that must be present if we are to obtain the effect. Hence, therein lies the merit of the power approach, namely, the ability to establish a necessary condition.

Blackwelder (1982) proposed a nonconventional null hypothesis approach based on power with an associated test statistic. Blackwelder and Chang (1984) presented an equation and graphs for sample size determination that complement Blackwelder's (1982) proposed procedure. In the Confidence Interval section of Blackwelder's (1982) work, he states the usefulness of the theory of hypothesis testing in planning a clinical trial and the usefulness of confidence interval methods of Westlake (1972), Metzler (1974), Westlake (1976), and Westlake (1979) for analyzing, explaining, and reporting of the accumulated data. Blackwelder (1982) states the basis of his rationale as follows: "a hypothesis test tells us whether the observed data are consistent with the null hypothesis, and a confidence interval tells us which hypotheses are consistent with the data" (p. 3), which is well documented in Lehmann (1959), Remington and Schork (1970), and Armitage (1971).

Blackwelder's (1982) paper presents a power approach that is accepted by many as proving the null hypothesis. From an inference perspective, such a statement may be misleading to nonstatisticians.

This approach described by Blackwelder is referred to as an "operational definition of zero technique" by some statisticians, where operational can be defined as one of the following: (i) something that is easily understood, (ii) something that one can put into formulas, (iii) something that is so small all parties of concern would consider it zero. If one wanted to prove the null hypothesis by use of the power approach or the operational definitions of zero technique, the following would occur:

1. Define an operational definition of zero, for example $\delta = 0.01$.

2. Setup an experiment that would detect the operational definition of zero with "high" probability.

3. If the experiment fails to detect the operational definition of zero difference, then one can conclude that the treatments are equal (a proved null hypothesis).

A more correct characterization of the above approach is the establishing of a necessary condition.

Pledger and Hall (1983) state that the work of Blackwelder and others addresses criticisms (i) and (ii) of the power approach but not (iii). Pledger and Hall's rationale is that their approach is content to answer the question "Are A and B equivalent?" without addressing the possibility that neither A nor B would have out performed a placebo had a placebo group been included in the trial.

Hsu (1983) states that, for ethical reasons, active control trials are increasingly more popular than placebo control trials. Hsu also states that the methods for

demonstrating drug efficacy for active control trials versus placebo control trials are different. In the assessment of active control clinical trials, Hsu states that there are deficiencies in the design of a clinical trial, such as: (i) inadequate sample size, (ii) inappropriate enrollment criteria and patient selection procedure, (iii) high drop out rate, (iv) unlimited and uncontrolled use of concomitant medication, (v) imprecise measurement of the response variables. These deficiencies tend to obscure the results when using stochastic ordering as the method of analysis. Hsu further states that active control trials are useful, but they do not always produce clear results for evaluation of new drug efficacy. Hsu concludes his writing with suggestions for points of consideration in planning active control trials.

Munk (1993) proposed the mixtest. The mixtest is an improvement of two commonly used methods in bioequivalence, namely, Shuirmann's (1987) procedure and Anderson and Hauck's (1983) procedure. Munk's method is an improvement in the sense that it exploits Schuirmann's procedure with respect to power when the variances are small and employs Anderson and Hauck's procedure with respect to power when the variances are large.

Shuirmann's (1987) procedure is referred to as the double t-test ($1-2\alpha$) confidence interval procedure. Anderson and Hauck's (1983) approach is a t-test procedure that is more powerful than methods based on usual (shortest) and symmetric confidence intervals.

Fluehler, Grieve, Mandallaz, Mau, and Moser (1983) presented a Bayesian approach which involves obtaining the posterior probability that the ratio of the true means of a new and a standard formulation lies within a given interval. Selwyn, Dempster,

and Hall (1981) proposed an alternative Bayesian approach in which the criterion for equivalence is that the difference in the response means is less than a specified percentage of the mean of the standard based on the posterior probability. Bartolucci and Singh (1993) propose a Bayesian approach that follows the credibility region methodology. The Bartolucci and Singh (1993) approach defines a general class of discrepancy measures between parameters of interest, shows specific limiting cases of the general measures, and then applies the Bayesian neighborhood null hypothesis theory to derive posterior credibility regions on the measures.

For the most part, in a particular application, the Bartolucci and Singh (1993) method yielded similar conclusions to the result of analyses by classical methods. Bartolucci and Singh assure researchers, given in general the nontractable analytical results of their method, with present day computing capabilities that this is not a disadvantage:

> The advantage to this approach is that one can clearly accommodate a variety of prior beliefs about behavior of the compounds involved and incorporate that information into the analysis to demonstrate whether or not the assumption of therapeutic equivalence is realistic (Bartolucci and Singh 1993).

More will be said about this approach in Chapter 4. In closing, it should be noted that Singh (1996) gives further details of the Bartolucci and Singh paper.

1.5 A Sketch of the Methodology of the Proposed Solution

In the context of a positive control clinical trials, in which there is a positive-control study upward bias (Pledger and Hall 1983), the approach taken in this dissertation will be an extension of Bartolucci and Singh's (1993) work. This methodology will be extended to include the Weibull and linear-exponential models. The Weibull and linear-exponential distributions were selected because of the increased

flexibility of the forms of their hazard functions when compared to the exponential model that Bartolucci and Singh used. The intent of a more flexible hazard function is to remedy the positive-control study upward bias because at the analysis stage of an experiment, a way to remedy this is by model selection. However, the success of this intent is not the primary focus of this dissertation. The overall objective of this dissertation is to provide researchers with a wider selection of models for the working theory established by Bartolucci and Singh. The action items of the objective are

1. Select two survival distributions that have the exponential distribution as a special case. The intent is to generalize from the exponential distribution. The selected distributions are Weibull and linear-exponential.

The Weibull distribution as defined in Chapter 4 is an exponential distribution when the shape parameter is one. The linear-exponential distribution as defined in Chapter 4 is an exponential distribution when the parameter of the nonexponential linear term is zero. In addition to the Weibull and linear-exponential distributions being selected as generalizations of the exponential, these distributions were also selected because of the properties of their hazard functions. The hazard function of the Weibull distribution can assume the following forms: (i) constant, (ii) increasing linearly, (iii) increasing nonlinearly, and (iv) decreasing nonlinearly. The hazard function of the linear-exponential distribution as defined in Chapter 3 can assume the following forms: (i) constant, (ii) increasing linearly, and (iii) decreasing linearly.

2. The assumed prior density for the scale parameter of the linear-exponential is the Inverted-Gamma-One. The nonexponential linear term of the linear-exponential model is estimated from the joint likelihood function. The shape parameter of the Weibull will be

estimated by obtaining the value that maximizes the joint likelihood function. An Inverted-Gamma-One prior will be assumed for the scale parameter for the Weibull distribution.

3. The ratio of the scale parameters in each of the distributions will be used as a discrepancy measure for equivalence.

4. The posterior distributions for the discrepancy measures will be derived.

5. The criteria for establishing a necessary condition regarding equivalence will be defined. The criteria will be based on a 100(1-α)% credible region for the discrepancy measure.

Note: Credibility is a wider and vaguer concept of probability which is defined as the amount of credence that it is logical to assign to a more or less uncertain proposition (Russell 1948).

1.6 Content of Other Chapters

The remainder of the document contains Chapter 2 through 7 with a reference list and appendices to support information in those chapters. Chapter 2 contains a detailed review of some of the references cited in section 1.4. The analyses and methods in this section vary from Bayesian and frequentist approaches. In some cases, the random variables are discrete, and in others cases some may be continuous.

In Chapter 3, an overview of active control clinical trials is given. The factors that influence clinical evaluations are presented. The attractiveness of the active control trial and the criticisms of that type of trial are presented.

Chapter 4 contains a detailed discussion of the methodology. This involves the stating of the hypotheses to the development of the test statistic.

Chapter 5 presents a discussion about the integration of posterior kernels and the method of integration used to obtain the posterior credibility region of the test statistic in Chapter 4. The discussion begins with a characterization of the problem when integrating posterior kernels in several dimensions.

Chapter 6 is an application of the methodology to a published study. The study was a phase III active control clinical trial. The formulations involved the treatment of leukemia.

Finally, Chapter 7 is a discussion of future research. Future research is suggested with respect to design and analysis.

2. SELECTED DETAILED REVIEW OF RELATED LITERATURE

2.1 Introduction

The different statistical approaches to the problem of equivalence are placed in different sections of this chapter. The selected approaches are in chronological order with respect to the date of the paper. The approaches are presented from the stating of the hypotheses to the derived test statistic. The details of the derivations are omitted. However, the reference for each approach is contained in the reference section if the reader requires further detail.

2.2 Selwyn et al. (1981)

The Selwyn et al. approach is based on their belief that a biologically meaningful measure of bioequivalence is the posterior probability that the difference in formulation means is less than a specified percentage of the mean of the standard drug. It is in the context of the 2 x 2 changeover design that the Selwyn et al. approach is developed. To this extent, it is assumed that data have been collected on the new and standard formulations according to a 2 x 2 changeover design with the response variable being a univariate characteristic of the concentration-time curve, such as AUC (area under the curve). Hence, the experiment is modeled as

$$\begin{aligned} Y_{ijk} &= \mu + P_j + T_l + S_{ik} + e_{ijk} \\ \textit{for } i &= 1,2, \quad j = 1,2, \quad k = 1,\ldots,m \quad l = 1,2 \end{aligned} \tag{2.2.1}$$

where μ denotes the overall mean, P_j denotes the period, T_i denotes the formulation, S_{ik} denotes the subject effects, and e_{ijk} denotes the error of measurement. This model assumes that S_{ik} and e_{ijk} are all independently normally distributed with means zero and variances σ_s^2 and σ_e^2, respectively.

Again, Selwyn et al. criterion for bioequivalence is a high posterior probability that the difference in formulation means is less than some fraction, say K, of the mean of the standard. Thus, they express the bioequivalence notation as

$$|2T| < K(\mu+T) \quad or \quad K_1\mu < T < K_2\mu \tag{2.2.2}$$

where $K_1 = -\frac{K}{2+K}$ and $K_2 = \frac{K}{2-K}$. Subsequently, the general approach is to calculate a posterior density, $p(\mu,T|\underline{y})$, and then to integrate this density over the region defined by eq. 2.2.2 to get the posterior probability. The formulations are considered bioequivalent if the posterior probability is high.

A reproduction of a portion Selwyn et al. Table 1 follows

*Selwyn et al.'s Table 1 (A selected portion)
General Form (carry-over effect omitted)

Source	Degrees of freedom	Sum of squares	Expected mean square
Formulations	1	$SS_1 = 2N\left(\frac{y_{11.}+y_{22.}}{2} - y_{...}\right)^2$	$\sigma_e^2 + 2NT^2$
Periods	1	$SS_2 = 2N(y_{.1.} - y_{...})^2$	$\sigma_e^2 + 2NP^2$
Subjects	N-1	$SS_3 = 2\sum_{i=1}^{2}\sum_{k=1}^{m}(y_{i.k} - y_{...})^2$	σ_A^2
Error	N-2	SS_4 (by subtraction)	σ_e^2

*Used with the permission of Biometrics (see Selwyn et al. (1981)).

The above portion of Table 1 is a general form of the analysis of variance with the carry-over effect omitted. From the above table, Selwyn et al. considered four priors when modeling without the carryover effects:

$$p\ (\mu,P,T,\sigma_e^2,\sigma_A^2) \propto {\sigma_e}^2{\sigma_A}^2 \tag{2.2.3}$$

$$p\ (\mu,P,T,\sigma_e^2,\sigma_A^2) \propto {\sigma_e}^2{\sigma_A}^2 \quad for \quad \sigma_A^2 > \sigma_e^2 \tag{2.2.4}$$

$$p\ (\mu,P,T,\sigma_e^2,\sigma_A^2) \propto {\sigma_e}^1{\sigma_A}^1 \tag{2.2.5}$$

$$p\ (\mu,P,T,\sigma_e^2,\sigma_A^2) \propto {\sigma_e}^1{\sigma_A}^1 \quad for \quad \sigma_A^2 > \sigma_e^2\ . \tag{2.2.6}$$

As a result, Selwyn et al. obtained the following posterior densities for the above priors:

$$p_1(\mu,T|\underline{y}) = N(N-2)\left\{\pi(SS_3 \times SS_4)^{\frac{1}{2}}\right\}^{-1}\left\{1+\frac{2N(\hat{\mu}-\mu)^2}{SS_3}\right\}^{-\frac{1}{2}N}\left\{1+\frac{2N(\hat{T}-T)}{SS_4}\right\}^{-\frac{1}{2}N-\frac{1}{2}} \tag{2.2.7}$$

$$p_2(\mu,T|\underline{y}) = \frac{p_1(\mu,T|\underline{y})p(C|\mu,T,\underline{y})}{p(C|y)} \tag{2.2.8}$$

$$p_3(\mu,T|\underline{y}) = N(N-3)\left\{\pi(SS_3 \times SS_4)^{\frac{1}{2}}\right\}^{-1}\left\{1+\frac{2N(\hat{\mu}-\mu)^2}{SS_3}\right\}^{-\frac{1}{2}N-\frac{1}{2}}\left\{1+\frac{2N(\hat{T}-T)^2}{SS_4}\right\}^{-\frac{1}{2}N-1} \tag{2.2.9}$$

$$p_4(\mu,T|\underline{y}) = \frac{p_3(\mu,T|\underline{y})p(C|\mu,T,\underline{y})}{p(C|y)} \tag{2.2.10}$$

where for p_2

$$\begin{aligned} p(C|\underline{y}) &= p\left[F_{N-1,N-2} < \frac{(N-2)SS_3}{(N-1)SS_4}\right] \\ p(C|\mu,T,\underline{y}) &= p\left[F_{N,N-1} < \frac{(N-1)Q_1}{NQ_2}\right] \end{aligned} \tag{2.2.11}$$

and for p_4

$$p(C|\underline{y}) = p\left[F_{N-2,N-3} < \frac{(N-3)SS_3}{(N-2)SS_4}\right]$$
$$p(C|\mu,T,\underline{y}) = p\left[F_{N-1,N-2} < \frac{(N-2)Q_1}{(N-1)Q_2}\right] \qquad (2.2.12)$$

Note: $Q_1 = 2N(\hat{\mu}-\mu)^2 + SS_3$; $Q_2 = 2N(\hat{T}-T)^2 + SS_4$; and C denotes the constraint that $\sigma_A^2 > \sigma_e^2$.

This is based on the independent components of the likelihood arising from

$$\hat{\mu} = y_{...} \sim N\left(\mu, \frac{1}{2}\frac{\sigma_A^2}{N}\right) \qquad (2.2.13)$$

$$\hat{P} = y_{.1.} - y_{...} \sim N\left(P, \frac{1}{2}\frac{\sigma_e^2}{N}\right) \qquad (2.2.14)$$

$$\hat{T} = \frac{1}{2}(y_{11.} + y_{22.}) - y_{...} \sim N\left(T, \frac{1}{2}\frac{\sigma_e^2}{N}\right) \qquad (2.2.15)$$

$$SS \sim \sigma_A^2 \chi^2_{N-1} \qquad (2.2.16)$$

$$SS \sim \sigma_e^2 \mathrm{X}^2_{N-2} \,. \qquad (2.2.17)$$

For the model that includes the carry-over effects, based on the independent components of the likelihood arising from

$$\hat{T} \sim N\left(T - \frac{1}{2}R, \frac{1}{2}\frac{\sigma_e^2}{N}\right) \qquad (2.2.18)$$

$$\hat{R} = y_{1..} - y_{2..} \sim N\left(R, \frac{2\sigma_A^2}{N}\right) \qquad (2.219)$$

$$SSS \sim \sigma^{\,2}\mathrm{X}^2_{N-2} \qquad (2.2.20)$$

and using the following prior

$$p(\mu,P,T,R,\sigma^{2},\sigma^{2}) \propto \sigma^{-2}\,\sigma^{-2}\,e^{-\frac{1}{2}\frac{R}{\sigma_r^2}} \qquad (2.2.21)$$

where the subject sum of squares has been partitioned into R, residual sum of squares, plus SSS, sum of squares for subjects within sequences, and R is centered at 0 with standard deviation σ_R. Hence, the posterior probability density is

$$p(\mu,T|R,y) = N(N-2)\left\{\pi\,(D\times SS_4)^{\frac{1}{2}}\right\}^{-1}\left\{1+\frac{2N(\hat{\mu}-\mu)^2}{D}\right\}^{-\frac{1}{2}N}\left\{1+\frac{2N(T-E)^2}{SS_4}\right\}^{-\frac{1}{2}N-\frac{1}{2}} \qquad (2.2.22)$$

Again, if the posterior probability is high then bioequivalence is accepted.

2.3 Blackwelder (1982)

Blackwelder's approach involves formulating a one-sided appropriate (when compared to the conventional null hypothesis) null hypothesis, confidence interval, test statistics, and sample size calculation for a dichotomous response variable regarding clinical trials. More to the point, Blackwelder writes the null hypothesis and alternative as such

$$\begin{aligned} H_0&: \pi_s \geq \pi_e + \delta \\ H&: \pi < \pi + \delta \end{aligned} \qquad (2.3.1)$$

where π_s denotes the true success proportion of the standard therapy, π_e denotes the true success proportion of the experimental therapy, and δ denotes a specified difference. He further writes the test statistic, confidence interval, and the sample size calculation as the following:

Test Statistic:

$$z = \frac{p_s - p_e - \delta}{SE} \qquad (2.3.2)$$

with SE equaling:

$$SE = \left[\frac{p_s(1-p_s)}{n_s} + \frac{p_e(1-p_e)}{n_e}\right]^{\frac{1}{2}} \tag{2.3.3}$$

where p_s denotes the observed success proportion of the standard therapy, p_e denotes the observed success proportion of the experimental therapy, n_s denotes the total number of patients observed in the standard therapy group, and n_e denotes the total number of patients observed in the experimental therapy group. The 100 $(1-\alpha)$% confidence inteval is

$$[-1, p_s - p_e + z_{1-\alpha}SE), \tag{2.3.4}$$

and the sample size in each of the two groups is

$$\frac{(z_{1-\alpha} + z_{1-\beta})^2[\pi_s(1-\pi_s) + \pi_e(1-\pi_e)]}{(\pi - \pi - \delta)^2} \tag{2.3.5}$$

where $\pi_s - \pi_e < \delta$.

One of the major aims of Blackwelder's paper is show the difference in hypothesis testing between that of the conventional approach and that of a specified difference for the purpose of a clinical trial. In Table 1 of Blackwelder's paper, the null and alternative hypothesis, test statistic, confidence interval, and sample size calculations for the conventional approach are expressed as follows:

Hypothesis:

$$\begin{aligned} H_0&: \pi_s \le \pi_e \\ H&: \pi > \pi \end{aligned} \tag{2.3.6}$$

Test statistic:

$$z = \frac{p_s - p_e}{SE} \tag{2.3.7}$$

where SE is previously defined above. Confidence interval and sample size are, respectively,

$$(p_s - p_e - z_{1-\alpha}SE, 1] \tag{2.3.8}$$

and

$$\frac{(z_{1-\alpha}+z_{1-\beta})^2[\pi_s(1-\pi_s)+\pi_e(1-\pi_e)]}{(\pi_s-\pi_e)^2} \qquad (2.3.9)$$

where $\pi_s > \pi_e$.

Blackwelder's paper also contains two additional tables that provide information on type I and II errors and sample size calculations. Reproductions of the tables are the following:

**Table 2

Classification of Possible Decisions Based on Hypothesis Tests
Result of test (choice of therapy)

Test difference $\pi_s - \pi_e$	Testing $H_0: \pi_s \le \pi_e$		Testing $H_0': \pi_s \ge \pi_e + \delta$	
(correct choice of therapy)	Fail to reject (experimental)	Reject (standard)	Reject (experimental)	Fail to reject (standard)
0 (experimental)	correct decision	type I error	correct decision	type II error
δ (standard)	type II error	correct decision	type I error	correct decision

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***Table 3

Sample Size Calculations for $\alpha = 0.05$, $\beta = 0.10$

Testing $H_0: \pi_s \le \pi_e$				Testing $H_0': \pi_s \ge \pi_e + \delta$			
π_s	π_e	$2n$		π_s	π_e	δ	$2n$
0.9	0.8	430		0.9	0.9	0.1	310
0.9	0.7	130		0.9	0.9	0.2	78

***Table 3 (Continued)

Sample Size Calculations for $\alpha = 0.05$, $\beta = 0.10$

Testing H_0: $\pi_c \leq \pi_e$				Testing H_0': $\pi_c \geq \pi_e + \delta$			
0.6	0.5	840		0.6	0.6	0.1	824
0.6	0.4	206		0.6	0.6	0.2	206
0.4	0.3	772		0.4	0.4	0.1	824
0.4	0.2	172		0.4	0.4	0.2	206
				0.9	0.85	0.1	1492
				0.9	0.8	0.2	430
				0.6	0.55	0.1	3342
				0.6	0.5	0.2	840

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Regarding Table 2 of Blackwelder's paper, it is important to note the change in the relationship of the type I and type II errors between the conventional and specified difference approaches. Pertaining to Table 3 of Blackwelder's paper, in the event that the sample size for the specified difference is not achievable, then a proposed approach for handling smaller studies involves expressing the hypothesis in terms of an odds ratio and constructing confidence intervals about that ratio.

In conclusion, one of the contributions that Blackwelder makes is to provide a statistical methodology to researchers for analyzing clinical trials. In doing so, Blackwelder provides a support discussion.

2.4 Anderson and Hauck (1983)

Anderson and Hauck's approach is motivated by the fact that in practice no two drug formulations will result in bioavailability profiles which are exactly alike. It is from

this point that they make a strong case for a finite interval hypothesis test and not the point test of equality with the hypothesis of equivalence being written as the alternative hypothesis because of the desire to demonstrate equivalence. Their approach begins with stating the hypothesis for the mean values of the experimental, μ_E, and standard, μ_S, formulations in the following manner:

$$\begin{aligned} H_0&: \ \mu_E - \mu_S \le A \quad or \quad \mu_E - \mu_S \ge B \\ H_A&: \ A < \mu_E - \mu_S < B \end{aligned} \tag{2.4.1}$$

where $A = -B$ (most often). Anderson and Hauck use X's to denote the data that are assumed to be normally distributed with a common variance σ^2. They further state that in some cases the X's will be natural logarithms of biological measures. In such a case, the hypotheses corresponding to (2.4.1) on the log scale can then be stated as

$$\begin{aligned} H_0'&: \ \frac{M_E}{M_S} \le A_0 \quad or \quad \frac{M_E}{M_S} \ge B_0 \\ H_A'&: \ A_0 < \frac{M_E}{M_S} < B_0 \end{aligned} \tag{2.4.2}$$

where M_E and M_S are the means in the original scale and $A_0 = \exp(A)$ and $B_0 = \exp(B)$.

The test statistic that Anderson and Hauck consider is

$$T = \bar{X}_E - \bar{X}_S - \frac{1}{2}(A+B) \div S\left(\frac{1}{n_E} + \frac{1}{n_S}\right)^{\frac{1}{2}} \tag{2.4.3}$$

where $\bar{X}_E$ and $\bar{X}_S$ are the sample means, n_E and n_S are the group sample sizes, and S is obtained from the analysis of variance with degrees of freedom γ. T has a noncentral t distribution. The noncentrality parameter is calculated as

$$\delta = \mu_E - \mu_S - \frac{1}{2}(A+B) \div \sigma\left(\frac{1}{n_E} + \frac{1}{n_S}\right)^{\frac{1}{2}}. \tag{2.4.4}$$

If the test is such that the magnitude of T is small, that is, $C_1 < T < C_2$, then H_0 is rejected and equivalence of the two formulations is concluded. The selection of C_1 and C_2 is done such that the test is unbiased at level α, that is

$$\begin{aligned} &P[C_1 < T < C_2 \mid \mu_E - \mu_S = B, \sigma] = \\ &P[C \quad < T < C \quad \mid \mu \quad - \mu \quad = A, \sigma] = \alpha \ . \end{aligned} \tag{2.4.5}$$

With the choice of a single C where $C_2 = C$ and $C_1 = -C$, the level α rejection region can be determined by solving

$$\begin{aligned} &P[|T| < C \mid \mu_E - \mu_S = A, \sigma] = \\ &P[|T| < C \mid \mu \ - \mu \ = B, \sigma] = \alpha \ . \end{aligned} \tag{2.4.6}$$

In order to calculate the exact distribution for the test statistic, T, then σ must be known or A and B must be such that they can be expressed as proportional to the unknown σ. In practice, when testing the hypothesis given a known noncentrality parameter, Anderson and Hauck state that it is more informative and easier to work with the empirical significance level, ρ. Hence, if t is the observed value of T, then ρ is given by

$$\rho = P[|T| < |t| \mid \mu_E - \mu_S = B, \sigma] \ . \tag{2.4.7}$$

As a result, an α level test is obtained by rejecting H_0 whenever $\rho \leq \alpha$.

When testing the hypothesis given an unknown noncentrality parameter, Anderson and Hauck propose approximations to the empirical significance level, ρ, in 2.4.7. They then substitute the approximate level, $\hat{\rho}$, for ρ and then proceed as if the noncentrality parameter were known.

2.5 Fluehler et al. (1983)

Fluehler et al. provide a Bayesian approach to comparative bioavailability studies. The comparative bioavailability studies are designed to gain knowledge of the pharmaceutical properties of two or more formulations of the same drug. Fluehler et al.'s

concentration curve (AUC) and the maximum concentration of that curve (C_{max}). Subsequently, by their method, bioequivalence is inferred if the ratio, say θ, of the true means of the new to the standard formulation of the measure, AUC or C_{max}, is within the given limits r_1 and r_2, that is

$$r_1 \le \theta \le r_2 . \tag{2.5.1}$$

The limits r_1 and r_2 are based on medical and/or regulatory grounds. An example of values for r_1 and r_2 are 0.8 and 1.2, but the values of r_1 and r_2 do not have to be symmetric about 1.

In comparative bioavailability studies, the design considered most appropriate is the crossover design. This is due to the large inter-subject variability with respect to the absorption distribution. The crossover design is characterized by each of the subjects, say n, receiving the new and standard formulations with a reasonably long washout period between treatment applications. The crossover design model is

$$x_{ijk} = \mu + \xi_i + \pi_j + \phi_k + \epsilon_{ijk} \tag{2.5.2}$$

where x_{ijk} denotes the observed values, μ denotes the overall mean, ξ_i denotes the i^{th} subject effect (i = 1,2,3,...,n), π_j denotes the j^{th} period effect (j = 1,2), and ϕ_k denotes the experimental error which is assumed $N(0,\sigma^2)$. The AUC random variables are assumed to be normally distributed according to the model in eq. 2.5.2. The C_{max} random variables are assumed to be lognormally distributed, so that $\ln(C_{max})$ conforms to the assumptions of the model in eq. 2.5.2.

In Fluehler et al.'s approach, the posterior probability that θ is between r_1 and r_2 is calculated by

$$P(r_1 \le \theta \le r_2) = \int_B^A t_\nu(\tau)\, d\tau \tag{2.5.3}$$

where $t_v(\tau)$ follows a Student's distribution and ν denotes the degrees of freedom of error mean square from the ANOVA. The AUC integration limits are

$$A = \frac{\left(\hat{\theta} - r_1\right)n^{\frac{1}{2}}}{CV\left(1 + r_1^2\right)^{\frac{1}{2}}} \tag{2.5.4}$$

$$B = \frac{\left(\hat{\theta} - r_2\right)n^{\frac{1}{2}}}{CV\left(1 + r_2^2\right)^{\frac{1}{2}}} \tag{2.5.5}$$

where

$$\hat{\theta} = \frac{\bar{x}_{NEW}}{\bar{x}_{STD}}, \tag{2.5.6}$$

and

$$CV = \frac{S}{\bar{x}_{STD}}, \tag{2.5.7}$$

$$S = \sqrt{Error\ Mean\ Square}\,. \tag{2.5.8}$$

The mean of the new formulation, $\bar{x}_{NEW}$, and the mean of the standard formulation, $\bar{x}_{STD}$, are observed treatment means. The $\ln(C_{max})$ integration limits are

$$A = \frac{\left[\bar{x}_{NEW} - \bar{x}_{STD} - \ln(r_1)\right]n^{\frac{1}{2}}}{2^{\frac{1}{2}}S} \tag{2.5.9}$$

$$B = \frac{\left[\bar{x}_{NEW} - \bar{x}_{STD} - \ln(r_2)\right]n^{\frac{1}{2}}}{2^{\frac{1}{2}}S} \tag{2.5.10}$$

where $\bar{x}_{NEW}$ and $\bar{x}_{STD}$ denote the observed formulation mean of the logged C_{max} values. The Fluehler et al. approach infers that if the probability in eq. 2.5.3 is large enough, then bioequivalence is accepted.

2.6 Schuirmann (1987)

Schuirmann writes that bioavailability is to be characterized by one or more blood concentration profile variables, such as AUC, C_{max}, etc. As a result, the profile variables are synonymous with the random variables of interest for determining equivalence.

Given two formulations, say T (test product) and R (reference product), in a bioavailability/bioequivalence study, the hypotheses of interest are

$$\begin{aligned} H_0&: \ \mu_T - \mu_R \le \theta_1 \quad or \quad \mu_T - \mu_R \ge \theta_2 \\ H_1&: \ \theta_1 < \mu_T - \mu_R < \theta_2 \end{aligned} \tag{2.6.1}$$

where μ_T denotes the mean bioavailability of the test product, μ_R denotes the mean bioavailability of the reference product, θ_1 denotes a specified lower limit, and θ_2 denotes a specified upper limit. The null hypothesis, H_0, is the hypothesis of nonequivalence between μ_T and μ_R. H_1, on the other hand, says that μ_T and μ_R are equivalent.

The assumptions of Schuirmann's approach are

1. The profile variable(s) are normally distributed.

2. The within-subject variances of the test and reference products are equal.

3. The study is a balanced crossover study, that is, there is an equal number of subjects in each treatment administration sequence and there are no missing observations from any subject.

The estimate of $\mu_T - \mu_R$ is the observed average bioavailability difference of $\bar{x}_T - \bar{x}_R$. $\sigma\left(\frac{2}{n}\right)^{\frac{1}{2}}$ is the standard deviation estimate for $\mu_T - \mu_R$. Because σ is unknown, it is estimated by the square root of the error mean square from the crossover design analysis of variance, say S. Consequently, S is the standard error of $\bar{x}_T - \bar{x}_R$.

Now, to use Schuirmann's methodology in a bioequivalence study, three measures are needed, namely, the degrees of freedom, say ν, the estimate $\bar{x}_T - \bar{x}_R$, and its standard

error $S\left(\frac{2}{n}\right)^{\frac{1}{2}}$. Schuirmann's two one-sided test procedure begins by restating the previously stated hypotheses in eq. 2.6.1 into two different sets of hypotheses, namely,

$$H_{01}: \mu_T - \mu_R \leq \theta_1 \qquad H_{11}: \mu_T - \mu_R > \theta_1 \tag{2.6.2}$$

$$H_{02}: \mu_T - \mu_R \geq \theta_2 \qquad H_{12}: \mu_T - \mu_R < \theta_2 . \tag{2.6.3}$$

Schuirmann's procedure rejects H_0 of eq. 2.6.1 and concludes equivalence if and only if both H_{01} and H_{02} are rejected at a chosen nominal level of significance α. Test statistics for the set of hypotheses in eq. 2.6.2 and eq. 2.6.3 are

$$t_1 = \frac{(\bar{x}_T - \bar{x}_R) - \theta_1}{S\left(\frac{2}{n}\right)^{\frac{1}{2}}} \geq t_{1-\alpha}(\nu) \tag{2.6.4}$$

and

$$t_2 = \frac{\theta_2 - (\bar{x}_T - \bar{x}_R)}{S\left(\frac{2}{n}\right)^{\frac{1}{2}}} \geq t_{1-\alpha}(\nu) \tag{2.6.5}$$

where t_1 and t_2 are the ordinary one-sided test statistics, respectively. The two one-sided test procedure is operationally identical to the confidence interval approach (recommended by Westlake 1981), if the ordinary $1-2\alpha$ (not $1-\alpha$) confidence interval for $\mu_T - \mu_R$ is completely contained in the equivalence interval $[\theta_1, \theta_2]$.

2.7 Bartolucci and Singh (1993)

The Bartolucci and Singh approach can be referred to as a survival/bioequivalence method versus a bioavailability/bioequivalence method because the random variable of interest is survival times of subjects given a test and standard drug formulations.

Bartolucci and Singh begin their approach with a statement of the hypotheses involved

$$\begin{aligned} H_0&: \eta \le 1-\theta \quad or \quad \eta \ge 1+\theta \\ H&: \quad 1-\theta < \eta < 1+\theta \end{aligned} \tag{2.7.1}$$

mean survival time of the subjects sampled from the population that received the i^{th} formulation (test or reference). The assumptions involved in the Bartolucci and Singh approach are

1. The number of subjects, n, may enter randomly into a trial.

2. The random variable, T_i (i denotes the different formulations), is distributed as a two-parameter exponential distribution.

3. The data are noncensored or right censored.

Bartolucci and Singh use the following definition for the two-parameter exponential:

$$f(t) = \frac{1}{\mu} e^{-\frac{1}{\mu}(t-\omega)} \qquad t \ge \omega \ge 0;\ \mu > 0. \tag{2.7.2}$$

Noting that their approach is Bayesian, Bartolucci and Singh assume a limiting form of the following prior structure for ω:

$$f(\omega|a,\nu) = \frac{\nu e^{\nu\omega}}{e^{\nu a}-1} \qquad 0 < \omega < a;\ \nu > 0 \tag{2.7.3}$$

$$\lim_{\nu \to 0} f(\omega|a,\nu) = \frac{1}{a}. \tag{2.7.4}$$

Hence, $\omega \sim U(0,a)$. The prior structure assumed for μ is the inverted-gamma-one ($I\gamma_1$) family having prior shape and scale parameters n_o and t_o, respectively, that is,

$$f(\mu|n_o,t_o) = \frac{t_o^{n_o}}{\Gamma(n_o)}\left(\frac{1}{\mu}\right)^{n_o+1} e^{-\frac{t_o}{\mu}} \qquad \mu > 0. \tag{2.7.5}$$

The methodology of the Bartolucci and Singh approach proceeds in the following manner. Suppose there are two independent exponential populations. One population is parameterized by (μ_1,ω_1), and the other population is parameterized by (μ_2,ω_2). From each sample of the j^{th} population there are r_j noncensored observations and $n_j - r_j$ censored data points. Subsequently, they proceed by obtaining the joint likelihood of the parameters, $(\underline{\mu},\underline{\omega})$ and performing the following one-to-one transformation:

$$\begin{aligned} \xi &= \mu_1 \qquad & \omega_1 &= \omega_1 \\ \eta &= \frac{\mu_2}{\mu} \qquad & \omega_2 &= \omega_2 \ . \end{aligned} \tag{2.7.6}$$

As a result, a new parameter vector is derived, namely, $(\xi,\eta,\omega_1,\omega_2)$.

Now, they are interested in the test of equivalence on η under the condition of either $\omega_1 = \omega_2$ *or* $\omega_1 \neq \omega_2$, with the intent of computing the posterior density of η under each of the conditions and then deriving a $1-\alpha$ posterior density probability region for η. They conclude that the two formulations are equivalent if the $1-\alpha$ posterior probability region for η is contained within the interval $(1-\theta, 1+\theta)$.

For case 1, $\omega_1 = \omega_2$, they obtained the following posterior density for η:

$$\begin{aligned} g(\eta|D,\omega_1 = \omega_2 = \omega) &= \frac{\eta^{-(r_2 + n_o + 1)}}{\left(\frac{n_1 + n_2}{\eta}\right)^3}\Gamma(r_1 + r_2 + n_o - 1) \\ &\times \left\{ \frac{\left[\left(\frac{T_2+t_o}{\eta}\right) + T_1 + t_o\right]^{r_1 - r_2 - 2n_o - 1} - \left[\left(\frac{T_2+t_o}{\eta}\right) + T_1 + t_o - \delta\right]^{r_1 - r_2 - 2n_o - 1}}{\left[\left(\frac{T_2+t_o}{\eta} + T_1 + t_o\right)\left(\frac{T_2+t_o}{\eta} + T_1 + t_o - \delta\right)\right]^{r_1 - r_2 - 2n_o - 1}} \right\} \\ &\times \left\{ \prod_{j=1}^{2}\Gamma(r_j + n_o) \right\} \int_0^{\infty} \prod_{j=1}^{2}(T_j + t_o - n_j x)^{(r_j - n_o)} dx \end{aligned} \tag{2.7.7}$$

where $T_j = \sum_{i=1}^{r} t_i + \sum_{k=r+1}^{n} t_k'$ (t_i = failure time, t_k' = censored observations, and $j = 1, 2$), δ = min[observations, a], and D denotes the data. For case 2, $\omega_1 \neq \omega_2$, they obtained the following posterior density:

$$g(\eta \mid D, \omega_1 \neq \omega_2) = \frac{\int_0^{\delta_2}\int_0^{\delta_1}\left\{\frac{\eta^{-(n_o+r_2+1)}}{\left[(T_1+t_o-n_1\omega_1)+\frac{1}{\eta}(T_2+t_o-n_2\omega_2)\right]^{-(2n_o-\gamma_1-\gamma_2-2)}}\right\}d\omega_1 d\omega_2}{\int_0^{\infty}\int_0^{\delta_2}\int_0^{\delta_1}\{Numerator\}\,d\omega_1 d\omega_2 d\eta} \quad . \tag{2.7.8}$$

To obtain the posterior credibility region, the Bartolucci and Singh approach is to plot $E[l(\eta)\mid \omega_1 = \omega_2]$ for case 1 and $E[l(\eta)\mid \omega_1 \neq \omega_2]$ for case 2, then compute the 90% and 95% posterior probability regions for η, the random variable of interest.

Bartolucci and Singh state some properties of the derived posterior densities under certain conditions. For $\omega_1 = \omega_2 = 0$, their posterior density takes the form of the F-distribution, that is,

$$\eta \mid D \sim \frac{(r_2+n_o)(T_1+t_o)}{(r_1+n_o)(T_2+t_o)} F[2(r_2+n_o), 2(r_1+n_o)] \quad . \tag{2.7.9}$$

For ω_1 and ω_2 known,

$$\eta \mid D \sim \frac{(r_2+n_o)(T_1+t_o-n_1\omega_1)}{(r_1+n_o)(T_2+t_o-n_2\omega_2)} F[2(r_2+n_o), 2(r_1+n_o)] \, . \tag{2.7.10}$$

Finally, if ω_1 and ω_2 are replaced in eq. 2.7.10 by $E(\omega_i \mid D) = \frac{\delta_i}{2}$, then an approximation for case 1 and 2 of the observed posterior value of η will take the form

$$\hat{\eta} \mid D = \frac{(T_1+t_o-n_1\delta/2)/(r_1+n_o)}{(T_2+t_o-n_2\delta/2)/(r_2+n_o)} \quad . \tag{2.7.11}$$

2.8 Munk (1993)

In the 1993 paper, Munk presents an approach that is based on the double t-test and Anderson and Hauck approaches. Munk's approach is uniformly more powerful than the double t-test method and maintains desirable asymptotic properties. The impetus for Munk's approach is derived from Muller-Cohrs (1990). Muller-Cohrs' paper is a study of the power of the Anderson-Hauck approach and the double t-test approach. As a result, Munk proposes a test that combines both the tests (double t-test and Anderson-Hauck) such that either of the tests is applied according to the empirical variance. Munk denotes this test as the "mixtest." Before presenting the mixtest, Munk gives an example that yields conflicting conclusions between the double t-test and Anderson-Hauck methods. Subsequently, this indicates the need for a better testing method, especially since the double t-test and Anderson-Hauck methods are the two most commonly used methods.

The mixtest involves the determinance of equivalency between two treatments. The difference of the two treatment effects is estimated by a normally distributed random variable, say z, with mean δ and standard deviation σ that are unknown, and the sample size is fixed. Let S be an estimate of σ that is independent of z such that

$$z \sim N(\delta, \sigma^2) \text{ and } \frac{rS^2}{\sigma^2} \sim \chi_r^2 . \qquad (2.8.1)$$

Let also F_r denote the central t-distribution such that $t_{1-\alpha,r}$ is the $(1-\alpha)$ quantile of F_r. The null and alternative hypotheses are

$$\begin{array}{l} H\colon |\delta| > \Delta \\ K\colon |\delta| \le \Delta \end{array} \qquad (2.8.2)$$

where Δ denotes the maximum bound on δ. The hypotheses are stated in the above with the objective of establishing equivalence, that is, to confirm that $|\delta| \le \Delta$ at a controlled

error rate. Continuing, Munk states the mixtest for $k \in [0,\infty)$ as

$$\varphi_k(z,s) = \begin{cases} \varphi_t, & \frac{\Delta}{tS} \geq k \\ \varphi^{\cdot}_{AH}, & \frac{\Delta}{tS} < k \end{cases} \qquad (2.8.3)$$

where k denotes the mixing constant, φ_k denotes the power function of the mixtest, φ_t denotes the power function of the double t-test, and $\varphi^{\cdot}_{AH}$ denotes the power function of the Anderson-Hauck method. Hence, the mixtest indicates that the double t-test should be used if $S \leq \frac{\Delta}{tk}$, and the Anderson-Hauck method should be used if $S > \frac{\Delta}{tk}$. Finally, a reproduction of Munk's Table 1 is the following:

****Table 1

Optimal levels α^* and constants k^* for the "mixing" test φ^* with respect to fixed degrees of freedom r and nominal level α

α:	0.01		0.025		0.05		0.1	
r:	α^*	k^*	α^*	k^*	α^*	k^*	α^*	k^*
5	0.005	0.71	0.015	0.79	0.033	0.84	0.074	0.92
10	0.006	0.91	0.018	0.95	0.040	1.00	0.085	1.87
15	0.007	0.98	0.020	1.01	0.042	1.01	0.089	1.12
20	0.008	1.01	0.021	1.04	0.044	1.03	0.092	1.15
25	0.008	1.03	0.022	1.06	0.045	1.05	0.093	1.17
30	0.008	1.04	0.022	1.07	0.046	1.08	0.094	1.19
35	0.008	1.04	0.022	1.08	0.046	1.11	0.095	1.20
40	0.009	1.05	0.023	1.09	0.047	1.13	0.095	1.21
45	0.009	1.05	0.023	1.10	0.047	1.14	0.096	1.22
50	0.009	1.06	0.023	1.11	0.048	1.15	0.096	1.23

****Used with the permission of Biometrics (see Munk (1993)).

The above table is a tabulation of the maximum $k^* = k^*(\alpha,r)$ which ascertains the optimal

test $\varphi_{\cdot}$ for a class of mixtests described above in eq. 2.8.3, where α is at a nominal level α^{*} and r is the degrees of freedom.

3. ACTIVE CONTROL TRIALS

An active control trial is a clinical trial. It is sometimes referred to as a positive control trial. The active control trial is similar to the placebo control with the exception that there is no placebo. For background information, a placebo is an inactive substance (with respect to the experiment under investigation) that has all of the similarities of the drug(s) under investigation, that is, taste, shape, appearance, etc. A placebo effect includes a large series of visceral, somatic, and psychic responses resulting from the symbolic implications of the physician, his ministrations, and his medicaments (Modell and Houde 1958). Active control trials usually involve two therapies, namely, an experimental and reference. The therapies are such that they have similar taste, shape, appearance, etc. This allows for the therapies to be distributed such that the patient is "blind" to the treatment he/she is receiving and the physician is "blind" to the treatment he/she is prescribing (Modell and Houde 1958). This technique is known as the double-blind technique.

In the design of any clinical trial, nine forces influence data in clinical evaluations, according to Modell and Houde (1958): (i) pharmacodynamic actions, (ii) dosage, (iii) choice of subject, (iv) use of controls, (v) collection of data, (vi) sensitivity of the method, (vii) placebo actions, (viii) bias, and (ix) forces extraneous to the experiment. In addition to the above, the regimen is another factor that should be considered when designing a clinical trial. Active control trials also include in their design some assurance

that historical estimates of the active control drug's efficacy relative to placebo are applicable to the new experimental setting (Makuch and Johnson 1989).

The fundamental assumption of the active control is that the active control drug would have performed better than a placebo, had a placebo been used in the trial (Makuch and Johnson 1989). There are many criticisms to this fundamental assumption in the literature. One of the earlier criticisms was given by Modell and Houde (1958) who stated that no method of drug examination is more likely to lead to erroneous conclusions, because it has none of the safeguards provided by other controls, that is, the elimination of placebo effects and bias. The term "control" in this context means a basis of comparison.

Active control trials are popular for practical and ethical reasons. Some of the practical reasons for their popularity are (i) smaller sample sizes, (ii) enhance subject recruitment because there is no placebo, and (iii) lower dropout rate. The ethical reason for their popularity often stated in the literature is that it is unethical to deny a patient immediate access to a known effective treatment (Leber 1986). Some reasons active control trials are criticized are (i) the absence of information regarding the reference therapy's ability to perform better than a placebo, (ii) the increased possibility of misleading conclusions by misinterpretations of the data, and (iii) the inability to distinguish between true drug effects and improvements due to a placebo effect.

As alluded to previously, the merit of the design and analysis of the active control trial lies in its ability to establish a necessary condition. It is from this perspective that inferences should be made as a result of the analyses.

4. PROPOSED METHODOLOGY

4.1 Introduction

The methodology begins by assuming a two parameter underlying distribution, and the desire is to determine the equivalence of the parameters of the underlying distribution. Hence, the methodology proceeds with the testing of each parameter. If the findings are such that each of the parameters (i.e., the nonscale and scale parameters from each of the distributions) are equivalent, then we conclude that we have established a necessary condition for equivalence for the two drug formulations.

For particular parameter values, the assumed distribution is the one-parameter exponential distribution. The parameters of the assumed distribution are classified as scale and nonscale parameters. In the case of the Weibull distribution, the nonscale of interest is called the shape parameter. In the case of the linear-exponential distribution, the nonscale parameter of interest is called the nonlinear exponential parameter. Consequently, the assumed two-parameter underlying distribution is either a Weibull or linear-exponential in terms of the context of this writing.

The methodology begins with a statement of hypotheses for each parameter. Beginning with the nonscale parameter for the Weibull distribution, the hypotheses are

$$\begin{aligned} H_{00}&: \ \frac{\gamma_1}{\gamma_2} > 1+\Delta \\ H_{10}&: \ 1 \le \frac{\gamma_1}{\gamma_2} \le 1+\Delta \, . \end{aligned} \tag{4.1.1}$$

The Thoman and Bain (1969) test is used to test the hypotheses. The reader should see Appendix O for the details of the Thoman and Bain test.

The hypotheses for the nonexponential linear parameter of the linear-exponential distribution are

$$\begin{aligned} H_{00}': \ & \frac{\gamma_1}{\gamma_2} < 1-\Delta \quad or \quad \frac{\gamma_1}{\gamma_2} > 1+\Delta \\ H_{10}': \ & 1-\Delta \le \frac{\gamma_1}{\gamma} \le 1+\Delta \ . \end{aligned} \tag{4.1.2}$$

A likelihood ratio test has been developed for testing the above hypotheses.

The testing of equivalence for the scale parameters for the Weibull and linear-exponential densities proceeds in a different manner. It begins with the methodology of Bartolucci and Singh (1993) that starts by the defining of a discrepancy measure, that is,

$$e^{\eta^{(c)}} \qquad where \ \eta^{(c)} = \frac{\lambda_2^c - \lambda_1^c}{c} \ . \tag{4.1.3}$$

Their approach involves the obtaining of a limiting form of $e^{\eta^{(c)}}$, namely,

$$\lim_{c \to 0} e^{\eta^{(c)}} = \frac{\lambda_2}{\lambda_1} \tag{4.1.4}$$

(see Appendix C). In eq. 4.1.3 , λ_i represents the scale parameters being tested with respect to a particular distribution (i.e., Weibull or linear-exponential), and c is a constant.

Redefining $\frac{\lambda_2}{\lambda_1} = \eta$, the null and alternative hypotheses regarding equivalence are

$$\begin{aligned} H_{01}: \ & \mu_\eta < 1-\Delta \ or \ \mu_\eta > 1+\Delta \\ H_{11}: \ & 1-\Delta < \mu_\eta < 1+\Delta. \end{aligned} \tag{4.1.5}$$

Notice in the above, that the null hypothesis is the hypothesis of nonequivalence, and the alternative hypothesis is the hypothesis of equivalence. This is also true for the way in which the hypotheses of the nonscale parameters are stated in eq. 4.1.1 and eq. 4.1.2.

Stating the hypothesis of equivalence, in this way, is consistent with statistical theory (see Hauck and Anderson 1986).

After obtaining the credibility limits for $\hat{\mu}_\eta$, say $(\hat{\mu}_{\eta_l},\hat{\mu}_{\eta_u})$, if $(\hat{\mu}_{\eta_l},\hat{\mu}_{\eta_u})$ is such that it is a subset of $(1-\Delta,1+\Delta)$, then one would reject H_{01} and conclude that the two drug formulations are equivalent. Otherwise, one would fail to reject H_{01}, the hypothesis of nonequivalence.

4.2 Weibull Model--Survival Models, Prior Probability Structures and Estimation

The two parameter Weibull probability density function may be defined (Lee 1992) as

$$f(t) = \lambda\gamma(\lambda t)^{\gamma-1} e^{-(\lambda t)^{\gamma}} \qquad t, \lambda, \gamma > 0 \tag{4.2.1}$$

with the following hazard and survivorship functions:

$$h(t) = \lambda\gamma(\lambda t)^{\gamma-1} \tag{4.2.2}$$

and

$$S(t) = e^{-(\lambda t)^{\gamma}} \tag{4.2.3}$$

(see Appendix H). The probability density function in a survival analysis context can be interpreted as the probability of an individual failing in a short interval; the hazard function can be interpreted as the probability of an individual failing within a short interval given that the individual has survived a certain length of time; finally, the survivorship function can be interpreted as the probability of an individual surviving longer than a particular time (see Lee 1992). Graphs of the probability density function, hazard function, and survivorship function for the Weibull distribution are in Appendix J.

Subjects, n, are assumed to enter the clinical trial randomly. Observations are made during the trial such that the survival or censored time can be determined. At the

final observation, the r survival times $(t_1, t_2, t_3, \ldots, t_r)$ and n-r censored times $(t'_{r+1}, t'_{r+2}, t'_{r+3}, \ldots, t'_n)$, respectively, are known. The likelihood function for λ and γ is

$$l(\lambda,\gamma) = \gamma^r \lambda^{\gamma r} \left[\prod_{i=1}^{r} t_i^{\gamma-1}\right] e^{-\lambda^{\gamma}\left[\sum_{i=1}^{r} t_i^{\gamma} + \sum_{k=r+1}^{n} (t'_k)^{\gamma}\right]} \tag{4.2.4}$$

(see Appendix A). The joint likelihood function for two independent populations sampled from a Weibull distribution is

$$l(\underline{\lambda},\underline{\gamma}) = \prod_{j=1}^{2}\left[\gamma_j^{r_j} \lambda_j^{\gamma_j r_j} \left[\prod_{i=1}^{r_j} t_i^{\gamma_j-1}\right] e^{-\lambda_j^{\gamma_j}\left[\sum_{i=1}^{r_j} t_i^{\gamma_j} + \sum_{k=r+1}^{n_j} (t'_k)^{\gamma_j}\right]}\right] \tag{4.2.5}$$

(see Appendix A).

4.2.1 Weibull--Prior Probability Structure for λ and the MLE of γ

The assumed prior probability structure for λ is the inverted-gamma-one with prior shape and scale parameter n_o and t_o, respectively. The $I\gamma_1(n_o, t_o)$ density is

$$f(\lambda|n_o,t_o) = \frac{t_o^{n_o}}{\Gamma(n_o)}\left(\frac{1}{\lambda}\right)^{n_o+1} e^{-\frac{t_o}{\lambda}} \tag{4.2.1.1}$$

where $\lambda, n_o, t_o > 0$. The estimate for γ, say $\hat{\gamma}$, is obtained by selecting that value of γ from the coordinate (λ,γ) that maximizes the joint likelihood function, eq. 4.2.4, (see Appendix E). An alternative way to get the MLE of γ is to integrate the product of eq. 4.2.4 and eq. 4.2.1.1 with respect to λ. This would result in a likelihood function in γ only. Subsequently, one would maximize that function. The general form of that likelihood function is the following:

$$l(\gamma) = \int_o^{\infty} f(\lambda|n_o,t_o)\, l(\lambda,\gamma)\, d\lambda . \tag{4.2.1.2}$$

4.3 Linear-Exponential--Survival Model, Prior Probability Structures and Estimation

The two-parameter linear-exponential probability density function is

$$f(t) = (\lambda + \gamma t)e^{-(\lambda t + \frac{1}{2}\gamma t^2)} \tag{4.3.1}$$

where $t, \lambda, \gamma > 0$. The hazard and survivorship functions of the Linear-Exponential model are

$$h(t) = \lambda + \gamma t \tag{4.3.2}$$

and

$$S(t) = e^{-(\lambda + \frac{1}{2}\gamma t^2)} \tag{4.3.3}$$

respectively (see Appendix I). Graphs of $f(t)$, $h(t)$, and $S(t)$ for the linear-exponential are in Appendix K.

With the observance or r survival times and $n-r$ censored times, the likelihood function for λ and γ is

$$l(\lambda,\gamma) = e^{-(\lambda T + \frac{1}{2}\gamma S)} \prod_{i=1}^{r}(\lambda + \gamma t_i) \tag{4.3.4}$$

where $T = \sum_{i=1}^{r} t_i + \sum_{k=r+1}^{n} t_k'$ *and* $S = \sum_{i=1}^{r} t_i^2 + \sum_{k=r+1}^{n} (t_k')^2$ (see Appendix B). For two independent populations sampled from the linear-exponential distribution, the joint likelihood function for $\underline{\lambda} = (\lambda_1, \lambda_2)$ and $\underline{\gamma} = (\gamma_1, \gamma_2)$ is

$$l(\underline{\lambda},\underline{\gamma}) = \prod_{j=1}^{2}\left[e^{-\left(\lambda_j T_j + \frac{1}{2}\gamma_j S_j\right)} \prod_{i=1}^{r_j}(\lambda_j + \gamma_j t_i)\right] \tag{4.3.5}$$

(see Appendix B).

4.3.1 Linear-Exponential--Prior Probability Structure for λ and the MLE of γ

An $I\gamma_1$ prior probability structure for λ is assumed for the Linear-Exponential model (see eq. 4.2.1.1). The MLE of γ is that value from the coordinate (λ,γ) which

maximizes the joint likelihood function for the linear-exponential model, eq. 4.3.4 (see Appendix D).

4.4 Methodology

Suppose the survival and censored times of a sample from a population are denoted as $t_1, t_2, \ldots, t_r$ and $t'_{r+1}, t'_{r+2}, \ldots, t'_n$, respectively. Let's refer to the total number of survival times as r_1 for one population (consequently, the total number of censored times is $n_1 - r_1$). Now suppose there is a second population with the total number of survival times referred to as r_2 (consequently, the total number of censored times is $n_2 - r_2$). Let the first population be parameterized by (λ_1, γ_1) and the second by (λ_2, γ_2). The joint likelihood of the parameters $(\underline{\lambda}, \underline{\gamma})$ is given by eq. 4.2.5 if sampling from the Weibull distribution, or eq. 4.3.5 if sampling from the linear-exponential distribution.

To test the hypothesis of equivalence for the shape parameter of the Weibull distribution (the hypothesis in eq. 4.1.1), the Thoman and Bain (1969) method is employed. The Thoman and Bain (1969) method begins with the obtaining of the maximum likelihood estimators for γ_1 and γ_2, say $\hat{\gamma}_1$ and $\hat{\gamma}_2$, respectively, by using eq. 4.2.4. Placing the larger estimate in the numerator (in our case $\hat{\gamma}_1$), the researcher computes $\frac{\hat{\gamma}_1}{\hat{\gamma}_2}$. If $\frac{\hat{\gamma}_1}{\hat{\gamma}_2} > (1+\Delta) l_{1-\gamma}$, then the researcher would fail to reject H_{00} (in eq. 4.1.1), where $l_{1-\gamma}$ is the percentage point of the distribution of $\frac{\hat{\gamma}_1^*}{\hat{\gamma}_2^*}$ that has the same distribution as $\frac{(\hat{\gamma}_1/\gamma_1)}{(\hat{\gamma}_2/\gamma_2)}$, where $\hat{\gamma}_1^*$ and $\hat{\gamma}_2^*$ are the maximum likelihood estimators of γ_1 and γ_2, respectively, for the two independent random samples from the standard Weibull distribution. Otherwise, reject H_{00} (in eq. 4.1.1) and conclude that a necessary condition for equivalence has been established with respect to the shape parameter. The

reader is referred to Appendix O for a more detailed presentation of the Thoman and Bain (1969) test.

To test the hypothesis for the nonlinear exponential parameter, stated in eq. 4.1.2 of the linear-exponential distribution, two likelihood ratio test statistics are derived. In order for the researcher to conclude equivalence, both of the test statistics must be such that they are greater than the critical value which would result in rejecting $H_{00}^{\prime}$.

In deriving the test statistics for the hypothesis in (4.1.2), let k_1 and k_2 be the following likelihood ratio statistics:

$$k_1 = \frac{L(\hat{\gamma}_1, \hat{\gamma}_2 | \lambda_1^*)}{L(\hat{\gamma}, \hat{\gamma} | \lambda_1^*)} \tag{4.4.1}$$

and

$$k_2 = \frac{L(\hat{\gamma}_1, \hat{\gamma}_2 | \lambda_2^*)}{L(\hat{\gamma}, \hat{\gamma} | \lambda_2^*)} \tag{4.4.2}$$

where $\hat{\gamma}_1$ and $\hat{\gamma}_2$ are the maximum likelihood estimators for the two independent samples; $\hat{\gamma}$ is the maximum likelihood estimator for the combined sample; and λ_j^* is

$$\lambda_i^* = E(\lambda_i) = \frac{\int_{R_\lambda} \lambda_i L(\lambda_i | \cdot) p(\lambda_i | \cdot) d\lambda_i}{\int_{R_\lambda} L(\lambda_i | \cdot) p(\lambda_i | \cdot) d\lambda_i} . \tag{4.4.3}$$

The numerator in eq. 4.4.1 and eq. 4.4.2 is the likelihood function for the two groups conditioned on λ_1^* which has the following functional form:

$$L(\hat{\gamma}_1, \hat{\gamma}_2 | \lambda_j^*) = \left[\prod_{i=1}^{r_1} (\lambda_j^* + \hat{\gamma}_1 t_i)\right]\left[\prod_{i=1}^{r_2} (\lambda_j^* + \hat{\gamma}_2 t_i)\right] \times e^{-\left[\lambda_j^*(T_1 - T_2) - \frac{1}{2}(\hat{\gamma}_1 S_1 - \hat{\gamma}_2 S_2)\right]} \tag{4.4.4}$$

where $j = 1, 2$. The denominator in eqs. 4.4.1 and 4.4.2 is the likelihood function for the combined sample, and it has the following function representation:

$$L(\hat{\gamma},\hat{\gamma}\,|\,\lambda_j^*) = \left[\prod_{i=1}^{r_1}(\lambda_j^* + \hat{\gamma}t_i)\right]\left[\prod_{i=1}^{r_2}(\lambda_j^* + \hat{\gamma}t_i)\right] \times e^{-\left[\lambda_j^*(T_1+T_2)+\frac{1}{2}\hat{\gamma}(S_1+S_2)\right]}. \tag{4.4.5}$$

Finally, the functional form of λ_j^* in eq. 4.4.3 is

$$\lambda_j^* = \frac{\int_0^\infty \lambda_j\left[\prod_{i=1}^{r_j}(\lambda_j+\hat{\gamma}_j t_i)\right]\left(\frac{1}{\lambda_j}\right)^{n_o+1} e^{-\left(\lambda_j T_j + \frac{t_o}{\lambda_j}+\frac{1}{2}\hat{\gamma}_j S_j\right)} d\lambda_j}{\int_0^\infty \left[\prod_{i=1}^{r_j}(\lambda_j+\hat{\gamma}_j t_i)\right]\left(\frac{1}{\lambda_j}\right)^{n_o+1} e^{-\left(\lambda_j T_j + \frac{t_o}{\lambda_j}+\frac{1}{2}\hat{\gamma}_j S_j\right)} d\lambda_j}. \tag{4.4.6}$$

The reader should see Appendix M for the details of the derivations concerning eqs. 4.4.4, 4.4.5, and 4.4.6.

Regarding the test of the nonlinear exponential parameter, if k_1 and k_2 are greater than k_0 (where k_0 is a fixed constant), then the researcher would reject H_{00}' and conclude that a necessary condition has been established for equivalence with respect to the nonlinear exponential parameter. Since the exact distribution of K_t is sometimes difficult to obtain, it was shown that $-2\log_e K_t$ has an approximate chi-square distribution with one degree of freedom for $N \geq 25$, where $N = n_1 + n_2$. In this case, H_{00}' is rejected if $-2\log_e k_t$ is below the 100α percentage point, $\chi^2_{1,\alpha}$ of the chi-square distribution with one degree of freedom.

Pertaining to the scale parameters for both of the models, the following one-to-one transformation

$$\xi = \lambda_1$$
$$\eta = \frac{\lambda_2}{\lambda} \tag{4.4.7}$$

results in the new parameter vector $(\xi,\eta,\hat{\gamma}_1,\hat{\gamma}_2)$. Now the parameter for the test of equivalence of interest is μ_η. The next step in the analysis process is to compute the posterior density of η and derive a $1-\alpha$ posterior credibility region for μ_η.

For the Weibull model, the posterior density is of the form

$$g(\eta|D,\hat{\gamma}_1,\hat{\gamma}_2) = \frac{\int_0^\infty g(\xi,\eta,D,\hat{\gamma}_1,\hat{\gamma}_2)\,d\xi}{\int_0^\infty\int_0^\infty g(\xi,\eta,D,\hat{\gamma}_1,\hat{\gamma}_2)\,d\xi\,d\eta} \tag{4.4.8}$$

where

$$g(\xi,\eta,D,\hat{\gamma}_1,\hat{\gamma}_2) = \left[\frac{t_o^{n_o}}{\Gamma(n_o)}\right]^2\left[\prod_{i=1}^{r_1} t_i^{\hat{\gamma}_1-1}\right]\left[\prod_{i=1}^{r_2} t_i^{\hat{\gamma}_2-1}\right]\hat{\gamma}_1^{r_1}\hat{\gamma}_2^{r_2}$$
$$\times\xi^{\hat{\gamma}_1 r_1+\hat{\gamma}_2 r_2-2n_o}\,\eta^{\hat{\gamma}_2 r_2-n_o-1} \tag{4.4.9}$$
$$\times e^{-\left(\xi^{\hat{\gamma}_1}\left[\sum_{i=1}^{r_1} t_i^{\hat{\gamma}_1}+\sum_{k=r_1+1}^{n_1}(t_k')^{\hat{\gamma}_1}\right]+(\xi\eta)^{\hat{\gamma}_2}\left[\sum_{i=1}^{r_2} t_i^{\hat{\gamma}_2}+\sum_{k=r_2+1}^{n_2}(t_k')^{\hat{\gamma}_2}\right]+\frac{t_o}{\xi}\left[1+\frac{1}{\eta}\right]\right)}$$

(see Appendix F). Again, for obtaining $\hat{\gamma}_1$ and $\hat{\gamma}_2$ in the Weibull model, the reader is directed to Appendix D.

The posterior density for the linear-exponential model is

$$g(\eta|D,\hat{\gamma}_1,\hat{\gamma}_2) = \frac{\int_0^\infty g(\xi,\eta,D,\hat{\gamma}_1,\hat{\gamma}_2)\,d\xi}{\int_0^\infty\int_0^\infty g(\xi,\eta,D,\hat{\gamma}_1,\hat{\gamma}_2)\,d\xi\,d\eta} \tag{4.4.10}$$

where

$$g(\xi,\eta,D,\hat{\gamma}_1,\hat{\gamma}_2) = \left[\frac{t_o^{n_o}}{\Gamma(n_o)}\right]^2\left(\frac{1}{\xi}\right)^{2n_o}\left(\frac{1}{\eta}\right)^{n_o+1}\left[\prod_{i=1}^{r_1}(\xi+\hat{\gamma}_1 t_{1i})\right] \times\left[\prod_{i=1}^{r_2}(\xi\eta+\hat{\gamma}_2 t_{2i})\right] e^{-\left[\xi(T_1+\eta T_2)+\frac{1}{2}(\hat{\gamma}_1 S_1+\hat{\gamma}_2 S_2)+\frac{t_o}{\xi}\left(1-\frac{1}{\eta}\right)\right]} \tag{4.4.11}$$

(see Appendix G). Again, the reader should see Appendix E regarding the estimating of $\hat{\gamma}_1$ and $\hat{\gamma}_2$ for the linear-exponential model.

Pertaining to the obtainment of the $100(1-\alpha)$ credibility regions, first the expected value, $E(\eta|D)$, and its error are determined. Second, asymptotic normal distributional theory is invoked to compute the $100(1-\alpha)$ credibility regions. This is the case for both models, Weibull and the linear-exponential. The reader is referred to Appendix N for the derivation and explanation of the asymptotic normality of $E(\eta|D)$ for the Weibull model. A similar derivation can be done for the linear-exponential model. Third, if a researcher desires to compute probability that the credibility region is a subset of an interval, the joint asymptotic distribution of the credibility limits is derived in Appendix P. This step is optional.

4.5 Motivation for the Discrepancy Measure

The methodology presented in this paper takes a different approach in several ways from the approaches presented in Chapter 2. One difference has to do with the hypothesis testing of the parameters. In the approaches presented in Chapter 2, all of them were concerned with making inferences about the mean of a distribution, whether the data were discrete or continuous. The hypothesis testing was done such that inferences can be made regarding the mean. The Bartolucci and Singh (1993) approach differs from

the other approaches by defining a random variable to be a ratio of the means and then finding the distribution of that random variable, whereas with the other methods, the inference is based on the difference between estimators or ratio estimators regarding the means. The methodology that is being proposed in this text is to assume that the data follows an underlying distribution; estimate the non-scale parameters and test them; define a random variable that is the ratio of the scale parameters of the underlying distribution; find the density of that random variable; and test the hypothesis regarding the mean of that random variable.

The motivation for approaching the equivalence problem from the perspective of parameter equivalence of an underlying distribution is due to the fact that if inferences can be made that the parameters of the assumed underlying distribution are equivalent, then this is tantamount to saying that the mean, variance, median, and other statistical measures of that underlying distribution are equivalent.

5. MULTIPLE INTEGRATION OF POSTERIOR KERNELS

5.1 Problem Statement

To begin to characterize a problem frequently faced by a Bayesian analysts, a restatement of an excerpt of the introduction of Geweke's (1991) work is in order:

> The central technical problem in Bayesian inference is multiple integration, often in high dimensions. The central technical problem in non-Bayesian inference is optimization, often in high dimensions. The latter problem has been solved with some degree of generality.... The former problem has not been solved in any such degree of generality, because multiple integration is technically more demanding than optimization. 'Because of the demanding nature of multiple integration,' problems in Bayesian inference have historically been solved on a case-by-case basis, with the solution of one problem providing little to help with the solution of the next. (Geweke 1991)

Now, it is important to understand that to a Bayesian analyst faced with the challenge of multiple integration, his or her primary interest is completing the statistical inference of the problem that gives rise to the challenge of the multiple integration of a posterior kernel. Highly desirable characteristics of the technique for multiple integration sought by the Bayesian analyst are the speed, ease, and flexibility of computation.

On the other hand, a desirable characteristic of primary interest to a numerical analyst, when faced with the challenge of multiple integration, is the accuracy of the result. Such a characteristic should be encouraged; but from the Bayesian analyst's perspective, the obtaining of such a result with a high order of accuracy is often a complex problem nested within a complex problem, such that the statistical inference process is clouded by secondary issues, which impedes the process and adds to the cost of producing results.

5.2 Some of the Issues

Unfortunately, in Bayesian analysis, the integrals necessary for calculating posterior probabilities are seldom amenable to analytical methods (Wolpert 1991). Often, the integrands encountered are not such that they are well behaved in certain regions, and with the application of certain mathematical techniques, the "curse of dimensionality" is present.

The nontractability of multiple integration of a posterior kernel, consequently, leads one to pursue numerical methods of integration. The use of numerical methods of multiple integration for posterior kernels can lead the analyst to modify the integration such that the numerical range of the computing device is not exceeded, in order to avoid the use of scaling methods as a circumvention and/or to modify the integrand such that it is computable within the range of interest.

These are some of the problems that one may encounter when multiple integration of posterior kernels is involved. But recall that the primary interest of the Bayesian analyst is completing the statistical inference process.

5.3 Proposed Approaches at 1991 Conference

In 1991, a conference was sponsored by the American Mathematical Society, AMS, to bring together researchers to present topics on and to encourage the discussion of multiple integration among numerical analyst and statisticians. The proceedings from the conference were complied into a text (American Mathematical Society 1991). Some of the approaches presented were Monte Carlo integration, asymptotic expansions of the integral, parallel system and adaptive integration, and others. The reader may refer to the bibliography for further information regarding the following authors' work: Doncker and

Kapenga (1991); Evans (1991); Genz (1991); Geweke (1991); Hardwick (1991); Kahaner (1991); Kaishev (1991); Kass, Tierney, and Kadane (1991); Luzar and Olkin (1991); Mascagni (1991); Monahan and Liddle (1991); Muller (1991); Oh (1991); Tong (1991); Tsutakawa (1991); and Wolpert (1991).

From the papers presented at the 1991 conference, no universal technique could be deemed a panacea for nontractable multiple integration of posterior kernels. Each of the methods has its advantages under certain conditions. But this is not to say that no progress in this area has been made. On the contrary, much progress has been made in solving difficult multiple integration problems. However, the techniques proposed provide good solutions only for a subset of the complicated multiple integration problems. For further information and independent discussions of the techniques proposed, the reader is referred to the following articles: Albert (1991), Flournoy (1991), Luzar et. al. (1991), and Shanmugan (1991).

In light of the above, a Bayesian analyst may find himself or herself exploring several techniques before selecting one he/she thinks is most conducive for the problem encountered. Even after selection of a method, sometimes the Bayesian analyst has to make modifications to the technique and/or "prepare the problem for numerical analysis."

5.4 Method of Integration

The method of integration over the region of interest is Monte Carlo. More specifically, it is a nonrestrictive (with respect to the number of samples evaluated within a strata) stratification sampling mean method. Technically speaking, let R be the region over which integration of the posterior kernel is desired. Subsequently, R can be partitioned such as $R = \bigcup_{i=1}^{m} R_i$, where $R_i \cap R_j = \varnothing$, for $i \neq j$. Now by definition

$$E_U[g(\underline{X})] = \int g(\underline{x})u(\underline{\mu},\sigma^2 I)d\underline{x} \tag{5.4.1}$$

where $U(\underline{\mu},\sigma_i^2 I)$ denotes a multidimensional uniform probability density function with mean vector $\underline{\mu}$ and covariance structure $\sigma_i^2 I$ (the previous I refers to the identity matrix).

Assuming that the expectation and integral exist, now let us suppose that we want to integrate

$$I = \int g(\underline{x})d\underline{x} \tag{5.4.2}$$

then by substitution we have

$$I = kE_U[g(\underline{X})] \tag{5.4.3}$$

where k is a constant.

Now eq. 5.4.2 can be rewritten as

$$I = \int_{R_1} g(\underline{x})d\underline{x} + \ldots + \int_{R_m} g(\underline{x})d\underline{x} \ . \tag{5.4.5}$$

Hence, we have

$$I = k_1 E_{U_1}[g(\underline{X})] + \ldots + k_m E_{U_m}[g(\underline{X})] \tag{5.4.6}$$

where

$$E_{U_i}[g(\underline{X})] = \int_R g(\underline{x})u_i(\underline{\mu}_i,\sigma_i^2 I)d\underline{x} \ . \tag{5.4.7}$$

Now suppose we write $g(\underline{x})$ (note: $g(\underline{x})$ is a pdf) as

$$g(\underline{x}) = \frac{h(\underline{x})d\underline{x}}{\int h(\underline{x})d\underline{x}} \ , \tag{5.4.8}$$

and suppose we are interested in the integration of $g(\underline{x})$ over the region R^c, where $R^c \subset R$; then

$$I = \int_{R^c} g(\underline{x})d\underline{x} = C^{-1}\int_{R^c} h(\underline{x})d\underline{x} \tag{5.4.9}$$

where $C = \int_R h(\underline{x})d\underline{x}$. Thus, we have

Now suppose we want the expected value of the random vector $\underline{X}$ with pdf, say

$$I = kE_{U_{R^c}}[g(\underline{X})] \ . \tag{5.4.10}$$

$b(\underline{x})$, then

$$I = \int_R \underline{x}b(\underline{x})d\underline{x} \ ; \tag{5.4.11}$$

consequently,

$$I = kE_{U_R}[f(\underline{X})] \tag{5.4.12}$$

where $f(\underline{x}) = \underline{x}b(\underline{x})$. A similar argument can be made for higher order moments.

5.5 Comments--Modified Stratified Monte Carlo Technique

First of all, the variance reduction property of stratification is attractive, and with the flexibility of unrestrictive sampling within a stratum, it becomes more appealing. Second, Monte Carlo methods are known for their ease of implementation and inexpensive cost with a lower order of accuracy. But the lower order of accuracy is compensated for by the standard deviation (Berger 1991). Finally, the region of interest in terms of the context of the problem is easily characterized.

6. APPLICATION OF THE METHODOLOGY

6.1 Problem Statement

An analysis of data from a published clinical study was performed. The objectives of the trial were (i) to compare the efficacy and toxicity of the combination of idarubicin (IDR) plus cytarabine (CA) to daunorubicin (DNR) plus CA for remission induction in previously untreated acute myelogenous leukemia; (ii) to compare the combination of IDR, CA and thioguanine (TG) to DNR, CA, and TG in consolidation; (iii) to compare IDR plus CA to DNR plus CA for intensification treatment during maintenance (Vogler et al. 1992). With respect to the context of this writing, the analysis performed is focused on the efficacy aspect of objective 1, where IDR (treatment 2) is the experimental drug and DNR (treatment 1) is the reference therapy.

6.2 Data Set Information

The total number of observations involved in the analysis was 225. The total number of survival times recorded for IDR is 109. Pertaining to IDR, there were 104 noncensored and 5 censored survival times. When compared to DNR, the total number survival times was 116. There were 104 noncensored and 12 censored survival times for DNR. The unit of measurement regarding survival times is months.

6.3 Analysis and Results

6.3.1 Introduction

Regarding the testing of the nonscale parameters, the Thoman and Bain (1969) methodology was used for the shape parameters of the Weibull distribution, and a likelihood ratio test was developed for the nonexponential linear parameter of the linear-exponential model. The results contained in Tables 2, 3, and 4 (in Appendix Q) pertain to the testing of the nonexponential linear parameter for the linear-exponential model.

Concerning the testing of the scale parameters, after deriving the posterior distribution for η for each model, $E(\eta|D)$ and $E\{[\eta - E(\eta|D)]^2|D\}$ were computed for each model. $Z_{0.05}$ and $Z_{0.025}$ are the multipliers needed for computing the 90% and 95% limits, respectively, based on asymptotic normal distribution theory. The $E(\eta|D)$ has an asymptotic normal distribution (see Appendix N for the Weibull model). Consequently, the 90% and 95% credibility limits are calculated and compared to a predetermined interval (0.8, 1.2). The selection of the interval (0.8, 1.2) is from the bioavailability protocol guideline produced by the Food and Drug Administration (see FDA 1977).

6.3.2 Weibull Model

The ML estimates for the shape parameters of the Weibull distribution for treatment 1 and treatment 2, respectively, are $\hat{\gamma}_1 = 0.815$ and $\hat{\gamma}_2 = 0.91$. Now, employing the Thoman and Bain (1969) test, $k = 1.11656$, where $k = \frac{\hat{\gamma}_2}{\hat{\gamma}_1}$. Because

$$k = 1.1166 < (1.2)(1.180) = 1.416 \text{ at } n_i = 120 \text{ for } \alpha = 0.05 \text{ and}$$

$$k = 1.1166 < (1.2)(1.199) = 1.4388 \text{ at } n_i = 100 \text{ for } \alpha = 0.05,$$

a researcher should reject H_{00} (in eq. 4.1.1) and conclude that a necessary condition for equivalence has been established with respect to the shape parameter of the Weibull

distribution. The reader should note that the values 1.180 and 1.199 were obtained from the table containing the percentage points of l_γ in the Thoman and Bain (1969) paper.

Regarding testing the hypothesis H_{01} (in eq. 4.1.5), concerning the scale parameter equivalence for μ_η, the general case posterior distribution of η was derived (see eqs. 4.4.2 and 4.4.3). Credibility limits were calculated for 16 different prior parameters combinations of the $I\gamma_1$ for the Weibull model at the 90% and 95% levels. The four selected values for the $I\gamma_1$ prior distribution parameters n_o and t_o were 1.7, 4, 6, 9.5, and 10, 17, 24, 33, respectively. The $I\gamma_1$ prior density parameters were selected for comparison purposes with the results obtained by Bartolucci and Singh (1993).

Table 1 in Appendix Q contains the Weibull model results concerning scale parameter equivalence. All of the credibility regions (both 90% and 95%) for the Weibull model are within the predetermined interval (0.8, 1.2). As a result, a researcher would reject H_{01} (eq. 4.1.5), and conclude that a necessary condition for equivalence has been established with respect to the scale parameters for the Weibull density. The overall inference, regarding the findings of this clinical trial with the underlying assumption of a Weibull distribution, is that a necessary condition for equivalence has been established because both parameters of the Weibull distribution are equivalent among the two treatment therapies.

6.3.3 Linear-Exponential Model

The ML estimates for the nonexponential linear parameters were zero, indicating a single parameter exponential distribution as a more appropriate model given the data set. However, to illustrate the linear-exponential model, 0.01 was selected as an estimate for $\hat{\gamma}_1$ and $\hat{\gamma}_2$, and 0.0101 was selected for $\hat{\gamma}$ of the combined data sets. Tables 2 and 3 in

Appendix Q contain the values of λ_j^* from eq. 4.4.6. These values (the values in Tables 2 and 3) are the expected values of the random variable Λ_j (where j denotes the j^{th} formulation) that has a posterior density as the one defined in eq. M.12 of Appendix M. Subsequently, the estimates in Tables 2 and 3 are used in the computation of $L(\hat{\gamma}_1,\hat{\gamma}_2|\lambda_j)$ in eq. 4.4.4 and $L(\hat{\gamma},\hat{\gamma}|\lambda_j)$ in eq. 4.4.5, and they are needed to compute the derived likelihood ratio statistics k_1 in eq. 4.4.1 and k_2 in eq. 4.4.2. Table 4 in Appendix Q contains the values of $-2\log(k_1)$ and $-2\log(k_2)$ from eqs. 4.4.1 and 4.4.2, respectively. As expected, because of the selection of $\hat{\gamma}_1$, $\hat{\gamma}_2$ and $\hat{\gamma}$, H_{00}' is rejected in all combinations of n_o and t_o because $-2\log(k_i) < 3.841$ $(\chi^2_{1,\alpha=0.05})$.

Pertaining to the testing of μ_η in the hypothesis given in eq. 4.1.5, while assuming an underlying inear-exponential density, the posterior density in the general case was derived (see eqs. 4.4.4 and 4.4.5). The values of n_o and t_o were the same as in the Weibull model case, and they were selected for the same reasons. The 90% and 95% credibility regions were computed for the 16 different combinations of the prior parameter of the $I\gamma_1$ density.

Table 5 in Appendix Q contains the linear-exponential model results with respect to scale parameter equivalence. Each of the credibility regions is a subset of the specified interval. As a result, in each of those cases, a researcher would reject H_{01} in eq. 4.1.5 and conclude that a necessary condition for equivalence has been established with respect to the scale parameters, while assuming the linear-exponential model as the underlying distribution. The capstone inference, concerning the analysis and results of this clinical trial with the underlying distributional assumption of a linear-exponential, is that a

necessary condition for equivalence has been established, because both parameters of the linear-exponential density are equivalent among the two treatment therapies.

These findings support the hypothesis of equivalence. However, the inference regarding the findings of this trial is that of a necessary condition which is that for two therapies equivalent in their effectiveness to the treatment of a disease, then a credibility region must be such that it is within the predetermined interval.

6.4 Discussion

These findings support the hypotheses of equivalence for the scale and nonscale parameters. As a result, a researcher would conclude that a necessary condition has been established for equivalence between the two therapies, regarding their effectiveness in the treatment of a disease.

The results of the data analysis by both models of this clinical trial indicate that a necessary condition has been established for equivalence using this methodology. The findings using this methodology are consistent with the findings of the classical methods. In this particular clinical trial, the experimental therapy was selected for its potential equivalence to the standard therapy and less severe side effects.

This research demonstrates the increased flexibility of the Bartolucci and Singh (1993) methodology by extension to the Weibull and linear-exponential models. This methodology of Bartolucci and Singh also allows researchers to include their knowledge of the active agents in the compound by the selection of the prior parameters of the $I\gamma_1$ distribution, namely, n_o and t_o.

7. AREAS FOR FURTHER RESEARCH

7.1 Introduction

There are four main areas relating to this topic and others in which grand strides to increase the scope of our knowledge and understanding regarding statistical methodologies of this topic and its derivative areas can be made. The four areas can be characterized as one indirectly relating to the topic of equivalence and three as directly relating to the topic. They are the integration of posterior kernels (indirectly related), the development of statistical theory to the proposed procedure, other inference constructions, and the developing of an experimental inference framework that would establish a sufficient condition for equivalence or better.

7.2 Integration of Posterior Kernels in Multiple Dimensions

In Chapter 4, some of the issues pertaining to the integration of posterior kernels were mentioned. A restatement of those issues is not the intent here, but rather an emphasis on the demanding nature of multidimensional integration of posterior kernels and the need for more global methods that are easy to implement from a computational perspective.

The integration of posterior kernels in multiple dimensions, as it relates to the topic of equivalence, may appear to be written with only the Bayesian statistician in mind. However, the assertion is that there are other areas of mathematics and statistics that would benefit measurably from further research in this area.

7.3 Statistical Theory of the Proposed Methodology

Statistical theory as stated by Berger (1991) is the study of properties of procedures. Some of the properties of this methodology were established in Bartolucci and Dickey's (1977) work. One such property is the form of a posterior kernel for different values of c regarding the discrepancy measure. Simply stated, different values for c in the general discrepancy measure yield different posterior kernels (Bartolucci and Dickey 1977). But other areas need more exploration, such as the estimation involved regarding the credibility region about $E(\eta)$ and the robustness of this methodology pertaining to misspecification of prior parameters during the elicitation process concerning the active metabolyte of the therapies involved.

7.4 Other Statistical Inference Constructions

There are at least three reasons to encourage the development of other statistical inference constructions. One is to handle the diversity of trials regarding the manner in which data is collected and concerning the amount of information available before, during, and after the trial. Another reason is that existing methods sometimes have advantages under different conditions and that the development of a new technique which is more flexible to the conditions involved may exploit the advantages of the existing methods. One such method was mentioned in the introduction, Munk's (1993) mixtest. A third reason is that new or other statistical inference constructions to the problem of equivalence bring fresh ideas that complement previous ones and help others evolve. It is by this process that we may approach and perhaps reach a methodology(ies) that are accepted industry-wide.

7.5 Sufficient Condition: Experimental Inference Framework

In the process of searching for truth, the researcher's desire is to have an experiment designed such that compelling empirical evidence is presented with respect to the hypothesis of interest conditioned on the truth of that hypothesis. From a statistical design perspective, the statistician's aim is to assist the experimenter with his/her design such that the above intent is met without bias or confounding. From a statistical analysis point of view, the statistician's interest is in making the strongest possible statement concerning the hypothesis. In the context of equivalence, such a statement would be that of a sufficient condition as generally defined in the introduction. But the statistician who performs the analysis is often restricted from making such inferences because of the limiting nature of the design of the experiment. This is perhaps the greatest challenge in the problem area of equivalence, that is, the design and analysis of an active control clinical trial such that a sufficient condition, with respect to the hypothesis of interest, can be made given the truth of that hypothesis.

APPENDIX A

JOINT LIKELIHOOD, WEIBULL

The likelihood function of the Weibull model for noncensored and censored data is

$$L(\lambda,\gamma) = \prod_{i=1}^{r} \lambda\gamma(\lambda t_i)^{\gamma-1} e^{-(\lambda t_i)^{\gamma}} \prod_{k=r+1}^{n} e^{(\lambda t_k')^{\gamma}}$$

$$= (\lambda\gamma)^r \lambda^{r(\gamma-1)} \left[\prod_{i=1}^{r} t_i^{\gamma-1}\right] e^{-\lambda^{\gamma}\sum_{i=1}^{r} t_i^{\gamma}} e^{-\lambda^{\gamma}\sum_{k=r+1}^{n} (t_k')^{\gamma}}$$

$$= \lambda^{\gamma r}\gamma^r \left[\prod_{i=1}^{r} t_i^{\gamma-1}\right] e^{-\lambda^{\gamma}\left[\sum_{i=1}^{r} t_i^{\gamma} - \sum_{k=r+1}^{n} (t_k')^{\gamma}\right]}.$$

Thus, for independent populations say l we have

$$L(\underline{\lambda},\underline{\gamma}) = \prod_{j=1}^{l} \lambda_j^{\gamma_j r_j}\gamma_j^{r_j} \left[\prod_{i=1}^{r_j} t_i^{\gamma_j-1}\right] e^{-\lambda_j^{\gamma_j}\left[\sum_{i=1}^{r_j} t_i^{\gamma_j} - \sum_{k=r_j+1}^{n_j} (t_k')^{\gamma_j}\right]}$$

where $l = 2$ for our purposes, t_i represents noncensored values, and t_k' represents censored values.

APPENDIX B

JOINT LIKELIHOOD, LINEAR-EXPONENTIAL

The likelihood function of the linear-exponential model for noncensored and censored data is

$$L(\lambda,\gamma) = \prod_{i=1}^{r}(\lambda+\gamma t_i)\, e^{-\left(\lambda t_i + \frac{1}{2}\gamma t_i^2\right)} \prod_{k=r+1}^{n} e^{-\left(\lambda t_k' + \frac{1}{2}\gamma (t_k')^2\right)}$$

$$= e^{-\sum_{i=1}^{r}\left(\lambda t_i + \frac{1}{2}\gamma t_i^2\right)} e^{-\sum_{k=r+1}^{n}\left(\lambda t_k' + \frac{1}{2}\gamma (t_k')^2\right)} \prod_{i=1}^{r}(\lambda+\gamma t_i)$$

where t_i represents noncensored values, and t_k' represents censored values.

But

$$-\left[\sum_{i=1}^{r}\left(\lambda t_i + \frac{1}{2}\gamma t_i^2\right) + \sum_{k=r+1}^{n}\left(\lambda t_k' + \frac{1}{2}\gamma (t_k)^2\right)\right] =$$

$$= -\left[\lambda\left(\sum_{i=1}^{r} t_i + \sum_{k=r+1}^{n} t_k'\right) + \frac{1}{2}\gamma\left(\sum_{i=1}^{r} t_i^2 + \sum_{k=r+1}^{n} (t_k')^2\right)\right].$$

Let

$$T = \sum_{i=1}^{r} t_i + \sum_{k=r+1}^{n} t_k'$$

$$S = \sum_{i=1}^{r} t_i^2 + \sum_{k=r+1}^{n} (t_k')^2 .$$

Thus,

$$L(\lambda,\gamma) = e^{-\left(\lambda T + \frac{1}{2}\gamma S\right)} \prod_{i=1}^{r}(\lambda+\gamma t_i) .$$

Hence, for independent populations, say l, it follows

$$L(\underline{\lambda},\underline{\gamma}) = \prod_{j=1}^{l}\left[e^{-(\lambda_j T_j + \frac{1}{2}\gamma_j S_j)} \prod_{i=1}^{r_j}(\lambda+\gamma t_i)\right]$$

where $l = 2$ for our purposes.

APPENDIX C

DISCREPANCY MEASURE, LIMITING FORMS

The discrepancy measure is defined as

$$e^{\eta(c)} = e^{\frac{\lambda_2^c - \lambda_1^c}{c}}.$$

The limit of $e^{\eta(c)}$ as $c \to 0$ is

$$\lim_{c\to 0} e^{\eta(c)} = \lim_{c\to 0} e^{\frac{\lambda_2^c - \lambda_1^c}{c}}.$$

Now applying L'hopital's Rule to $\frac{\lambda_2^c - \lambda_1^c}{c}$, hence, rewriting as $\frac{e^{c\ln\lambda_2} - e^{c\ln\lambda_1}}{c}$.

Now let $f(c) = e^{c\ln\lambda_2} - e^{c\ln\lambda_1}$ and $g(c) = c$; thus, the derivatives of $f(c)$ and $g(c)$ are

$$\begin{aligned} f'(c) &= D_c\left(e^{c\ln\lambda_2}\right) - D_c\left(e^{c\ln\lambda_1}\right) \\ &= \left(e^{c\ln\lambda_2}\right)\ln\lambda_2 - \left(e^{c\ln\lambda_1}\right)\ln\lambda_1 \\ &= \lambda_2^c \ln\lambda_2 - \lambda_1^c \ln\lambda_1 \\ &= \ln\frac{\lambda_2^{\left(\lambda_2^c\right)}}{\lambda_1^{\left(\lambda_1^c\right)}} \end{aligned}$$

and $g'(c) = 1$.

Now evaluating

$$\lim_{c\to 0} e^{\left(\frac{f'(c)}{g'(c)}\right)} = \lim_{c\to 0} e^{\left(\frac{\ln\frac{\lambda_2^{\left(\lambda_2^c\right)}}{\lambda_1^{\left(\lambda_1^c\right)}}}{1}\right)} = \lim_{c\to 0} e^{\left[\ln\frac{\lambda_2^{\left(\lambda_2^c\right)}}{\lambda_1^{\left(\lambda_1^c\right)}}\right]}$$

$$= \lim_{c\to 0} \frac{\lambda_2^{\left(\lambda_2^c\right)}}{\lambda_1^{\left(\lambda_1^c\right)}} = \frac{\lambda_2^{\lambda_2^0}}{\lambda_1^{\lambda_1^0}} = \frac{\lambda_2^1}{\lambda_1^1}$$

$$= \frac{\lambda_2}{\lambda_1}.$$

Now if $\lambda_1 = \lambda_2 = \lambda$, then

$$e^{\eta(c)} = e^{\frac{\lambda_2^c - \lambda_1^c}{c}} = e^{\frac{\lambda^c - \lambda^c}{c}} = e^{\frac{0}{c}} = e^0 = 1 \ .$$

Thus, $e^{\eta(c)} = 1$, if $\lambda_1 = \lambda_2$.

APPENDIX D

MLE OF γ, LINEAR-EXPONENTIAL

The linear-exponential distribution is defined as

$$f(t) = (\lambda + \gamma t)e^{-\left(\lambda t + \frac{1}{2}\gamma t^2\right)} \qquad t,\gamma,\lambda > 0 \ .$$

From Appendix B, the joint likelihood function for the linear-exponential with noncensored and censored values is

$$L(\lambda,\gamma) = e^{-\left(\lambda T - \frac{1}{2}\gamma S\right)} \prod_{i=1}^{r}(\lambda + \gamma t_i)$$

$$\text{where } T = \sum_{i=1}^{r} t_i + \sum_{k=r+1}^{n} t_k'$$

$$S = \sum_{i=1}^{r} t_i^2 + \sum_{k=r+1}^{n} (t_k')^2 \ .$$

The joint likelihood function is plotted for $\lambda > 0$ and $\gamma > 0$. The maximum likelihood estimator for γ, say $\hat{\gamma}$, is obtained from coordinate (λ,γ) such that (λ,γ) maximizes $L(\lambda,\gamma)$.

APPENDIX E

MLE OF γ, WEIBULL

The Weibull distribution is defined as

$$f(t) = \gamma\lambda(\lambda t)^{\gamma-1} e^{-(\lambda t)^{\gamma}} \qquad t,\gamma,\lambda > 0 .$$

From Appendix A, the joint likelihood function for the Weibull with noncensored and censored values is

$$L(\lambda,\gamma) = \gamma^{r}\lambda^{\gamma r}\left[\prod_{i=1}^{r} t_i^{\gamma-1}\right] e^{-\lambda^{\gamma}\left[\sum_{i=1}^{r} t_i^{\gamma} + \sum_{k=r+1}^{n} (t_k')^{\gamma}\right]} .$$

The joint likelihood function is plotted for $\lambda > 0$ and $\gamma > 0$. The maximum likelihood estimator for γ, say $\hat{\gamma}$, is obtained from coordinate (λ,γ) such that (λ,γ) maximizes $L(\lambda,\gamma)$.

APPENDIX F

POSTERIOR KERNEL FOR η, WEIBULL

The Weibull Model is defined as

$$f(t) = \lambda\gamma(\lambda t)^{\gamma-1}e^{-(\lambda t)^{\gamma}} \qquad t,\gamma,\lambda > 0 .$$

It is assumed that λ_1 and λ_2 have independently and identically distributed (iid) prior distributions. The assumed prior distribution is the Iverted-Gamma-One, $I\gamma_1$, that is,

$$f(\lambda_i) = \frac{t_o^{n_o}}{\Gamma(n_o)}\left(\frac{1}{\lambda_i}\right)^{n_o-1} e^{-\frac{t_o}{\lambda_i}} \qquad \lambda_i, t_o, n_o > 0 .$$

Now let us find $f(\xi,\eta)$ where $\xi = \lambda_1$ and $\eta = \frac{\lambda_2}{\lambda_1} \Rightarrow \lambda_2 = \xi\eta$.

NOTE: The subscript 1 in λ_1 denotes $\lambda_{standard\ therapy}$, and the subscript 2 in λ_2 denotes $\lambda_{new\ therapy}$.

Since λ_1 *and* λ_2 are iid, it follows that

$$f(\lambda_1,\lambda_2) = f(\lambda_1)f(\lambda_2) = \frac{t_o^{n_o}}{\Gamma(n_o)}\left(\frac{1}{\lambda_1}\right)^{n_o-1} e^{-\frac{t_o}{\lambda}} \frac{t_o^{n_o}}{\Gamma(n_o)}\left(\frac{1}{\lambda_2}\right)^{n_o-1} e^{-\frac{t_o}{\lambda_2}}$$

$$= \left(\frac{t_o}{\Gamma(n_o)}\right)^2\left(\frac{1}{\lambda_1\lambda_2}\right)^{n_o-1} e^{-t_o\left(\frac{1}{\lambda_1}-\frac{1}{\lambda_2}\right)} .$$

Now performing the change of variables,

$$\xi = \lambda_1$$

$$\eta = \frac{\lambda_2}{\lambda_1} \Rightarrow \lambda_2 = \lambda_1\eta = \xi\eta$$

redefining $h_1(\lambda_1,\lambda_2) = \xi$ and $h_2(\lambda_1,\lambda_2) = \xi\eta$ and finding the absolute value of the Jacobian, it follows

$$|j| = \left\| \begin{bmatrix} \dfrac{\partial h_1(\xi,\eta)}{\partial \xi} & \dfrac{\partial h_1(\xi,\eta)}{\partial \eta} \\ \dfrac{\partial h_2(\xi,\eta)}{\partial \xi} & \dfrac{\partial h_2(\xi,\eta)}{\partial \eta} \end{bmatrix} \right\| = \left\| \begin{bmatrix} 1 & 0 \\ \eta & \xi \end{bmatrix} \right\| = |\xi| = \xi$$

hence,

$$\begin{aligned} f(\xi,\eta) &= \left[f_{\lambda_1,\lambda_2}(\xi,\xi\eta) \right] |j| \\ &= \frac{t_o^{2n_o}}{\left[\Gamma(n_o)\right]^2} \left(\frac{1}{\xi\xi\eta} \right)^{n_o-1} e^{-t_o\left(\frac{1}{\xi}+\frac{1}{\xi\eta}\right)} (\xi) \\ &= \frac{t_o^{2n_o}}{\left[\Gamma(n_o)\right]^2} \left(\frac{1}{\xi} \right)^{2n_o-2} \left(\frac{1}{\eta} \right)^{n_o-1} (\xi)\, e^{-t_o\left(\frac{1}{\xi}+\frac{1}{\xi\eta}\right)} \\ &= \left[\frac{t_o^{n_o}}{\Gamma(n_o)} \right]^2 \left(\frac{1}{\xi} \right)^{2n_o-1} \left(\frac{1}{\eta} \right)^{n_o-1} e^{-\frac{t_o}{\xi}\left(1+\frac{1}{\eta}\right)} . \end{aligned}$$

Now let us obtain the posterior density for η, that is,

$$g(\eta|D,\hat{\gamma}_1,\hat{\gamma}_2) = \frac{\int_0^\infty g(\xi,\eta,D,\hat{\gamma}_1,\hat{\gamma}_2)\,d\xi}{\int_0^\infty \int_0^\infty g(\xi,\eta,D,\hat{\gamma}_1,\gamma_2)\,d\xi\,d\eta} .$$

Proceeding,

$$g(\xi,\eta,D,\hat{\gamma}_1,\hat{\gamma}_2) = L(\xi,\eta|D,\hat{\gamma}_1,\hat{\gamma}_2)\, f(\xi,\eta) .$$

Now performing the transformation on $L(\lambda_1,\lambda_2|D,\hat{\gamma}_1,\hat{\gamma}_2)$,

$$\xi = \lambda_1$$
$$\eta = \frac{\lambda_2}{\lambda_1} \qquad |j| = \xi$$

previously shown. Thus,

$$L(\xi,\eta|D,\hat{\gamma}_1,\hat{\gamma}_2) = [L_{\lambda_1,\lambda_2}(\xi,\xi\eta|D,\hat{\gamma}_1,\hat{\gamma}_2)]\,|\xi|$$

$$= \xi\,\hat{\gamma}_1^{r_1}\,\xi^{\hat{\gamma}_1 r_1}\left[\prod_{i=1}^{r_1} t_i^{\hat{\gamma}_1-1}\right] e^{-\xi^{\hat{\gamma}_1}\left[\sum_{i=1}^{r_1} t_i^{\hat{\gamma}_1} - \sum_{k=r_1+1}^{n_1} (t_k')^{\hat{\gamma}_1}\right]}$$

$$\times\ \hat{\gamma}_2^{r_2}\,(\xi\eta)^{\hat{\gamma}_2 r_2}\left[\prod_{i=1}^{r_2} t_i^{\hat{\gamma}_2-1}\right] e^{-(\xi\eta)^{\hat{\gamma}_2}\left[\sum_{i=1}^{r_2} t_i^{\hat{\gamma}_2} - \sum_{k=r_2+1}^{n_2} (t_k')^{\hat{\gamma}_2}\right]}$$

$$= \hat{\gamma}_1^{r_1}\,\hat{\gamma}_2^{r_2}\,\xi^{\hat{\gamma}_1 r_1-\hat{\gamma}_2 r_2-1}\,\eta^{\hat{\gamma}_2 r_2}\left[\prod_{i=1}^{r_1} t_i^{\hat{\gamma}_1-1}\right]\left[\prod_{i=1}^{r_2} t_i^{\hat{\gamma}_2-1}\right]$$

$$\times\ e^{-\left(\xi^{\hat{\gamma}_1}\left[\sum_{i=1}^{r_1} t_i^{\hat{\gamma}_1} - \sum_{k=r_1+1}^{n_1} (t_k')^{\hat{\gamma}_1}\right] + (\xi\eta)^{\hat{\gamma}_2}\left[\sum_{i=1}^{r_2} t_i^{\hat{\gamma}_2} - \sum_{k=r_2+1}^{n_2} (t_k')^{\hat{\gamma}_2}\right]\right)}.$$

Note: $L_{\lambda_1,\lambda_2}(\cdot)$ is the likelihood function for independent populations for the Weibull (see Appendix A).

Hence,

$$g(\xi,\eta,D,\hat{\gamma}_1,\hat{\gamma}_2) = L(\xi,\eta|D,\hat{\gamma}_1,\hat{\gamma}_2)f(\xi,\eta)$$

$$= \hat{\gamma}_1^{r_1}\,\hat{\gamma}_2^{r_2}\,\xi^{\hat{\gamma}_1 r_1-\hat{\gamma}_2 r_2+1}\,\eta^{\hat{\gamma}_2 r_2}\left[\prod_{i=1}^{r_1} t_i^{\hat{\gamma}_1-1}\right]\left[\prod_{i=1}^{r_2} t_i^{\hat{\gamma}_2-1}\right]$$

$$\times\ e^{-\left(\xi^{\hat{\gamma}_1}\left[\sum_{i=1}^{r_1} t_i^{\hat{\gamma}_1} - \sum_{k=r_1+1}^{n_1} (t_k')^{\hat{\gamma}_1}\right] + (\xi\eta)^{\hat{\gamma}_2}\left[\sum_{i=1}^{r_2} t_i^{\hat{\gamma}_2} - \sum_{k=r_2+1}^{n_2} (t_k')^{\hat{\gamma}_2}\right]\right)}$$

$$\times\left[\frac{t_o^{n_o}}{\Gamma(n_o)}\right]^2\left(\frac{1}{\xi}\right)^{2n_o-1}\left(\frac{1}{\eta}\right)^{n_o-1} e^{-\frac{t_o}{\xi}\left(1-\frac{1}{\eta}\right)}$$

$$= \left[\frac{t_o^{n_o}}{\Gamma(n_o)}\right]^2\left[\prod_{i=1}^{r_1} t_i^{\hat{\gamma}_1-1}\right]\left[\prod_{i=1}^{r_2} t_i^{\hat{\gamma}_2-1}\right]\hat{\gamma}_1^{r_1}\,\hat{\gamma}_2^{r_2}\,\xi^{\hat{\gamma}_1 r_1-\hat{\gamma}_2 r_2-2n_o}\,\eta^{\hat{\gamma}_2 r_2-n_o-1}$$

$$\times\ e^{-\left(\xi^{\hat{\gamma}_1}\left[\sum_{i=1}^{r_1} t_i^{\hat{\gamma}_1} - \sum_{k=r_1+1}^{n_1} (t_k')^{\hat{\gamma}_1}\right] + (\xi\eta)^{\hat{\gamma}_2}\left[\sum_{i=1}^{r_2} t_i^{\hat{\gamma}_2} - \sum_{k=r_2+1}^{n_2} (t_k')^{\hat{\gamma}_2}\right] + \frac{t_o}{\xi}\left(1-\frac{1}{\eta}\right)\right)}.$$

APPENDIX G

POSTERIOR KERNEL FOR η, LINEAR-EXPONENTIAL

The linear-exponential model is defined as

$$f(t) = (\lambda+\gamma t)e^{-(\lambda t+\frac{1}{2}\gamma t^2)} \qquad \lambda,\gamma,t > 0 .$$

The joint probability density function for $f(\xi,\eta)$ was previously derived for the Weibull model, and it is

$$f(\xi,\eta) = \left[\frac{t_0^{n_0}}{\Gamma(n_0)}\right]^2 \left(\frac{1}{\xi}\right)^{2n_0-1} \left(\frac{1}{\eta}\right)^{n_0-1} e^{-\frac{t_0}{\eta}(1-\frac{1}{\eta})}$$

where $\xi = \lambda_1$ and $\eta = \frac{\lambda_2}{\lambda_1} \Rightarrow \lambda_2 = \xi\eta$.

Note: The subscript 1 in λ_1 denotes $\lambda_{standard\ therapy}$, and the subscript 2 in λ_2 denotes $\lambda_{new\ therapy}$.

Now performing a transformation on the likelihood of the linear-exponential model, the likelihood was previously shown to be

$$l(\underline{\lambda},\underline{\gamma}) = \prod_{j=1}^{l}\left[e^{-(\lambda_j T_j - \frac{1}{2}\gamma_j S_j)} \prod_{i=1}^{r_j}(\lambda + \gamma t_i)\right];$$

for $l = 2$ we have

$$l(\underline{\lambda},\underline{\gamma}) = e^{-(\lambda_1 T_1-\frac{1}{2}\gamma_1 S_1)} \prod_{i=1}^{r_1}(\lambda_1+\gamma_1 t_{i1})\ e^{-(\lambda_2 T_2-\frac{1}{2}\gamma_2 S_2)} \prod_{i=1}^{r_2}(\lambda_2+\gamma_2 t_{i2})$$

Now performing the following transformation on $l(\underline{\lambda},\underline{\gamma})$ for $l = 2$, we have

$$\eta = \frac{\lambda_2}{\lambda_1}$$
$$\xi = \lambda .$$

Thus, $\lambda_2 = \eta\xi$. Now rewriting η and ξ, we have

$$h_1(\xi,\eta) = \xi$$
$$h_2(\xi,\eta) = \xi\eta$$

and finding the absolute value of the jacobian

$$|J| = \left| \begin{bmatrix} \frac{\partial h_1}{\partial \xi} & \frac{\partial h_1}{\partial \eta} \\ \frac{\partial h_2}{\partial \xi} & \frac{\partial h_2}{\partial \eta} \end{bmatrix} \right| = \left| \begin{bmatrix} 1 & 0 \\ \eta & \xi \end{bmatrix} \right| = |\xi| = \xi \ .$$

Thus,

$$L(\xi,\eta) = \left[L_{\lambda_1,\lambda_2}(\xi,\eta\xi|D,\hat{\gamma}_1,\hat{\gamma}_2)\right] \xi$$
$$= \xi\left[\prod_{i=1}^{r_1}(\xi + \hat{\gamma}_1 t_{1i})\right] e^{-(\xi T_1 - \frac{1}{2}\hat{\gamma}_1 S_1)}\left[\prod_{i=1}^{r_2}(\eta\xi + \hat{\gamma}_2 t_{2i})\right] e^{-(\eta\xi T_2 - \frac{1}{2}\hat{\gamma}_2 S_2)} \ .$$

NOTE:

$$T_j = \sum_{i=1}^{r_j} t_{ji} + \sum_{k=r_j+1}^{n_j} t'_{jk}$$
$$S_j = \sum_{i=1}^{r_j} t_{ji}^2 + \sum_{k=r_j+1}^{n_j} (t'_{ji})^2 \ .$$

But the posterior kernel, that is, $L(\xi,\eta|D,\hat{\gamma}_1,\hat{\gamma}_2)\, f(\xi,\eta)$, say, $g(\xi,\eta|D,\hat{\gamma}_1,\hat{\gamma}_2)$ is

$$
\begin{aligned}
g(\xi,\eta|D,\hat{\gamma}_1,\hat{\gamma}_2) &= L(\xi,\eta|D,\hat{\gamma}_1,\hat{\gamma}_2)\, f(\xi,\eta) \\
&= \left[\prod_{i=1}^{r_1}(\xi+\hat{\gamma}_1 t_{1i})\right] e^{-(\xi T_1+\frac{1}{2}\hat{\gamma}_1 S_1)} \left[\prod_{i=1}^{r_2}(\xi\eta+\hat{\gamma}_2 t_{2i})\right] e^{-(\xi\eta T_2+\frac{1}{2}\hat{\gamma}_2 S_2)} \\
&\times \xi\left[\frac{t_o^{n_o}}{\Gamma(n_o)}\right]^2\left(\frac{1}{\xi}\right)^{2n_o-1}\left(\frac{1}{\eta}\right)^{n_o-1} e^{-\frac{t_o}{\xi}\left(1-\frac{1}{\eta}\right)} \\
&= \left[\frac{t_o^{n_o}}{\Gamma(n_o)}\right]^2\left(\frac{1}{\xi}\right)^{2n_o}\left(\frac{1}{\eta}\right)^{n_o-1}\left[\prod_{i=1}^{r_1}(\xi+\hat{\gamma}_1 t_{1i})\right]\left[\prod_{i=1}^{r_2}(\xi\eta+\hat{\gamma}_2 t_{2i})\right] \\
&\times e^{-\left(\xi T_1+\frac{1}{2}\hat{\gamma}_1 S_1+\xi\eta T_2+\frac{1}{2}\hat{\gamma}_2 S_2+\frac{t_o}{\xi}\left(1-\frac{1}{\eta}\right)\right)} \\
&= \left[\frac{t_o^{n_o}}{\Gamma(n_o)}\right]^2\left(\frac{1}{\xi}\right)^{2n_o}\left(\frac{1}{\eta}\right)^{n_o-1}\left[\prod_{i=1}^{r_1}(\xi+\hat{\gamma}_1 t_{1i})\prod_{i=1}^{r_2}(\xi\eta+\hat{\gamma}_2 t_{2i})\right] \\
&\times e^{-\left[\xi(T_1+\eta T_2)+\frac{1}{2}(\hat{\gamma}_1 S_1+\hat{\gamma}_2 S_2)-\frac{t_o}{\xi}\left(1-\frac{1}{\eta}\right)\right]}.
\end{aligned}
$$

Consquently, the posterior distribution of the parameter of interest, η, is

$$
g(\eta|D,\hat{\gamma}_1,\hat{\gamma}_2) = \frac{\int_0^\infty g(\xi,\eta|D,\hat{\gamma}_1,\hat{\gamma}_2)\, d\xi}{\int_0^\infty\int_0^\infty g(\xi,\eta|D,\hat{\gamma}_1,\hat{\gamma}_2)\, d\xi\, d\eta}.
$$

APPENDIX H

DENSITY; SURVIVORSHIP; AND HAZARD FUNCTIONS, WEIBULL

The Weibull density is defined as

$$f(t) = \lambda\gamma(\lambda t)^{\gamma-1} e^{-(\lambda t)^{\gamma}} \qquad t,\lambda,\gamma \geq 0 .$$

Note: The survivorship function is defined as

$$S(t) = 1 - F(t)$$

where

$$F(t) = \int_{-\infty}^{t} f(x)dx$$

and the hazard function is defined as

$$h(t) = \frac{f(t)}{S(t)} .$$

Now, let us find F(t):

$$F(t) = \int_{-\infty}^{t} f(x)dx = \int_{0}^{t} \lambda\gamma(\lambda x)^{\gamma-1} e^{-(\lambda x)^{\gamma}} dx .$$

Let

$$u = x^{\gamma} \qquad 0 < u < u(t) .$$
$$du = \gamma x^{\gamma-1}$$

Hence,

$$\int_{0}^{u(t)} \lambda^{\gamma} e^{-(\lambda^{\gamma}\mu)} du = \frac{\lambda^{\gamma} e^{\lambda^{\gamma} u}}{-\lambda^{\gamma}} \Big|_{0}^{u(t)}$$

but $u = x^{\gamma}$

$$= -e^{-(\lambda x)^{\gamma}}\Big|_0^t = -e^{-(\lambda t)^{\gamma}} - (-e^{-\lambda^{\gamma}(0)})$$
$$= 1 - e^{-(\lambda t)^{\gamma}} .$$

Thus,

$$F(t) = 1 - e^{-(\lambda t)^{\gamma}} .$$

Consequently, the survivorship function of the Weibull density is

$$\begin{aligned} S(t) &= 1 - F(t) \\ &= 1 - [1 - e^{-(\lambda t)^{\gamma}}] \\ &= e^{-(\lambda t)^{\gamma}} \end{aligned}$$

and the hazard function of the Weibull density is

$$\begin{aligned} h(t) &= \frac{f(t)}{S(t)} = \frac{\lambda\gamma(\lambda t)^{\gamma-1}e^{-(\lambda t)^{\gamma}}}{e^{-(\lambda t)^{\gamma}}} \\ &= \lambda\gamma(\lambda t)^{\gamma-1} . \end{aligned}$$

APPENDIX I

DENSITY; SURVIVORSHIP; AND HAZARD FUNCTIONS, LINEAR-EXPONENTIAL

The linear-exponential density is defined as

$$f(t) = (\lambda + \gamma t)\, e^{-(\lambda t + \frac{1}{2}\gamma t^2)} \qquad t,\ \lambda,\gamma > 0 \ .$$

Note: The survivorship function is defined as

$$S(t) = 1 - F(t)$$

where

$$F(t) = \int_{-\infty}^{t} f(x)dx$$

and the hazard function is defined as

$$h(t) = \frac{f(t)}{S(t)} \ .$$

Now, let us find F(t)

$$F(t) = \int_{-\infty}^{t} f(x)dx = \int_{0}^{t} (\lambda+\gamma x) e^{-(\lambda x + \frac{1}{2}\gamma x^2)} dx \ .$$

Let

$$u = \lambda x + \frac{1}{2}\gamma x^2 \qquad 0 < u < u(t) \ .$$
$$du = (\lambda+\gamma x)dx$$

Hence,

$$= \int_{0}^{u(t)} e^{-u} du = -e^{-u}\Big|_{0}^{u(t)}$$

but $u = \lambda x + \frac{1}{2}\gamma x^2$

$$= -e^{-(\lambda x + \frac{1}{2}\gamma x^2)}\Big|_0^t$$
$$= -e^{-(\lambda t + \frac{1}{2}\gamma t^2)} - (-e^{-(\lambda(0) + \frac{1}{2}\gamma(0)}) $$
$$= 1 - e^{-(\lambda t + \frac{1}{2}\gamma t^2)} .$$

Thus,

$$F(t) = 1 - e^{-(\lambda t + \frac{1}{2}\gamma t^2)} .$$

Consequently, the survivorship function of the linear-exponential density is

$$S(t) = 1 - F(t)$$
$$= 1 - \left[1 - e^{-(\lambda t + \frac{1}{2}\gamma t^2)} \right]$$
$$= e^{-(\lambda t + \frac{1}{2}\gamma t^2)}$$

and the hazard function of the linear-exponential density is

$$h(t) = \frac{f(t)}{s(t)} = \frac{(\lambda + \gamma t) e^{-(\lambda t + \frac{1}{2}\gamma t^2)}}{e^{-(\lambda t + \frac{1}{2}\gamma t^2)}}$$
$$= \lambda + \gamma t .$$

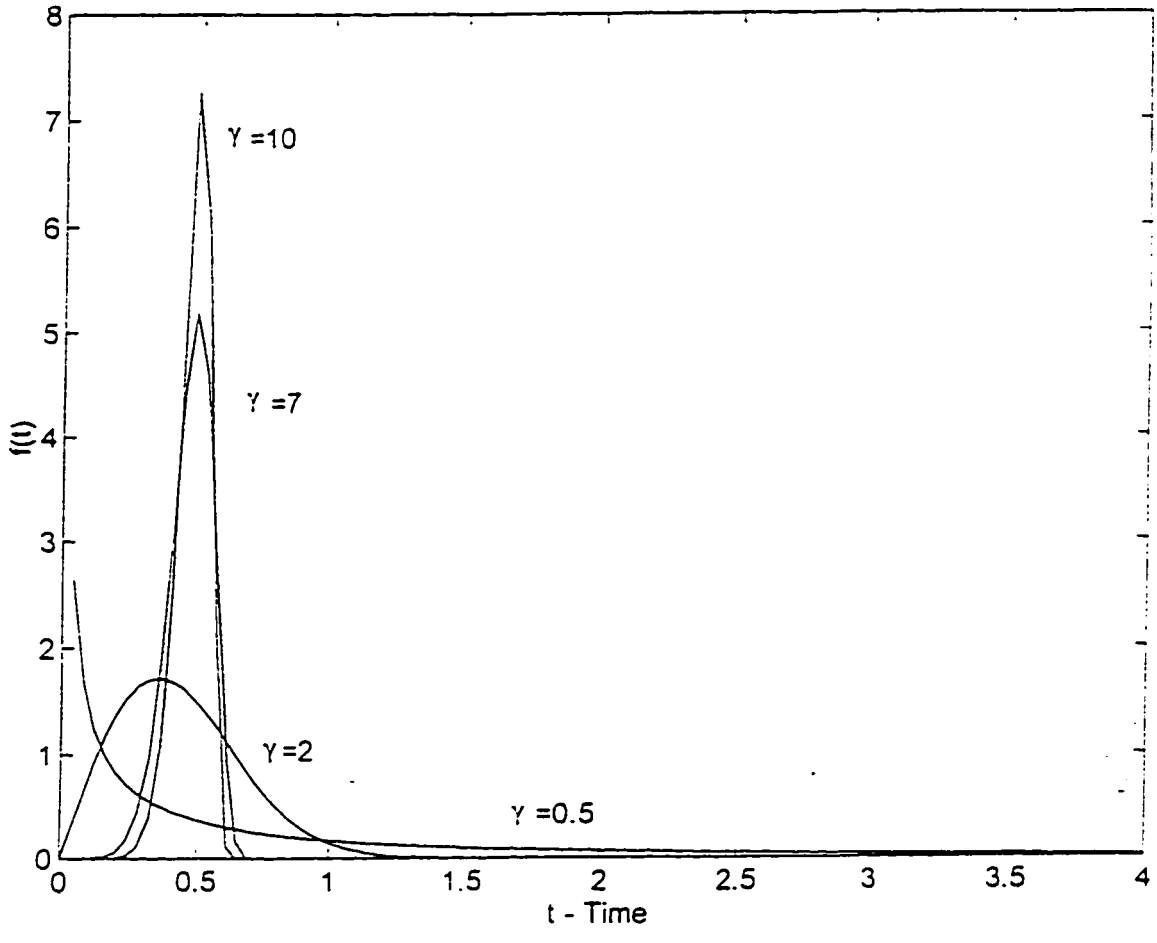
APPENDIX J

GRAPHS, WEIBULL

Weibull Density Function:

$$f(t) = \lambda\gamma(\lambda t)^{\gamma-1} e^{-(\lambda t)^{\gamma}} \qquad t,\lambda,\gamma > 0$$

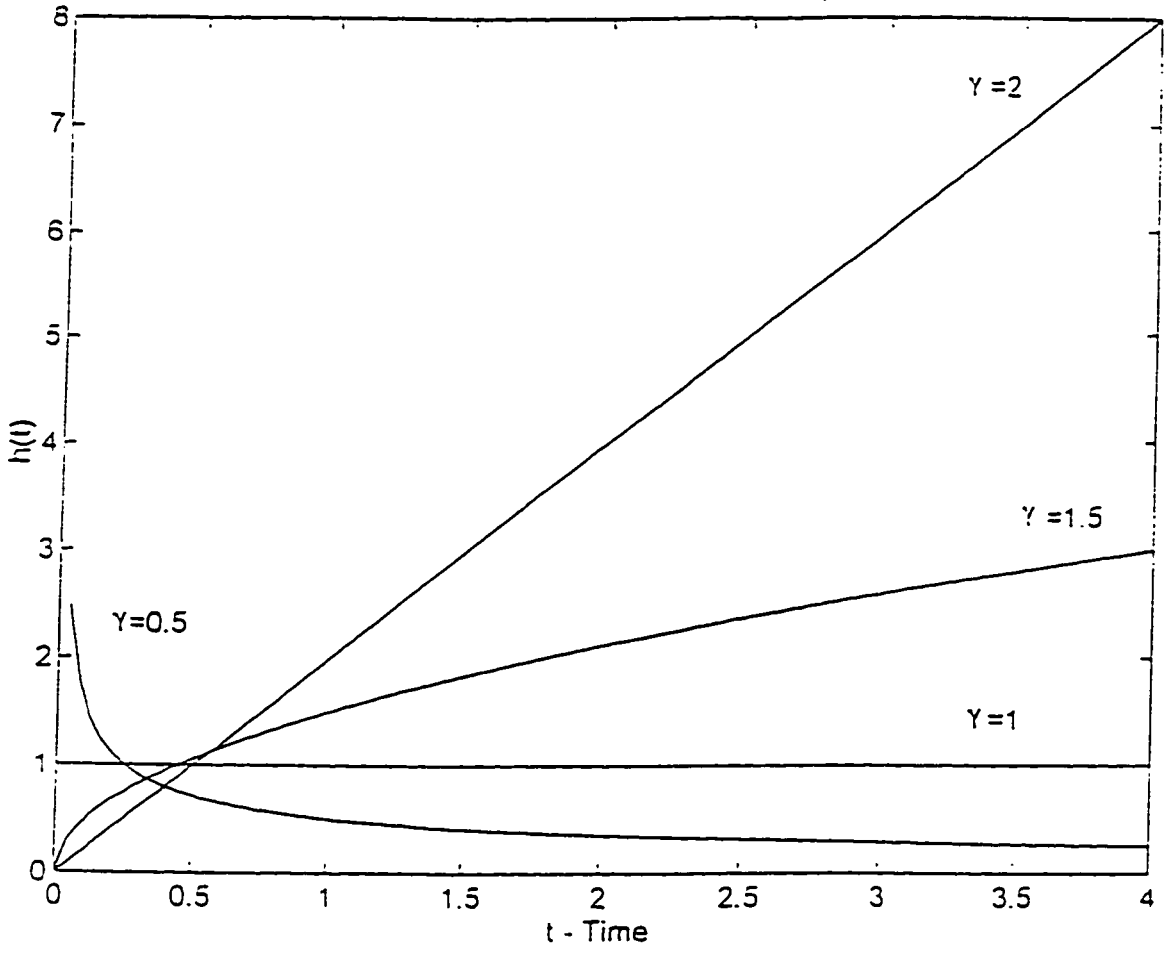
FIGURE 1
Weibull Density Curves, $\lambda = 2$



Weibull Hazard Function:

$$h(t) = \lambda\gamma(\lambda t)^{\gamma-1} \qquad t,\lambda,\gamma > 0$$

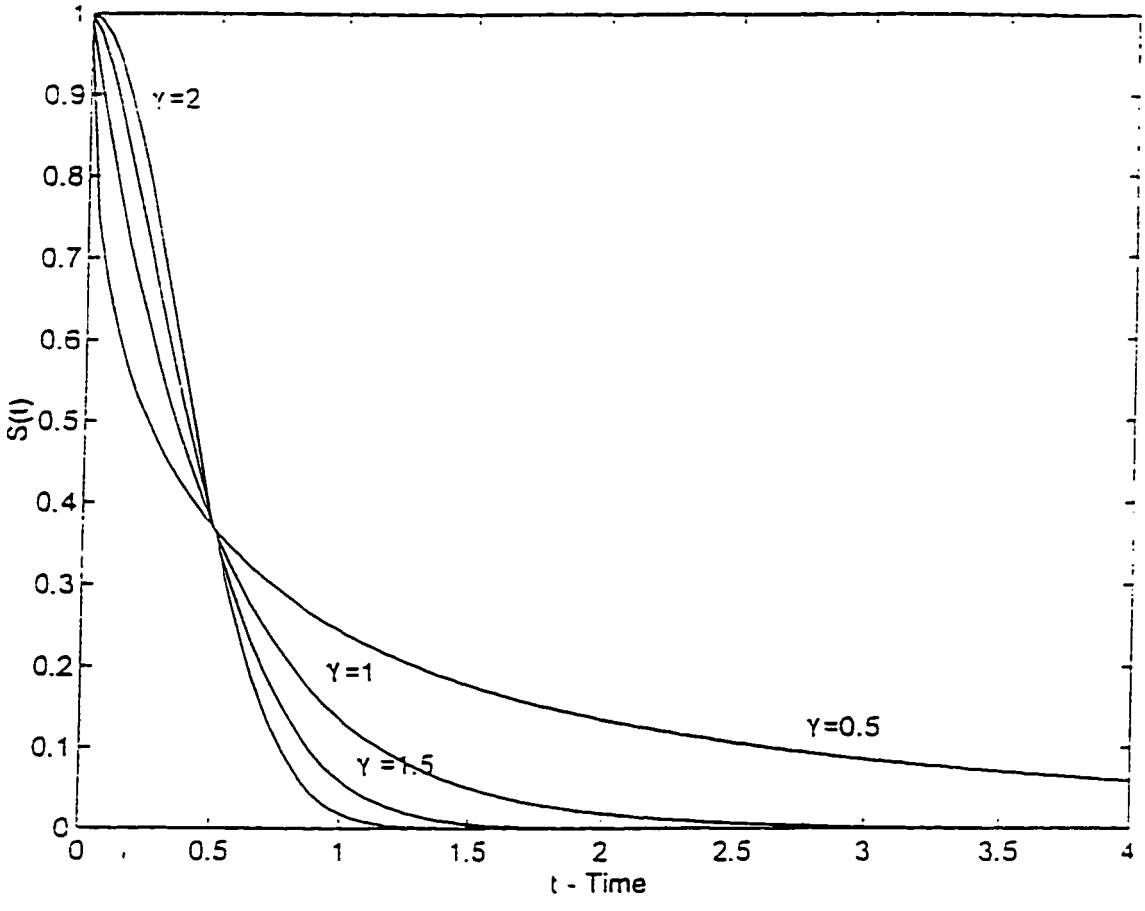
FIGURE 2
Weibull Hazard Function Curves, $\lambda = 1$



Weibull Survivorship Function:

$$S(t) = e^{-(\lambda t)^{\gamma}} \qquad t,\lambda,\gamma > 0$$

FIGURE 3
Weibull Survivorship Function Curves, $\lambda = 2$



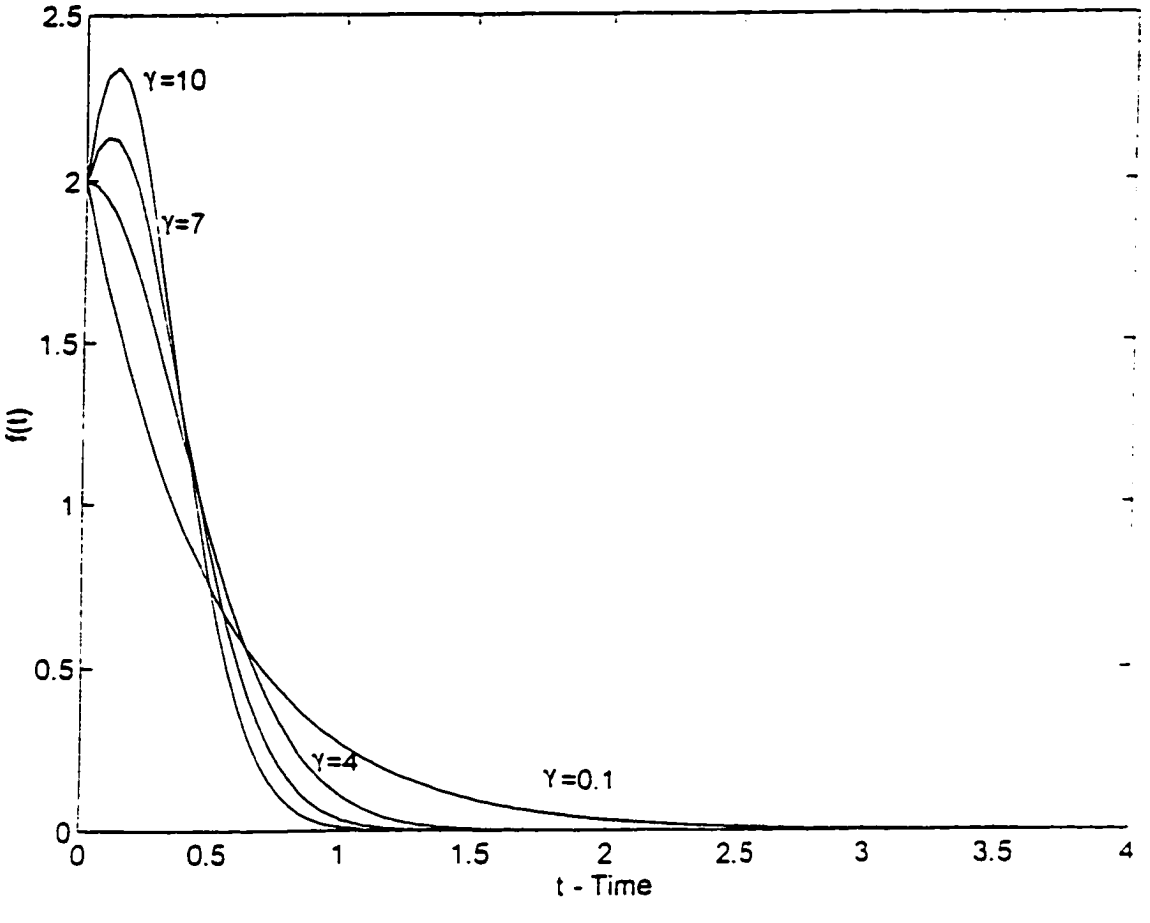
APPENDIX K

GRAPHS, LINEAR-EXPONENTIAL

Linear-Exponential Density Function:

$$f(t) = (\lambda + \gamma t)e^{-(\lambda t - \frac{1}{2}\gamma t^2)} \qquad t, \lambda, \gamma > 0$$

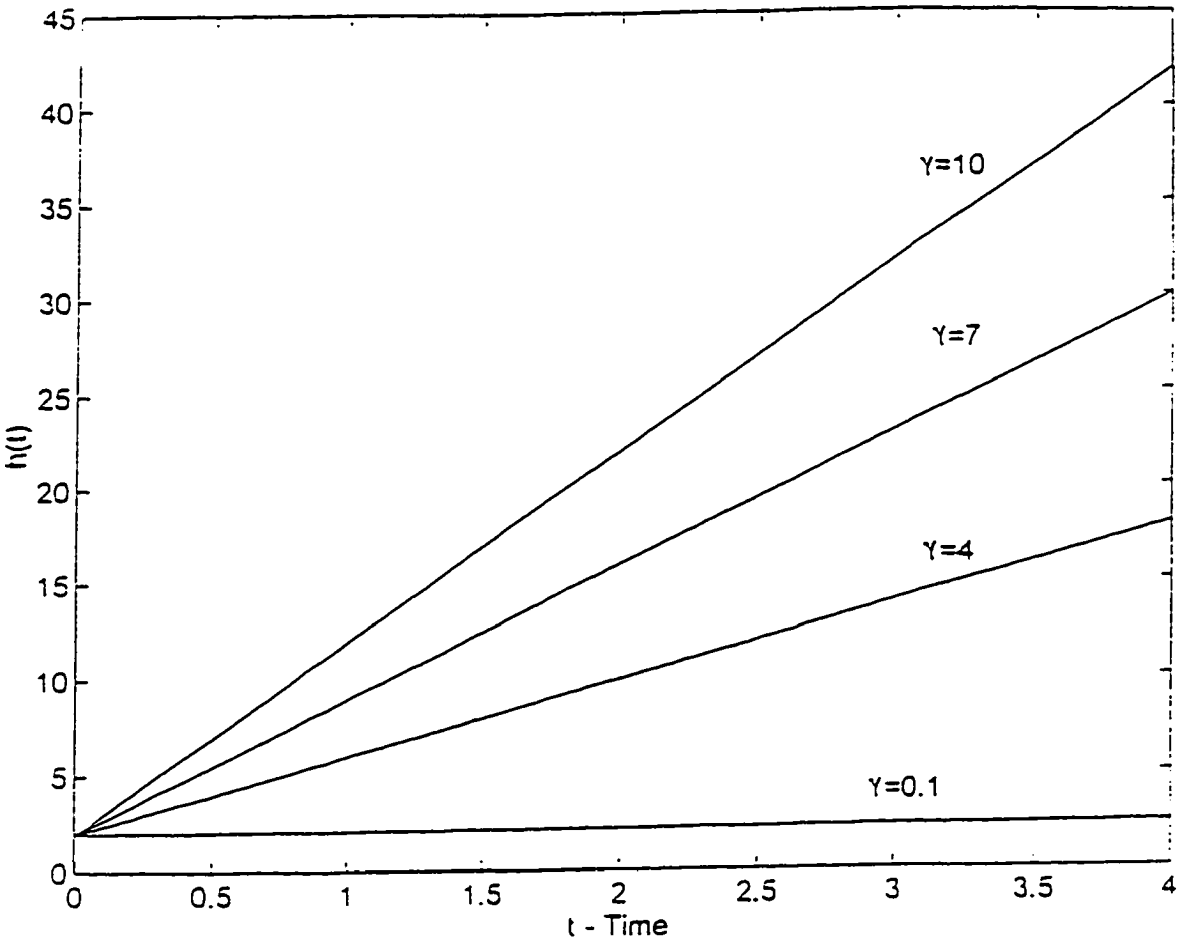
FIGURE 4
Linear-Exponential Density Curves, $\lambda = 2$



Linear-Exponential Hazard Function:

$$h(t) = \lambda + \gamma t \qquad t,\lambda,\gamma > 0$$

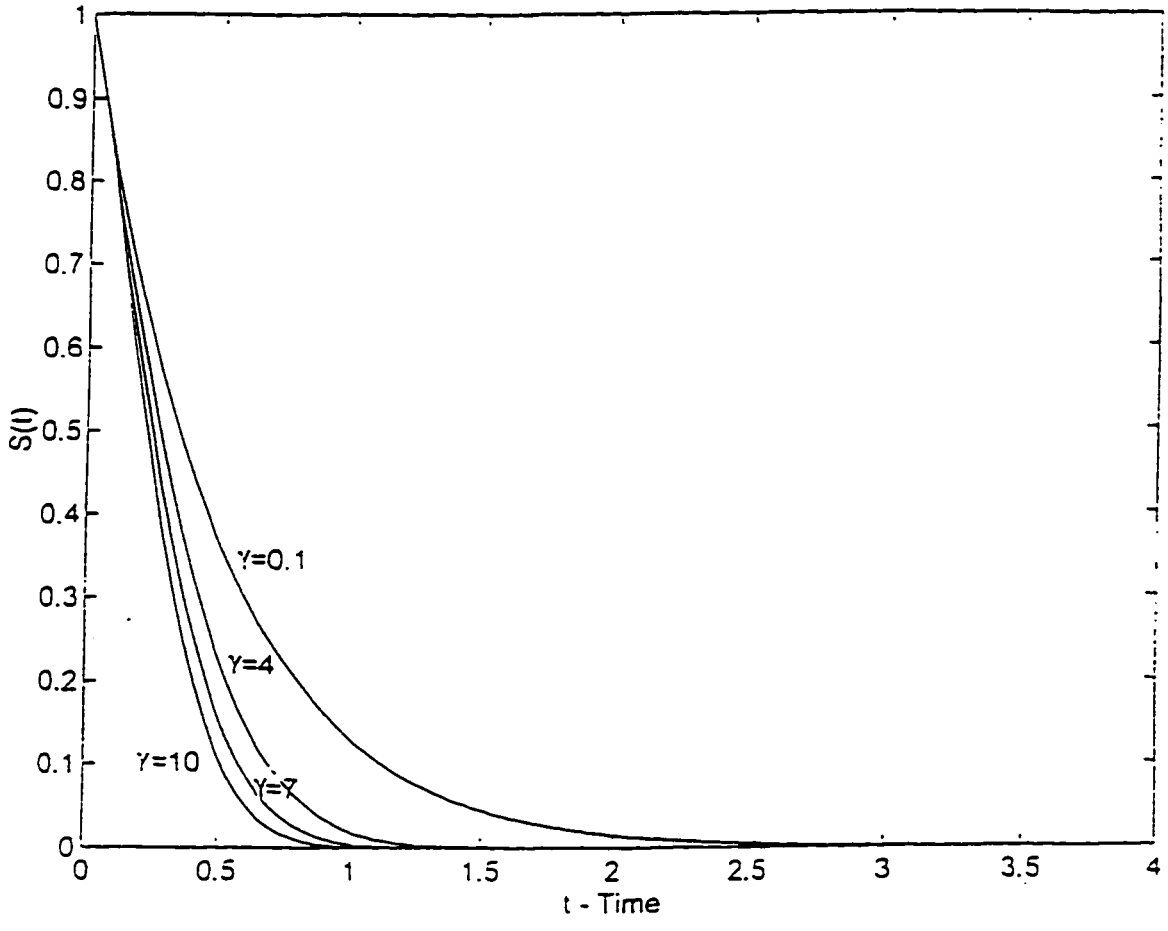
FIGURE 5
Linear-Exponential Hazard Function Curves, $\lambda = 2$



Linear-Exponential Survivorship Function:

$$S(t) = e^{-(\lambda t - \frac{1}{2}\gamma t^2)} \qquad t,\lambda,\gamma > 0$$

FIGURE 6
Linear-Exponential Survivorship Function Curves, $\lambda = 2$



APPENDIX L

NUMERICAL INTEGRATION PROGRAMS, WEIBULL AND LINEAR-EXPONENTIAL

```
PROGRAM INTEGRATION
C
C     Weibull Model - Integration of the Normalizing Constant
C
C     Defining Variables involved in the Program
C
      DOUBLE PRECISION XM(32),XA(32),YM(32),YA(32),SEED2(32),SEED3(32)
      DOUBLE PRECISION G(32),VG(32),S11(16),S22(16),TS11(16),ITER(16)
      DOUBLE PRECISION NO11(16),TO11(16),TS22(16),TS1,TS2,S1,S2,NO1

      INTEGER N, Q, I1, P, TO1

      N=6000

      OPEN(UNIT=12,FILE='INTPAR',STATUS='OLD')

      OPEN(UNIT=30,FILE='OPUTS',STATUS='NEW')

      DO 750 Q=1,16
      READ(UNIT=12,FMT=*) ITER(Q),TO11(Q),NO11(Q),S11(Q),S22(Q),
     +                TS11(Q),TS22(Q)
 750  CONTINUE

      OPEN(UNIT=15,FILE='IPUTS',STATUS='OLD')

      DO 450 P=1,32
       READ(UNIT=15,FMT=*) XM(P),XA(P),YM(P),YA(P),SEED2(P),
     +                 SEED3(P)
 450  CONTINUE



      DO 850 I1=1,16

      PRINT*,'ITER=',ITER(I1),to11(i1),no11(i1),s11(i1),s22(i1),
     +       ts11(i1),ts22(i1)

       NO1=NO11(I1)
       TO1=TO11(I1)
       TS1=TS11(I1)
       TS2=TS22(I1)
       S1=S11(I1)
       S2=S22(I1)

      CALL INTEG(XM,XA,YM,YA,SEED2,SEED3,G,VG,N,TO1,NO1,
```

```
     +          TS1,TS2,S1,S2)
        WRITE (30,40) ANSN(G), ANSD(G), TO1, NO1
   40   FORMAT (1X,'NUM. AREA=',E10.2E4,
     +        'DEN. AREA=',E15.6E5,'TO1=',I3,'NO1=',F5.3)

  850  CONTINUE
       STOP
       END
C
C      Calculation of the Intergation
C
       SUBROUTINE INTEG(XM,XA,YM,YA,SEED2,SEED3,G,VG,N,TO1,
     +              NO1,TS1,TS2,S1,S2)

       DOUBLE PRECISION XM(32), XA(32), R(2000), TEMP, VAR, S(2000)
       DOUBLE PRECISION YM(32), YA(32), LTEMP, LTEMP1, LTEMP2, SUM
       DOUBLE PRECISION SEED2(32), SEED3(32), G(32), VG(32), S1, S2
       DOUBLE PRECISION TS1, TS2, X, Y, NO1

       INTEGER I, J, N, N1, K, C, TO1

       SUM=0.0D0
       VAR=0.0D0
       N1=N/2000
       K=0

       DO 1000 C=1,32

       DO 10 I=1, N1
       CALL URAN2(R,SEED2,2000,C)
       CALL URAN3(S,SEED3,2000,C)

       DO 20 J=1,2000

       X=XM(C)*R(J)+ XA(C)
       Y=YM(C)*S(J)+ YA(C)

       LTEMP1=(((S1*104)+(S2*104)-(2*NO1))*LOG(X)) +
     +       (((S2*104)-NO1-1)*LOG(Y))

         LT1=(X**S1)*TS1
         LT2=((X*Y)**S2)*TS2
         LT3=(TO1/X)*(1+(1/Y))
       ltemp2=-(LT1+LT2+LT3)
       LTEMP=0.001*(LTEMP1+LTEMP2)
```

```
      K=K+1
      TEMP=DEXP(LTEMP)
      IF (K .EQ. 1) then
       SUM=TEMP
       goto 20
       end if
       SUM=SUM+((TEMP-SUM)/DFLOAT(K))
       VAR=VAR+(K-1)*(TEMP-SUM)*((TEMP-SUM)/DFLOAT(K))
   20  CONTINUE

      IF (I .EQ. N1) G(C)=XM(C)*YM(C)*SUM
      IF (I .EQ. N1) VG(C)=VAR/DFLOAT(K-1)
   10  CONTINUE
 1000  CONTINUE
      RETURN
      END
C
C     Computing the Integral
C
      FUNCTION ANSD(G)
      DOUBLE PRECISION DEN, G(32)
      INTEGER B

      DEN=0.0D0
      VDEN=0.0D0
      DO 3000 B=1,32
      DEN=DEN+G(B)
 3000  CONTINUE
      ANSD=DEN
      END
C
C     Generation of Random Variables for 1st Dimension
C
      SUBROUTINE URAN2 (R, SEED2, N, C)
      DOUBLE PRECISION R(2000),SEED2(32),A,B,SCALE,M

      INTEGER I, N, C

      A=950706376.0D0
      M=2147483647.0D0
      SCALE=65536.0D0
      B=550007125.0D0

      DO 200 I=1,N
      SEED2(C)=B*DINT(SEED2(C)/SCALE)+A*DMOD(SEED2(C),SCALE)
      SEED2(C)=DMOD(SEED2(C),M)
```

```
      R(I)=SEED2(C)/M
  200 CONTINUE
      RETURN
      END
C
C     Generation of Random Variables for the 2nd Dimension
C
      SUBROUTINE URAN3 (R, SEED3, N, C)
      DOUBLE PRECISION R(2000),SEED3(32),A,B,SCALE,M

      INTEGER I, N, C

      A=950706376.0D0
      M=2147483647.0D0
      SCALE=65536.0D0
      B=550007125.0D0

      DO 200 I=1,N
      SEED3(C)=B*DINT(SEED3(C)/SCALE)+A*DMOD(SEED3(C),SCALE)
      SEED3(C)=DMOD(SEED3(C),M)
      R(I)=SEED3(C)/M

  200 CONTINUE
      RETURN
      END
```

```
      PROGRAM INTEGRATION
C
C       Weibull Model - Integrating First Moment's Numerator
C
C      Defining Variables involved in the Program
C
      DOUBLE PRECISION XM(32),XA(32),YM(32),YA(32),SEED2(32),SEED3(32)
      DOUBLE PRECISION G(32),VG(32),S11(16),S22(16),TS11(16),ITER(16)
      DOUBLE PRECISION NO11(16),TO11(16),TS22(16),TS1,TS2,S1,S2,NO1

      INTEGER N, Q, I1, P, TO1

      N=6000

      OPEN(UNIT=12,FILE='INTPAR',STATUS='OLD')

      OPEN(UNIT=30,FILE='EVWO',STATUS='NEW')

      DO 750 Q=1,16
      READ(UNIT=12,FMT=*) ITER(Q),TO11(Q),NO11(Q),S11(Q),S22(Q),
     +                TS11(Q),TS22(Q)
  750 CONTINUE

      OPEN(UNIT=15,FILE='IPUT1',STATUS='OLD')

      DO 450 P=1,32
       READ(UNIT=15,FMT=*) XM(P),XA(P),YM(P),YA(P),SEED2(P),
     +                SEED3(P)
  450 CONTINUE

      DO 850 I1=1,16

      PRINT*,'ITER=',ITER(I1)

        NO1=NO11(I1)
        TO1=TO11(I1)
        TS1=TS11(I1)
        TS2=TS22(I1)
        S1=S11(I1)
        S2=S22(I1)

      CALL INTEG(XM,XA,YM,YA,SEED2,SEED3,G,VG,N,TO1,NO1,
     +          TS1,TS2,S1,S2)
      WRITE (30,40)  ANSD(G), TO1, NO1
   40 FORMAT (1X,'DEN. AREA=',E15.6E5,
     +          'TO1=',I3,'NO1=',F5.3)
```

```
  850  CONTINUE
       STOP
       END
C
C      Intergation
C
       SUBROUTINE INTEG(XM,XA,YM,YA,SEED2,SEED3,G,VG,N,TO1,
     +              NO1,TS1,TS2,S1,S2)

       DOUBLE PRECISION XM(32), XA(32), R(2000), TEMP, VAR, S(2000)
       DOUBLE PRECISION YM(32), YA(32), LTEMP, LTEMP1, LTEMP2, SUM
       DOUBLE PRECISION SEED2(32), SEED3(32), G(32), VG(32), S1, S2
       DOUBLE PRECISION TS1, TS2, X, Y, NO1

       INTEGER I, J, N, N1, K, C, TO1

       SUM=0.0D0
       VAR=0.0D0
       N1=N/2000
       K=0

       DO 1000 C=1,32

       DO 10 I=1, N1
       CALL URAN2(R,SEED2,2000,C)
       CALL URAN3(S,SEED3,2000,C)

       DO 20 J=1,2000

       X=XM(C)*R(J)+ XA(C)
       Y=YM(C)*S(J)+ YA(C)

       LTEMP1=(((S1*104)+(S2*104)-(2*NO1))*LOG(X)) +
     +       (((S2*104)-NO1)*LOG(Y))

         LT1=(X**S1)*TS1
         LT2=((X*Y)**S2)*TS2
         LT3=(TO1/X)*(1+(1/Y))
       ltemp2=-(LT1+LT2+LT3)
       LTEMP=LTEMP1+LTEMP2

       K=K+1
       TEMP=DEXP(LTEMP)
       IF (K .EQ. 1) then
        SUM=TEMP
        goto 20
```

```
      end if
      SUM=SUM+((TEMP-SUM)/DFLOAT(K))
      VAR=VAR+(K-1)*(TEMP-SUM)*((TEMP-SUM)/DFLOAT(K))
   20 CONTINUE

      IF (I .EQ. N1) G(C)=XM(C)*YM(C)*SUM
      IF (I .EQ. N1) VG(C)=VAR/DFLOAT(K-1)
   10 CONTINUE
 1000 CONTINUE
      RETURN
      END
C
C     Computing the Integral
C

      FUNCTION ANSD(G)
      DOUBLE PRECISION DEN, G(32)
      INTEGER B

      DEN=0.0D0
      VDEN=0.0D0
      DO 3000 B=1,32
      DEN=DEN+G(B)
 3000 CONTINUE
      ANSD=DEN
      END
C
C     Generation of Random Variables for 1st Dimension
C
      SUBROUTINE URAN2 (R, SEED2, N, C)
      DOUBLE PRECISION R(2000),SEED2(32),A,B,SCALE,M

      INTEGER I, N, C

      A=950706376.0D0
      M=2147483647.0D0
      SCALE=65536.0D0
      B=550007125.0D0

      DO 200 I=1,N
      SEED2(C)=B*DINT(SEED2(C)/SCALE)+A*DMOD(SEED2(C),SCALE)
      SEED2(C)=DMOD(SEED2(C),M)
      R(I)=SEED2(C)/M
  200 CONTINUE
      RETURN
      END
```

```
C
C     Generation of Random Variables for the 2nd Dimension
C
      SUBROUTINE URAN3 (R, SEED3, N, C)
      DOUBLE PRECISION R(2000),SEED3(32),A,B,SCALE,M

      INTEGER I, N, C

      A=950706376.0D0
      M=2147483647.0D0
      SCALE=65536.0D0
      B=550007125.0D0

      DO 200 I=1,N
      SEED3(C)=B*DINT(SEED3(C)/SCALE)+A*DMOD(SEED3(C),SCALE)
      SEED3(C)=DMOD(SEED3(C),M)
      R(I)=SEED3(C)/M
200   CONTINUE
      RETURN
      END
```

```
      PROGRAM INTEGRATION
C
C     Weibull Model - Integrating The Second Moment About The Mean Numerator
C
C     Defining Variables involved in the Program
C
      DOUBLE PRECISION XM(32),XA(32),YM(32),YA(32),SEED2(32),SEED3(32)
      DOUBLE PRECISION G(32),VG(32),S11(16),S22(16),TS11(16),ITER(16)
      DOUBLE PRECISION NO11(16),TO11(16),TS22(16),TS1,TS2,S1,S2,NO1
      DOUBLE PRECISION AVGY, YBAR(16)

      INTEGER N, Q, I1, P, TO1

      N=6000

      OPEN(UNIT=12,FILE='INTPAR2',STATUS='OLD')

      OPEN(UNIT=30,FILE='EVW2O',STATUS='NEW')

      DO 750 Q=1,16
      READ(UNIT=12,FMT=*) ITER(Q),TO11(Q),NO11(Q),S11(Q),S22(Q),
     +              TS11(Q),TS22(Q),YBAR(Q)
750   CONTINUE

      OPEN(UNIT=15,FILE='IPUT2',STATUS='OLD')

      DO 450 P=1,32
       READ(UNIT=15,FMT=*) XM(P),XA(P),YM(P),YA(P),SEED2(P),
     +               SEED3(P)
450   CONTINUE


      DO 850 I1=1,16

      PRINT*,'ITER=',ITER(I1)

       AVGY=YBAR(I1)
       NO1=NO11(I1)
       TO1=TO11(I1)
       TS1=TS11(I1)
       TS2=TS22(I1)
       S1=S11(I1)
       S2=S22(I1)
      CALL INTEG(XM,XA,YM,YA,SEED2,SEED3,G,VG,N,TO1,NO1,
     +       TS1,TS2,S1,S2,AVGY)
```

```
      WRITE (30,40) ANSD(G), TO1, NO1
   40 FORMAT (1X,'DEN. AREA=',E15.6E5,
     +        'TO1=',I3,'NO1=',F5.3)

  850 CONTINUE
      STOP
      END
C
C     Intergation
C

      SUBROUTINE INTEG(XM,XA,YM,YA,SEED2,SEED3,G,VG,N,TO1,
     +             NO1,TS1,TS2,S1,S2,AVGY)

      DOUBLE PRECISION XM(32), XA(32), R(2000), TEMP, VAR, S(2000)
      DOUBLE PRECISION YM(32), YA(32), LTEMP, LTEMP1, LTEMP2, SUM
      DOUBLE PRECISION SEED2(32), SEED3(32), G(32), VG(32), S1, S2
      DOUBLE PRECISION TS1, TS2, X, Y, NO1, AVGY

      INTEGER I, J, N, N1, K, C, TO1

      SUM=0.0D0
      VAR=0.0D0
      N1=N/2000
      K=0

      DO 1000 C=1,32

      DO 10 I=1, N1
      CALL URAN2(R,SEED2,2000,C)
      CALL URAN3(S,SEED3,2000,C)

      DO 20 J=1,2000

      X=XM(C)*R(J)+ XA(C)
      Y=YM(C)*S(J)+ YA(C)

      LTEMP1=(2*LOG(ABS(Y-AVGY))) +
     +       (((S1*104)+(S2*104)-(2*NO1))*LOG(X)) +
     +       (((S2*104)-NO1-1)*LOG(Y))
        LT1=(X**S1)*TS1
        LT2=((X*Y)**S2)*TS2
        LT3=(TO1/X)*(1+(1/Y))
      ltemp2=-(LT1+LT2+LT3)
      LTEMP=0.001*(LTEMP1+LTEMP2)
```

```
      K=K+1
      TEMP=DEXP(LTEMP)
      IF (K .EQ. 1) then
       SUM=TEMP
       goto 20
       end if
       SUM=SUM+((TEMP-SUM)/DFLOAT(K))
       VAR=VAR+(K-1)*(TEMP-SUM)*((TEMP-SUM)/DFLOAT(K))
   20  CONTINUE

      IF (I .EQ. N1) G(C)=XM(C)*YM(C)*SUM
      IF (I .EQ. N1) VG(C)=VAR/DFLOAT(K-1)
   10  CONTINUE
  1000  CONTINUE
      RETURN
      END
C
C     Computing the Integral
C
      FUNCTION ANSD(G)
      DOUBLE PRECISION DEN, G(32)
      INTEGER B

      DEN=0.0D0
      VDEN=0.0D0
      DO 3000 B=1,32
      DEN=DEN+G(B)
  3000  CONTINUE
      ANSD=DEN
      END
C
C     Generation of Random Variables for 1st Dimension
C
      SUBROUTINE URAN2 (R, SEED2, N, C)
      DOUBLE PRECISION R(2000),SEED2(32),A,B,SCALE,M

      INTEGER I, N, C
      A=950706376.0D0
      M=2147483647.0D0
      SCALE=65536.0D0
      B=550007125.0D0

      DO 200 I=1,N
      SEED2(C)=B*DINT(SEED2(C)/SCALE)+A*DMOD(SEED2(C),SCALE)
      SEED2(C)=DMOD(SEED2(C),M)
      R(I)=SEED2(C)/M
```

```
200  CONTINUE
     RETURN
     END
C
C     Generation of Random Variables for the 2nd Dimension
C
     SUBROUTINE URAN3 (R, SEED3, N, C)
     DOUBLE PRECISION R(2000),SEED3(32),A,B,SCALE,M

     INTEGER I, N, C

     A=950706376.0D0
     M=2147483647.0D0
     SCALE=65536.0D0
     B=550007125.0D0

     DO 200 I=1,N
     SEED3(C)=B*DINT(SEED3(C)/SCALE)+A*DMOD(SEED3(C),SCALE)
     SEED3(C)=DMOD(SEED3(C),M)
     R(I)=SEED3(C)/M
200  CONTINUE
     RETURN
     END
```

```
      PROGRAM INTEGRATION
C
C     Integrating the Linear-Exponentail Model - Normalizing Constant
C
C     Defining Variables involved in the Program
C
      DOUBLE PRECISION XM(32),XA(32),YM(32),YA(32),SEED2(32),SEED3(32)
      DOUBLE PRECISION G(32),VG(32),S1,S2,T1,T2,T11(16),T22(16)
      DOUBLE PRECISION S11(16),S22(16),A1,A2, TO1, NO1
      DOUBLE PRECISION MO1(104),MO2(104),ITER(16),TO11(16),NO11(16)

      INTEGER N,Q,I1,J1,L,P

      N=6000

      OPEN(UNIT=12,FILE='LINTPAR',STATUS='OLD')

      OPEN(UNIT=30,FILE='LOPUTS',STATUS='NEW')

      DO 750 Q=1,16
      READ(UNIT=12,FMT=*) ITER(Q),TO11(Q),NO11(Q),S11(Q),S22(Q),
     +              T11(Q),T22(Q)
750   CONTINUE

      OPEN(UNIT=11,FILE='MONTHA',STATUS='OLD')

      DO 950 J1=1,104
       READ(UNIT=11,FMT=*) MO1(J1)
950   CONTINUE

      OPEN(UNIT=10,FILE='MONTHB',STATUS='OLD')

      DO 955 L=1,104
       READ(UNIT=10,FMT=*) MO2(L)
955   CONTINUE

      OPEN(UNIT=15,FILE='LIPUTS',STATUS='OLD')

      DO 450 P=1,32
       READ(UNIT=15,FMT=*) XM(P),XA(P),YM(P),YA(P),SEED2(P),
     +              SEED3(P)
450   CONTINUE

      DO 850 I1=1,6

      PRINT*, 'ITER=',ITER(I1)
```

```
      NO1=NO11(I1)
      TO1=TO11(I1)
      T1=T11(I1)
      T2=T22(I1)
      S1=S11(I1)
      S2=S22(I1)
      A1=0.01
      A2=0.01

      CALL INTEG(XM,XA,YM,YA,SEED2,SEED3,G,VG,
     +          N,TO1,NO1,T1,T2,S1,S2,A1,A2,MO1,MO2)

      WRITE (30,40) ANSD(G), TO1, NO1
   40 FORMAT (1X,'DEN. AREA=',E15.6E5,'TO1=',F5.3,'NO1=',F5.3)
  850 CONTINUE
      STOP
      END
C
C     Integration
C
      SUBROUTINE INTEG(XM,XA,YM,YA,SEED2,SEED3,G,VG,N,
     +               TO1,NO1,T1,T2,S1,S2,A1,A2,MO1,MO2)

      DOUBLE PRECISION XM(32), XA(32), R(2000), TEMP, VAR, S(2000)
      DOUBLE PRECISION YM(32), YA(32), LTEMP, LTEMP1, LTEMP2, SUM
      DOUBLE PRECISION SEED2(32), SEED3(32), G(32), VG(32), S1, S2
      DOUBLE PRECISION T1, T2
      DOUBLE PRECISION A1,A2,MO1(104),MO2(104),X,Y,TO1,NO1

      INTEGER I, J, N, N1, K, C

      SUM=0.0D0
      VAR=0.0D0
      N1=N/2000
      K=0

      DO 1000 C=1,32

      DO 10 I=1, N1
      CALL URAN2(R,SEED2,2000,C)
      CALL URAN3(S,SEED3,2000,C)

      DO 20 J=1,2000

      X=XM(C)*R(J)+ XA(C)
      Y=YM(C)*S(J)+ YA(C)
```

```
      LTEMP1= -2*NO1*LOG(X)-(NO1+1)*LOG(Y)
     +       + LOG(V1(X,A1,MO1)) + LOG(V2(X,Y,A2,MO2))

        LT1=(X*T1)+((1/2)*A1*S1)
        LT2= (X*Y*T2)+((1/2)*A2*S2)
        LT3= (TO1/X)*(1+(1/Y))
      ltemp2=-(LT1+LT2+LT3)
      LTEMP=0.001*(LTEMP1+LTEMP2)

      K=K+1
      TEMP=DEXP(LTEMP)
      IF (K .EQ. 1) then
       SUM=TEMP
       goto 20
       end if
       SUM=SUM+((TEMP-SUM)/DFLOAT(K))
       VAR=VAR+(K-1)*(TEMP-SUM)*((TEMP-SUM)/DFLOAT(K))
   20  CONTINUE

      IF (I .EQ. N1) G(C)=XM(C)*YM(C)*SUM
      IF (I .EQ. N1) VG(C)=VAR/DFLOAT(K-1)
   10  CONTINUE
 1000  CONTINUE

      RETURN
      END
C
C     Computing the Integral
C
      FUNCTION ANSD(G)
      DOUBLE PRECISION DEN, G(32)
      INTEGER B

      DEN=0.0D0
      VDEN=0.0D0
      DO 3000 B=1,32
      DEN=DEN+G(B)
 3000  CONTINUE
      ANSD=DEN
      END
C
C     Computing the Observations: Summed & Squared Summed
C     for Treatment A/1
C
      FUNCTION V1(X,A1,MO1)
      DOUBLE PRECISION X,A1,MO1(104)
```

```
      INTEGER I

       PV1=1.0D0
       DO 650 I=1,104
       PV1=PV1*(X+(A1*MO1(I)))
  650  CONTINUE
      V1=PV1
      END
C
C   Computing the Observations: Summed & Squared Summed
C   for Treatment B/2
C
      FUNCTION V2(X,Y,A2,MO2)
      DOUBLE PRECISION X,Y,A2,MO2(104)
      INTEGER I
      PV2=1.0D0
       DO 550 I=1,104
        PV2=PV2*((X*Y)+(A2*MO2(I)))
  550  CONTINUE
      V2=PV2
      END
C
C     Generation of Random Variables for 1st Dimension
C
      SUBROUTINE URAN2 (R, SEED2, N, C)
      DOUBLE PRECISION R(2000),SEED2(32),A,B,SCALE,M

      INTEGER I, N, C

      A=950706376.0D0
      M=2147483647.0D0
      SCALE=65536.0D0
      B=550007125.0D0

      DO 200 I=1,N
      SEED2(C)=B*DINT(SEED2(C)/SCALE)+A*DMOD(SEED2(C),SCALE)
      SEED2(C)=DMOD(SEED2(C),M)
      R(I)=SEED2(C)/M

  200  CONTINUE
      RETURN
      END
C
C     Generation of Random Variables for the 2nd Dimension
C
      SUBROUTINE URAN3 (R, SEED3, N, C)
```

```
      DOUBLE PRECISION R(2000),SEED3(32),A,B,SCALE,M

      INTEGER I, N, C

      A=950706376.0D0
      M=2147483647.0D0
      SCALE=65536.0D0
      B=550007125.0D0

      DO 200 I=1,N
      SEED3(C)=B*DINT(SEED3(C)/SCALE)+A*DMOD(SEED3(C),SCALE)
      SEED3(C)=DMOD(SEED3(C),M)
      R(I)=SEED3(C)/M

  200 CONTINUE
      RETURN
      END
```

```
      PROGRAM INTEGRATION
C
C     Integrating the Linear-Exponentail Model - Numerator 1st Moment
C
C     Defining Variables involved in the Program
C
      DOUBLE PRECISION XM(32),XA(32),YM(32),YA(32),SEED2(32),SEED3(32)
      DOUBLE PRECISION G(32),VG(32),S1,S2,T1,T2,T11(16),T22(16)
      DOUBLE PRECISION S11(16),S22(16),A1,A2,TO1,NO1
      DOUBLE PRECISION MO1(104),MO2(104),ITER(16),TO11(16),NO11(16)

      INTEGER N,Q,I1,J1,L,P

       N=6000

      OPEN(UNIT=12,FILE='LINTPAR',STATUS='OLD')

      OPEN(UNIT=30,FILE='EVLO',STATUS='NEW')

      DO 750 Q=1,16
      READ(UNIT=12,FMT=*) ITER(Q),TO11(Q),NO11(Q),S11(Q),S22(Q),
     +                T11(Q),T22(Q)
750   CONTINUE

      OPEN(UNIT=11,FILE='MONTHA',STATUS='OLD')

      DO 950 J1=1,104
       READ(UNIT=11,FMT=*) MO1(J1)
950   CONTINUE

      OPEN(UNIT=10,FILE='MONTHB',STATUS='OLD')

      DO 955 L=1,104
        READ(UNIT=10,FMT=*) MO2(L)
955   CONTINUE

      OPEN(UNIT=15,FILE='LIPUT1',STATUS='OLD')

      DO 450 P=1,32
       READ(UNIT=15,FMT=*) XM(P),XA(P),YM(P),YA(P),SEED2(P),
     +                SEED3(P)
450   CONTINUE

      DO 850 I1=1,6

      PRINT*, 'ITER=',ITER(I1)
```

```
      NO1=NO11(I1)
      TO1=TO11(I1)
      T1=T11(I1)
      T2=T22(I1)
      S1=S11(I1)
      S2=S22(I1)
      A1=0.01
      A2=0.01

      CALL INTEG(XM,XA,YM,YA,SEED2,SEED3,G,VG,
     +          N,TO1,NO1,T1,T2,S1,S2,A1,A2,MO1,MO2)

      WRITE (30,40) ANSD(G), TO1, NO1
   40 FORMAT (1X,'DEN. AREA=',E15.6E5,'TO1=',F5.3,'NO1=',F5.3)

  850 CONTINUE
      STOP
      END
C
C     Intergation
C
      SUBROUTINE INTEG(XM,XA,YM,YA,SEED2,SEED3,G,VG,N,
     +          TO1,NO1,T1,T2,S1,S2,A1,A2,MO1,MO2)

      DOUBLE PRECISION XM(32), XA(32), R(2000), TEMP, VAR, S(2000)
      DOUBLE PRECISION YM(32), YA(32), LTEMP, LTEMP1, LTEMP2, SUM
      DOUBLE PRECISION SEED2(32), SEED3(32), G(32), VG(32), S1, S2
      DOUBLE PRECISION T1, T2
      DOUBLE PRECISION A1,A2,MO1(104),MO2(104),X,Y,TO1,NO1

      INTEGER I, J, N, N1, K, C

      SUM=0.0D0
      VAR=0.0D0
      N1=N/2000
      K=0

      DO 1000 C=1,32

      DO 10 I=1, N1
      CALL URAN2(R,SEED2,2000,C)
      CALL URAN3(S,SEED3,2000,C)

      DO 20 J=1,2000

      X=XM(C)*R(J)+ XA(C)
```

```
      Y=YM(C)*S(J)+ YA(C)

      LTEMP1= -2*NO1*LOG(X)-NO1*LOG(Y)
     +       + V1(X,A1,MO1) + V2(X,Y,A2,MO2)

        LT1=(X*T1)+((1/2)*A1*S1)
        LT2= (X*Y*T2)+((1/2)*A2*S2)
        LT3= (TO1/X)*(1+(1/Y))
      ltemp2=-(LT1+LT2+LT3)
      LTEMP=0.001*(LTEMP1+LTEMP2)

      K=K+1
      TEMP=DEXP(LTEMP)
      IF (K .EQ. 1) then
       SUM=TEMP
       goto 20
       end if
       SUM=SUM+((TEMP-SUM)/DFLOAT(K))
       VAR=VAR+(K-1)*(TEMP-SUM)*((TEMP-SUM)/DFLOAT(K))
   20  CONTINUE

      IF (I .EQ. N1) G(C)=XM(C)*YM(C)*SUM
      IF (I .EQ. N1) VG(C)=VAR/DFLOAT(K-1)
   10  CONTINUE
 1000  CONTINUE
      RETURN
      END
C
C     Computing the Integral
C
      FUNCTION ANSD(G)
      DOUBLE PRECISION DEN, G(32)
      INTEGER B

      DEN=0.0D0
      VDEN=0.0D0
      DO 3000 B=1,32
      DEN=DEN+G(B)
 3000  CONTINUE
      ANSD=DEN
      END
C
C     Computing the Observations: Summed & Squared Summed
C     for Treatment A/1
C
      FUNCTION V1(X,A1,MO1)
```

```
      DOUBLE PRECISION X,A1,MO1(104)
      INTEGER I

       PV1=0.0D0
       DO 650 I=1,104
       PV1=PV1+LOG((X+(A1*MO1(I))))
  650  CONTINUE
      V1=PV1
      END
C
C   Computing the Observations: Summed & Squared Summed
C   for Treatment B/2
C
      FUNCTION V2(X,Y,A2,MO2)
      DOUBLE PRECISION X,Y,A2,MO2(104)
      INTEGER I
      PV2=0.0D0
       DO 550 I=1,104
        PV2=PV2+LOG(((X*Y)+(A2*MO2(I))))
  550  CONTINUE
      V2=PV2
      END
C
C     Generation of Random Variables for 1st Dimension
C
      SUBROUTINE URAN2 (R, SEED2, N, C)
      DOUBLE PRECISION R(2000),SEED2(32),A,B,SCALE,M

      INTEGER I, N, C

      A=950706376.0D0
      M=2147483647.0D0
      SCALE=65536.0D0
      B=550007125.0D0

      DO 200 I=1,N
      SEED2(C)=B*DINT(SEED2(C)/SCALE)+A*DMOD(SEED2(C),SCALE)
      SEED2(C)=DMOD(SEED2(C),M)
      R(I)=SEED2(C)/M

  200  CONTINUE
      RETURN
      END


C
```

```
C     Generation of Random Variables for the 2nd Dimension
C
      SUBROUTINE URAN3 (R, SEED3, N, C)
      DOUBLE PRECISION R(2000),SEED3(32),A,B,SCALE,M

      INTEGER I, N, C

      A=950706376.0D0
      M=2147483647.0D0
      SCALE=65536.0D0
      B=550007125.0D0

      DO 200 I=1,N
      SEED3(C)=B*DINT(SEED3(C)/SCALE)+A*DMOD(SEED3(C),SCALE)
      SEED3(C)=DMOD(SEED3(C),M)
      R(I)=SEED3(C)/M

  200 CONTINUE
      RETURN
      END
```

```
      PROGRAM INTEGRATION
C
C     Integrating the Linear-Exponentail Model - Numerator 2nd Moment
C
C     Defining Variables involved in the Program
C
      DOUBLE PRECISION XM(32),XA(32),YM(32),YA(32),SEED2(32),SEED3(32)
      DOUBLE PRECISION G(32),VG(32),S1,S2,T1,T2,T11(16),T22(16)
      DOUBLE PRECISION S11(16),S22(16),A1,A2, NO1,AVGY,YBAR(16)
      DOUBLE PRECISION MO1(104),MO2(104),ITER(16),TO11(16),NO11(16)

      INTEGER N,Q,I1,J1,L,P,TO1

       N=6000

      OPEN(UNIT=12,FILE='LINTPAR2',STATUS='OLD')

      OPEN(UNIT=30,FILE='EVL2O',STATUS='NEW')

      DO 750 Q=1,16
      READ(UNIT=12,FMT=*) ITER(Q),TO11(Q),NO11(Q),S11(Q),S22(Q),
     +              T11(Q),T22(Q),YBAR(Q)
750   CONTINUE

      OPEN(UNIT=11,FILE='MONTHA',STATUS='OLD')

      DO 950 J1=1,104
       READ(UNIT=11,FMT=*) MO1(J1)
950   CONTINUE

      OPEN(UNIT=10,FILE='MONTHB',STATUS='OLD')

      DO 955 L=1,104
       READ(UNIT=10,FMT=*) MO2(L)
955   CONTINUE

      OPEN(UNIT=15,FILE='LIPUT2',STATUS='OLD')

      DO 450 P=1,32
       READ(UNIT=15,FMT=*) XM(P),XA(P),YM(P),YA(P),SEED2(P),
     +              SEED3(P)
450   CONTINUE

      DO 850 I1=1,16

      PRINT*, 'ITER=',ITER(I1)
```

```
      AVGY=YBAR(I1)
      NO1=NO11(I1)
      TO1=TO11(I1)
      T1=T11(I1)
      T2=T22(I1)
      S1=S11(I1)
      S2=S22(I1)
      A1=0.01
      A2=0.01

      CALL INTEG(XM,XA,YM,YA,SEED2,SEED3,G,VG,
     +          N,TO1,NO1,T1,T2,S1,S2,A1,A2,MO1,MO2,AVGY)

      WRITE (30,40) ANSN(G), ANSD(G), TO1, NO1
   40 FORMAT (1X,'DEN. AREA=',E15.6E5,'TO1=',I3,'NO1=',F5.3)
  850 CONTINUE
      STOP
      END
C
C     Intergation
C
      SUBROUTINE INTEG(XM,XA,YM,YA,SEED2,SEED3,G,VG,N,
     +          TO1,NO1,T1,T2,S1,S2,A1,A2,MO1,MO2,AVGY)

      DOUBLE PRECISION XM(32), XA(32), R(2000), TEMP, VAR, S(2000)
      DOUBLE PRECISION YM(32), YA(32), LTEMP, LTEMP1, LTEMP2, SUM
      DOUBLE PRECISION SEED2(32), SEED3(32), G(32), VG(32), S1, S2
      DOUBLE PRECISION T1, T2, AVGY
      DOUBLE PRECISION A1,A2,MO1(104),MO2(104),X,Y,NO1

      INTEGER I, J, N, N1, K, C, TO1

      SUM=0.0D0
      VAR=0.0D0
      N1=N/2000
      K=0

      DO 1000 C=1,32

      DO 10 I=1, N1
      CALL URAN2(R,SEED2,2000,C)
      CALL URAN3(S,SEED3,2000,C)

      DO 20 J=1,2000

      X=XM(C)*R(J)+ XA(C)
```

```
      Y=YM(C)*S(J)+ YA(C)

      LTEMP1= 2*LOG(ABS(Y-AVGY))-2*NO1*LOG(X)-((NO1+1)*LOG(Y))
     +       + V1(X,A1,MO1) + V2(X,Y,A2,MO2)

        LT1=(X*T1)+((1/2)*A1*S1)
        LT2= (X*Y*T2)+((1/2)*A2*S2)
        LT3= (TO1/X)*(1+(1/Y))
      ltemp2=-(LT1+LT2+LT3)
      LTEMP=0.001*(LTEMP1+LTEMP2)

      K=K+1
      TEMP=DEXP(LTEMP)
      IF (K .EQ. 1) then
       SUM=TEMP
       goto 20
       end if
       SUM=SUM+((TEMP-SUM)/DFLOAT(K))
       VAR=VAR+(K-1)*(TEMP-SUM)*((TEMP-SUM)/DFLOAT(K))
   20  CONTINUE

      IF (I .EQ. N1) G(C)=XM(C)*YM(C)*SUM
      IF (I .EQ. N1) VG(C)=VAR/DFLOAT(K-1)
   10  CONTINUE
 1000  CONTINUE
      RETURN
      END
C
C     Computing the Integral
C
      FUNCTION ANSD(G)
      DOUBLE PRECISION DEN, G(32)
      INTEGER B

      DEN=0.0D0
      VDEN=0.0D0
      DO 3000 B=1,32
      DEN=DEN+G(B)
 3000  CONTINUE
      ANSD=DEN
      END
C
C     Computing the Observations: Summed & Squared Summed
C     for Treatment A/1
C
      FUNCTION V1(X,A1,MO1)
```

```
      DOUBLE PRECISION X,A1,MO1(104)
      INTEGER I

       PV1=0.0D0
       DO 650 I=1,104
       PV1=PV1+ LOG((X+(A1*MO1(I))))
 650  CONTINUE
      V1=PV1
      END
C
C   Computing the Observations: Summed & Squared Summed
C   for Treatment B/2
C
      FUNCTION V2(X,Y,A2,MO2)
      DOUBLE PRECISION X,Y,A2,MO2(104)
      INTEGER I
      PV2=0.0D0
       DO 550 I=1,104
        PV2=PV2+LOG(((X*Y)+(A2*MO2(I))))
 550  CONTINUE
      V2=PV2
      END
C
C     Generation of Random Variables for 1st Dimension
C
      SUBROUTINE URAN2 (R, SEED2, N, C)
      DOUBLE PRECISION R(2000),SEED2(32),A,B,SCALE,M

      INTEGER I, N, C

      A=950706376.0D0
      M=2147483647.0D0
      SCALE=65536.0D0
      B=550007125.0D0

      DO 200 I=1,N
      SEED2(C)=B*DINT(SEED2(C)/SCALE)+A*DMOD(SEED2(C),SCALE)
      SEED2(C)=DMOD(SEED2(C),M)
      R(I)=SEED2(C)/M

 200  CONTINUE
      RETURN
      END
```

```
C
C     Generation of Random Variables for the 2nd Dimension
C
      SUBROUTINE URAN3 (R, SEED3, N, C)
      DOUBLE PRECISION R(2000),SEED3(32),A,B,SCALE,M

      INTEGER I, N, C

      A=950706376.0D0
      M=2147483647.0D0
      SCALE=65536.0D0
      B=550007125.0D0

      DO 200 I=1,N
      SEED3(C)=B*DINT(SEED3(C)/SCALE)+A*DMOD(SEED3(C),SCALE)
      SEED3(C)=DMOD(SEED3(C),M)
      R(I)=SEED3(C)/M
200   CONTINUE
      RETURN
      END
```

APPENDIX M

LIKELIHOOD RATIO STATISTIC COMPONENTS DERIVATION, LINEAR-EXPONENTIAL--NONSCALE PARAMETER

The derivation of the function in eqs. 4.4.4, 4.4.5, and 4.4.6 may proceed in the following manner:

for eq. 4.4.4,

$$L(\hat{\gamma}\ ,\hat{\gamma}\ |\lambda_j) = L(\hat{\gamma}\ |\lambda_j)L(\hat{\gamma}\ |\lambda_j) \tag{M.1}$$

but from Appendix D,

$$L(\hat{\gamma}_h|\lambda_j^*) = \left[\prod_{i=1}^{r}\left(\lambda_j^* + \hat{\gamma}_h^* t_i\right)\right] e^{-\left(\lambda_j^* - \frac{1}{2}\hat{\gamma}_h S\right)} \tag{M.2}$$

where $T = \sum_{i=1}^{r} t_i + \sum_{k=r+1}^{n} t_k'$ and $S = \sum_{i=1}^{r} t_i^2 + \sum_{k=r+1}^{n} (t_k')^2$;

hence, continuing from eq. M.1,

$$= \left[\prod_{i=1}^{r_1}\left(\lambda_j^* + \hat{\gamma}_1 t_i\right)\right] e^{-\left(\lambda_j^* - \frac{1}{2}\hat{\gamma}_1 S_1\right)} \left[\prod_{i=1}^{r_2}\left(\lambda_j^* + \hat{\gamma}_2 t_i\right)\right] e^{-\left(\lambda_j^* T_2 - \frac{1}{2}\hat{\gamma}_2 S_2\right)}. \tag{M.3}$$

Thus,

$$L(\hat{\gamma}_1,\hat{\gamma}_2|\lambda_j^*) = \left|\prod_{i=1}^{r_1}\left(\lambda_j^* + \hat{\gamma}_1 t_i\right)\right| \left|\prod_{i=1}^{r_2}\left(\lambda_j^* + \hat{\gamma}_2 t_i\right)\right| e^{-\left[\lambda_j^*(T_1 - T_2) - \frac{1}{2}(\hat{\gamma}_1 S_1 + \hat{\gamma}_2 S_2)\right]}. \tag{M.4}$$

Now for eq. 4.4.5,

$$L(\hat{\gamma},\hat{\gamma}\,|\lambda_j) = L(\hat{\gamma}\ =\hat{\gamma}\,|\lambda_j)L(\hat{\gamma}\ =\hat{\gamma}\,|\lambda_j) \tag{M.5}$$

from eq. M.2,

$$= \left[\prod_{i=1}^{r_1}\left(\lambda_j^* + \hat{\gamma} t_i\right)\right] e^{-\left(\lambda_j^* T_1 - \frac{1}{2}\hat{\gamma} S_1\right)} \left[\prod_{i=1}^{r_2}\left(\lambda_j^* + \hat{\gamma} t_i\right)\right] e^{-\left(\lambda_j^* T_2 - \frac{1}{2}\hat{\gamma} S_2\right)}. \tag{M.6}$$

Therefore,

$$L(\hat{\gamma},\hat{\gamma}\,|\lambda_j^*) = \left[\prod_{i=1}^{r_1}\left(\lambda_j^* + \hat{\gamma} t_i\right)\right]\left[\prod_{i=1}^{r_2}\left(\lambda_j^* + \hat{\gamma} t_i\right)\right] e^{-\left(\lambda_j^*(T_1 - T_2) - \frac{1}{2}\hat{\gamma}(S_1 - S_2)\right)}. \tag{M.7}$$

Regarding eq. 4.4.6, to compute λ_j^* (where $\lambda_j^* = E(\lambda_j)$) one would obtain the posterior distribution for λ_j. From Appendix D, the likelihood for $L(\lambda,\gamma)$ can be written in the following manner:

$$L(\lambda,\gamma) = \left|\prod_{i=1}^{r}(\lambda+\gamma t_i)\right| e^{-\left(\lambda T-\frac{1}{2}\gamma S\right)} \tag{M.8}$$

but one may condition the likelihood on a particular value for γ, say $\hat{\gamma}$, hence,

$$L(\lambda\,|\,\hat{\gamma}) = \left|\prod_{i=1}^{r}(\lambda+\hat{\gamma} t_i)\right| e^{-\left(\lambda T-\frac{1}{2}\hat{\gamma} S\right)}. \tag{M.9}$$

An $I\gamma_1$ prior distribution is assumed for λ. The $I\gamma_1$ density is written as

$$p_1(\lambda\,|\,n_o,t_o) = \frac{t_o^{\,n_o}}{\Gamma(n_o)}\left(\frac{1}{\lambda}\right)^{n_o+1} e^{-\frac{t_o}{\lambda}}. \tag{M.10}$$

Consequently, the posterior density for

$$p_2(\lambda\,|\,\hat{\gamma},n_o,t_o) = \frac{L(\lambda|\hat{\gamma})p_1(\lambda|n_o,t_o)}{\int_o^{\infty} L(\lambda|\hat{\gamma})p_1(\lambda|n_o,t_o)d\lambda} =$$

$$= \frac{\left[\prod_{i=1}^{r}(\lambda+\hat{\gamma} t_i)\right]\frac{t_o^{\,n_o}}{\Gamma(n_o)}\left(\frac{1}{\lambda}\right)^{n_o+1} e^{-\left(\lambda T-\frac{t_o}{\lambda}-\frac{1}{2}\hat{\gamma} S\right)}}{\int_0^{\infty}\left[\prod_{i=1}^{r}(\lambda+\hat{\gamma} t_i)\right]\frac{t_o^{\,n_o}}{\Gamma(n_o)}\left(\frac{1}{\lambda}\right)^{n_o+1} e^{-\left(\lambda T-\frac{t_o}{\lambda}-\frac{1}{2}\hat{\gamma} S\right)}d\lambda}. \tag{M.11}$$

For distingushing between samples purposes, eq. M.11 is written as

$$p_2(\lambda_j|\hat{\gamma},n_o,t_o)=\frac{\left[\prod_{i=1}^{r_j}(\lambda_j+\hat{\gamma}t_i)\right]\frac{t_o^{n_o}}{\Gamma(n_o)}\left(\frac{1}{\lambda_j}\right)^{n_o-1}e^{-\left(\lambda_j T-\frac{t_o}{\lambda_j}-\frac{1}{2}\hat{\gamma}S\right)}}{\int_0^{\infty}\left[\prod_{i=1}^{r_j}(\lambda_j+\hat{\gamma}t_i)\right]\frac{t_o^{n_o}}{\Gamma(n_o)}\left(\frac{1}{\lambda_j}\right)^{n_o-1}e^{-\left(\lambda_j T-\frac{t_o}{\lambda_j}-\frac{1}{2}\hat{\gamma}S\right)}d\lambda_j}. \quad \text{(M.12)}$$

Now, λ_j^* is the following:

$$\lambda_j^*=E(\lambda_j)=\int_o^{\infty}\lambda_j p_2(\lambda_j|\hat{\gamma},n_o,t_o)d\lambda_j=$$

$$=\frac{\int_0^{\infty}\lambda_j\left[\prod_{i=1}^{r_j}(\lambda_j+\hat{\gamma}t_i)\right]\frac{t_o^{n_o}}{\Gamma(n_o)}\left(\frac{1}{\lambda_j}\right)^{n_o-1}e^{-\left(\lambda_j T-\frac{t_o}{\lambda_j}-\frac{1}{2}\hat{\gamma}S\right)}d\lambda_j}{\int_0^{\infty}\left[\prod_{i=1}^{r_j}(\lambda_j+\hat{\gamma}t_i)\right]\frac{t_o^{n_o}}{\Gamma(n_o)}\left(\frac{1}{\lambda_j}\right)^{n_o-1}e^{-\left(\lambda_j T-\frac{t_o}{\lambda_j}-\frac{1}{2}\hat{\gamma}S\right)}d\lambda_j}. \quad \text{(M.13)}$$

APPENDIX N

PROOF OF $E(\hat{\eta}) \overset{d}{\rightarrow} Y \sim N(\mu,\sigma^2)$, WEIBULL

The intent is to show that, $E(\hat{\eta}) \xrightarrow{d} Y \sim N(\mu, \sigma^2)$. The proof begins in the following way, that is, showing that $E(\eta^2) < \infty$. This is done by the use of a constructive proof (i.e., show that the object exists or produce the object).

Since it is desirable to show that $E(\eta) < \infty$, the following is stated:

$$\lim_{n\to\infty} E(\eta^2) = \lim_{n\to\infty} \frac{\int_0^\infty \int_0^\infty \eta^2 g(\eta,\xi)\, d\xi d\eta}{\int_0^\infty \int_0^\infty g(\eta,\xi) d\xi d\eta} = \infty \ . \tag{P.1}$$

If $\lim_{n\to\infty} E(\eta^2) = \infty$, then this may occur in two ways, that is,

$$\lim_{n\to\infty} \int_0^\infty \int_0^\infty \eta^2 g(\eta,\xi) d\xi d\eta = \infty \ , \tag{P.2}$$

while

$$\lim_{n\to\infty} \int_0^\infty \int_0^\infty g(\eta,\xi) d\xi d\eta = C \ , \tag{P.3}$$

where C is some constant. This is denoted as Case 1. The second way is

$$\lim_{n\to\infty} \int_0^\infty \int_0^\infty g(\eta,\xi) d\xi d\eta = 0 \tag{P.4}$$

while

$$\lim_{n\to\infty} \int_0^\infty \int_0^\infty \eta^2 g(\eta,\xi) d\xi d\eta = C \ , \tag{P.5}$$

where, again, C is some constant. This is denoted as Case 2.

Now one can proceed by showing that Case 1 and Case 2 are not true. For the Weibull model

$$g(\eta,\xi,D,\hat{\gamma}_1,\hat{\gamma}_2) = \left(\frac{t_o^{n_o}}{\Gamma(n_o)}\right)^2 \left(\prod_{i=1}^{r_1} t_i^{\hat{\gamma}_1-1}\right)\left(\prod_{i=1}^{r_2} t_i^{\hat{\gamma}_2-1}\right) \hat{\gamma}_1^{r_1}\hat{\gamma}_2^{r_2}\,\xi^{\hat{\gamma}_1 r_1+\hat{\gamma}_2 r_2-2n_o}\,\eta^{\hat{\gamma}_2 r_2-n_o-1} \times e^{-\left(\xi^{\hat{\gamma}_1}\left[\sum_{i=1}^{r_1} t_i^{\hat{\gamma}_1}+\sum_{k=r_1+1}^{n_1}(t_k')^{\hat{\gamma}_1}\right]+(\xi\eta)^{\hat{\gamma}_2}\left[\sum_{i=1}^{r_2} t_i^{\hat{\gamma}_2}+\sum_{k=r_2+1}^{n_2}(t_k')^{\hat{\gamma}_2}\right]+\frac{t_o}{\xi}\left(1+\frac{1}{\eta}\right)\right)} \quad \text{(P.6)}$$

But because $\left(\frac{t_o^{n_o}}{\Gamma(n_o)}\right)^2 \left(\prod_{i=1}^{r_1} t_i^{\hat{\gamma}_1-1}\right)\left(\prod_{i=1}^{r_2} t_i^{\hat{\gamma}_2-1}\right) \hat{\gamma}_1^{r_1}\hat{\gamma}_2^{r_2}$ is a constant and is present in the numerator and denominator, it cancels. Now, letting $T_1 = \sum_{i=1}^{r_1} t_i^{\hat{\gamma}_1} + \sum_{k=r_1+1}^{n_1} (t_k')^{\hat{\gamma}_1}$ and $T_2 = \sum_{i=1}^{r_2} t_i^{\hat{\gamma}_2} + \sum_{k=r_2+1}^{n_2} (t_k')^{\hat{\gamma}_2}$, for the evaluation of Case 1 and Case 2 $g(\eta,\xi,D,\hat{\gamma}_1,\hat{\gamma}_2)$ becomes $g^*(\eta,\xi,D,\hat{\gamma}_1,\hat{\gamma}_2)$, where

$$g^*(\eta,\xi,D,\hat{\gamma}_1,\hat{\gamma}_2) = \xi^{\hat{\gamma}_1 r_1+\hat{\gamma}_2 r_2-2n_o}\,\eta^{\hat{\gamma}_2 r_2-n_o-1}\, e^{-(\xi^{\hat{\gamma}_1}T_1+(\xi\eta)^{\hat{\gamma}_2}T_2+\frac{t_o}{\xi}(1+\frac{1}{\eta}))} \quad \text{(P.7)}$$

Thus, for Case 1, it follows

$$\lim_{n\to\infty}\int_0^{\infty}\int_0^{\infty}\eta^2 g^*(\eta,\xi,D,\hat{\gamma}_1,\hat{\gamma}_2)\,d\xi\,d\eta = \int_0^{\infty}\int_0^{\infty}\eta^2\,\xi^{\hat{\gamma}_1 r_1+\hat{\gamma}_2 r_2-2n_o}\,\eta^{\hat{\gamma}_2 r_2-n_o-1} \times e^{-\left(\xi^{\hat{\gamma}_1}T_1+(\xi\eta)^{\hat{\gamma}_2}T_2+\frac{t_o}{\xi}\left(1+\frac{1}{\eta}\right)\right)}d\xi\,d\eta \quad \text{(P.8)}$$

$$= \lim_{n\to\infty}\int_{\infty}\int_{\infty}\xi^{\hat{\gamma}_1 r_1+\hat{\gamma}_2 r_2-2n_o}\,\eta^{\hat{\gamma}_2 r_2-n_o-1}\, e^{-\left(\xi^{\hat{\gamma}_1}T_1+\xi^{\hat{\gamma}_2}\eta^{\hat{\gamma}_2}T_2+\frac{t_o}{\xi}\left(1+\frac{1}{\eta}\right)\right)}d\xi\,d\eta .$$

Because of the improper nature of the integral of the inner most integral, eq. P.8 is written in the following manner:

$$= \lim_{n\to\infty}\left[\int_0^{\infty}\left\{\lim_{b\to\infty}\int_0^{b}\xi^{\hat{\gamma}_1 r_1-\hat{\gamma}_2 r_2-2n_o}\eta^{\hat{\gamma}_2 r_2-n_o-1}e^{-\left(\xi^{\hat{\gamma}_1}T_1+\xi^{\hat{\gamma}_2}\eta^{\hat{\gamma}_2}T_2-\frac{t_o}{\xi}\left(1-\frac{1}{\eta}\right)\right)}d\xi\right\}d\eta\right]. \qquad \text{(P.9)}$$

Now, integrating the inner most integral of eq. P.9, it follows

$$= \lim_{n\to\infty}\left[\int_0^{\infty}\lim_{b\to\infty}\left(\frac{\xi^{\hat{\gamma}_1 r_1-\hat{\gamma}_2 r_2-2n_o}\eta^{\hat{\gamma}_2 r_2-n_o-1}e^{-\left(\xi^{\hat{\gamma}_1}T_1+\xi^{\hat{\gamma}_2}\eta^{\hat{\gamma}_2}T_2-\frac{t_o}{\xi}\left(1-\frac{1}{\eta}\right)\right)}}{\frac{(\hat{\gamma}_1 r_1+\hat{\gamma}_2 r_2-n_o)}{\xi}-\left\{\hat{\gamma}_1\xi^{\hat{\gamma}_1-1}T_1+\hat{\gamma}_2\xi^{\hat{\gamma}_2-1}\eta^{\hat{\gamma}_2}T_2-\frac{t_o}{\xi}\left(1+\frac{1}{\eta}\right)\right\}}\right)\Bigg|_0^{b}d\eta\right]. \qquad \text{(P.10)}$$

Now, evaluating the inner most integral at 0 and b, eq. P.10 becomes

$$= \lim_{n\to\infty}\left[\int_0^{\infty}\lim_{b\to\infty}\left(\frac{b^{\hat{\gamma}_1 r_1-\hat{\gamma}_2 r_2-2n_o}\eta^{\hat{\gamma}_2 r_2-n_o-1}e^{-\left(b^{\hat{\gamma}_1}T_1+b^{\hat{\gamma}_2}\eta^{\hat{\gamma}_2}T_2-\frac{t_o}{b}\left(1-\frac{1}{\eta}\right)\right)}}{\frac{(\hat{\gamma}_1 r_1+\hat{\gamma}_2 r_2-n_o)}{b}-\left\{\hat{\gamma}_1 b^{\hat{\gamma}_1-1}T_1+\hat{\gamma}_2 b^{\hat{\gamma}_2-1}\eta^{\hat{\gamma}_2}T_2-\frac{t_o}{b}\left(1+\frac{1}{\eta}\right)\right\}}\right)d\eta\right]. \qquad \text{(P.11)}$$

Hence, when evaluating eq. P.11 as b approaches ∞, then the integral $\int_{0^{\infty}}^{b}\eta^2 g^{*}(\cdot)d\xi \to 0$. Letting b be the point at which the *l.u.b.* (least upper bound) of the $\lim_{n\to\infty}\int_0^{\infty}\eta^2 g(\cdot)d\xi$ is obtained. Consequently, it follows that eq. P.11 then becomes,

$$= \lim_{n\to\infty}\left[\int_0^{\infty}\frac{b^{\hat{\gamma}_1 r_1-\hat{\gamma}_2 r_2-2n_o}\eta^{\hat{\gamma}_2 r_2-n_o-1}e^{-\left(b^{\hat{\gamma}_1}T_1+b^{\hat{\gamma}_2}\eta^{\hat{\gamma}_2}T_2-\frac{t_o}{b}\left(1-\frac{1}{\eta}\right)\right)}}{\frac{(\hat{\gamma}_1 r_1+\hat{\gamma}_2 r_2-n_o)}{b}-\left\{\hat{\gamma}_1 b^{\hat{\gamma}_1-1}T_1+\hat{\gamma}_2 b^{\hat{\gamma}_2-1}\eta^{\hat{\gamma}_2}T_2-\frac{t_o}{b}\left(1+\frac{1}{\eta}\right)\right\}}d\eta\right]. \qquad \text{(P.12)}$$

Now, let us rewrite eq. P.12 as

$$= \lim_{n\to\infty}\left[\int_0^m \frac{b^{\hat{\gamma}_1 r_1+\hat{\gamma}_2 r_2-2n_o}\,\eta^{\hat{\gamma}_2 r_2-n_o-1}\,e^{-\left(b^{\hat{\gamma}_1}T_1-b^{\hat{\gamma}_2}\eta^{\hat{\gamma}_2}T_2-\frac{t_o}{b}\left(1-\frac{1}{\eta}\right)\right)}}{\frac{(\hat{\gamma}_1 r_1+\hat{\gamma}_2 r_2-n_o)}{b}-\left\{\hat{\gamma}_1 b^{\hat{\gamma}_1-1}T_1+\hat{\gamma}_2 b^{\hat{\gamma}_2-1}\eta^{\hat{\gamma}_2}T_2-\frac{t_o}{b}\left(1+\frac{1}{\eta}\right)\right\}}\,d\eta\right] \tag{P.13}$$

$$+\lim_{n\to\infty}\left[\lim_{x\to\infty}\int_m^x \frac{b^{\hat{\gamma}_1 r_1+\hat{\gamma}_2 r_2-2n_o}\,\eta^{\hat{\gamma}_2 r_2-n_o-1}\,e^{-\left(b^{\hat{\gamma}_1}T_1-b^{\hat{\gamma}_2}\eta^{\hat{\gamma}_2}T_2-\frac{t_o}{b}\left(1-\frac{1}{\eta}\right)\right)}}{\frac{(\hat{\gamma}_1 r_1+\hat{\gamma}_2 r_2-n_o)}{b}-\left\{\hat{\gamma}_1 b^{\hat{\gamma}_1-1}T_1+\hat{\gamma}_2 b^{\hat{\gamma}_2-1}\eta^{\hat{\gamma}_2}T_2-\frac{t_o}{b}\left(1+\frac{1}{\eta}\right)\right\}}\,d\eta\right].$$

because

$$\lim_{n\to\infty}\left[\int_0^m \frac{b^{\hat{\gamma}_1 r_1+\hat{\gamma}_2 r_2-2n_o}\,\eta^{\hat{\gamma}_2 r_2-n_o-1}\,e^{-\left(b^{\hat{\gamma}_1}T_1-b^{\hat{\gamma}_2}\eta^{\hat{\gamma}_2}T_2-\frac{t_o}{b}\left(1-\frac{1}{\eta}\right)\right)}}{\frac{(\hat{\gamma}_1 r_1+\hat{\gamma}_2 r_2-n_o)}{b}-\left\{\hat{\gamma}_1 b^{\hat{\gamma}_1-1}T_1+\hat{\gamma}_2 b^{\hat{\gamma}_2-1}\eta^{\hat{\gamma}_2}T_2-\frac{t_o}{b}\left(1+\frac{1}{\eta}\right)\right\}}\,d\eta\right] \tag{P.14}$$

is a regular integral representing the area under the curve and as $n\to\infty$ then $T_1, T_2\to\infty$, subsequently, the integrand of eq. P.14 approaches zero. Therefore, eq. P.14 is bounded.

Now, focusing on

$$\lim_{n\to\infty}\left[\lim_{x\to\infty}\int_m^x \frac{b^{\hat{\gamma}_1 r_1-\hat{\gamma}_2 r_2-2n_o}\,\eta^{\hat{\gamma}_2 r_2-n_o-1}\,e^{-\left(b^{\hat{\gamma}_1}T_1-b^{\hat{\gamma}_2}\eta^{\hat{\gamma}_2}T_2-\frac{t_o}{b}\left(1-\frac{1}{\eta}\right)\right)}}{\frac{(\hat{\gamma}_1 r_1+\hat{\gamma}_2 r_2-n_o)}{b}-\left\{\hat{\gamma}_1 b^{\hat{\gamma}_1-1}T_1+\hat{\gamma}_2 b^{\hat{\gamma}_2-1}\eta^{\hat{\gamma}_2}T_2-\frac{t_o}{b}\left(1+\frac{1}{\eta}\right)\right\}}\,d\eta\right] \tag{P.15}$$

it is obvious that

$$\frac{e^{-\left(b^{\hat{\gamma}_2}\eta^{\hat{\gamma}_2}T_2-\frac{t_o}{b}\left(1-\frac{1}{\eta}\right)\right)}}{\frac{(\hat{\gamma}_1 r_1+\hat{\gamma}_2 r_2-n_o)}{b}-\left\{\hat{\gamma}_1 b^{\hat{\gamma}_1-1}T_1+\hat{\gamma}_2 b^{\hat{\gamma}_2-1}\eta^{\hat{\gamma}_2}T_2-\frac{t_o}{b}\left(1+\frac{1}{\eta}\right)\right\}} \tag{P.16}$$

decreases faster than η^{-k}, for $k > 0$. Hence, without loss of generality, one can assume m is a point, such that, for all values of $\eta > m$, then eq. P.16 $< \eta^{-k}$. Thus,

$$0 < \int_m^x \frac{b^{\hat{\gamma}_1 r_1 - \hat{\gamma}_2 r_2 - 2n_o} \eta^{\hat{\gamma}_2 r_2 - n_o - 1} e^{-\left(b^{\hat{\gamma}_1} T_1 - b^{\hat{\gamma}_2} \eta^{\hat{\gamma}_2} T_2 - \frac{t_o}{b}\left(1 - \frac{1}{\eta}\right)\right)}}{\frac{(\hat{\gamma}_1 r_1 + \hat{\gamma}_2 r_2 - n_o)}{b} - \left\{\hat{\gamma}_1 b^{\hat{\gamma}_1 - 1} T_1 + \hat{\gamma}_2 b^{\hat{\gamma}_2 - 1} \eta^{\hat{\gamma}_2} T_2 - \frac{t_o}{b}\left(1 + \frac{1}{\eta}\right)\right\}} d\eta \qquad \text{(P.17)}$$

$$< \int_m^x \eta^{\hat{\gamma}_2 r_2 - n_o - 1} \eta^{-k} d\eta \ .$$

If $k = \hat{\gamma}_2 r_2 - n_o + 3$, then the second integral of eq. P.17 becomes

$$\int_m^x \eta^{\hat{\gamma}_2 r_2 - n_o - 1} \eta^{-\hat{\gamma}_2 r_2 - n_o - 3} d\eta = \int_m^x \eta^{-2} d\eta = \frac{1}{\eta}\Big|_x^m = \frac{1}{m} - \frac{1}{x} \ . \qquad \text{(P.18)}$$

But as $x \to \infty$, the limit of eq. P.18 is $\frac{1}{m}$. Thus,

$$\int_0^\infty \frac{b^{\hat{\gamma}_1 r_1 - \hat{\gamma}_2 r_2 - 2n_o} \eta^{\hat{\gamma}_2 r_2 - n_o - 1} e^{-\left(b^{\hat{\gamma}_1} T_1 - b^{\hat{\gamma}_2} \eta^{\hat{\gamma}_2} T_2 - \frac{t_o}{b}\left(1 - \frac{1}{\eta}\right)\right)}}{\frac{(\hat{\gamma}_1 r_1 + \hat{\gamma}_2 r_2 - n_o)}{b} - \left\{\hat{\gamma}_1 b^{\hat{\gamma}_1 - 1} T_1 + \hat{\gamma}_2 b^{\hat{\gamma}_2 - 1} \eta^{\hat{\gamma}_2} T_2 - \frac{t_o}{b}\left(1 + \frac{1}{\eta}\right)\right\}} d\eta$$

$$= \lim_{x \to \infty} \int_0^m \frac{b^{\hat{\gamma}_1 r_1 - \hat{\gamma}_2 r_2 - 2n_o} \eta^{\hat{\gamma}_2 r_2 - n_o - 1} e^{-\left(b^{\hat{\gamma}_1} T_1 - b^{\hat{\gamma}_2} \eta^{\hat{\gamma}_2} T_2 - \frac{t_o}{b}\left(1 - \frac{1}{\eta}\right)\right)}}{\frac{(\hat{\gamma}_1 r_1 + \hat{\gamma}_2 r_2 - n_o)}{b} - \left\{\hat{\gamma}_1 b^{\hat{\gamma}_1 - 1} T_1 + \hat{\gamma}_2 b^{\hat{\gamma}_2 - 1} \eta^{\hat{\gamma}_2} T_2 - \frac{t_o}{b}\left(1 + \frac{1}{\eta}\right)\right\}} d\eta \qquad \text{(P.19)}$$

$$< \frac{1}{m} \ .$$

Futhermore, as $n \to \infty$, then $T_1, T_2 \to \infty$, and the integrand of eq. P.19 approaches zero. But this contradicts eq. P.1 for Case 1. Therefore, the $\lim_{n \to \infty} E(\eta) < \infty$ by contradiction for Case 1.

For Case 2 of the Weibull model, there is a theorem (Trench 1978, p. 161) which states that

> If f in nonnegative and locally integrable on $[a,b)$, then $\int_a^b f(x)dx$ converges if the function $F(x) = \int_a^x f(t)dt$ is bounded on $[a,b)$ and $\int_a^b f(x)dx = \infty$ if it is not. These are the only possbilities and in either case $\int_a^b f(t)dt = \underset{a \le x < b}{l.u.b.}\ F(x)$.

As a result, this contradicts Case 2 of $\lim_{n\to\infty} E(\eta^2)$ for eq. P.4 and eq. P.5. Therefore, the $\lim_{n\to\infty} E(\eta^2) < \infty$ for Case 2.

Thus , since it has been proved that the $\lim_{n\to\infty} E(\eta^2) < \infty$, then by part (a) of the Theorem 6.9 from Arnold (1990, p. 243), which states

> Let $X_1, X_2,\ldots$ be a sequence of independently identically distributed random variables with $EX_i = \mu$. Let $\bar{X}_n$ and S_n^2 respectively be the sample mean and sample variance computed from n of the X_i. Let
>
> $$t_n = \frac{n^{\frac{1}{2}}(\bar{X}_n - \mu)}{S}.$$
>
> a) If $\sigma^2 = var(X_i) < \infty$, then
>
> $$S_n^2 \xrightarrow{P} \sigma^2, \qquad S_n \xrightarrow{P} \sigma, \qquad t_n \xrightarrow{d} Z \sim N(0,1).$$
>
> b) Suppose that $\gamma = \frac{E(X-\mu)^4}{\sigma^4} < \infty$. Then
>
> $$n(S_n^2 - \sigma^2) \xrightarrow{d} W \sim N(0,(\gamma - 1)\sigma^4).$$

$E(\eta) \sim N(\mu, S_n^2)$, since if $Z \sim N(0,1)$, where $Z = \frac{n(\bar{X}_n - \mu)}{S_n}$, one can derive the distribution of $\bar{X}_n$ as

$$\bar{X}_n = \frac{ZS_n}{n} + \mu$$

$$h(\bar{X}_n) = \frac{n(\bar{X}_n - \mu)}{S_n}$$

$$h'(\bar{X}_n) = \frac{n}{S_n}$$

$$f_{\bar{X}_n}(\bar{X}_n) = f_Z(h(\bar{X}_n)) = \frac{n^{\frac{1}{2}}}{\sqrt{2\pi S_n^2}} e^{-\frac{n(\bar{X}_n - \mu)^2}{2S_n^2}}.$$

A similar proof can be constructed for the linear-exponential model.

APPENDIX O

THOMAN AND BAIN, SHAPE PARAMETER EQUALITY

The Thoman and Bain method for testing the equality of the shape parameters from two independent Weibull densities is based on the maximum likelihood estimator property that $\frac{\hat{\gamma}}{\gamma}$ (where $\hat{\gamma}$ is the maximum likelihood estimator of γ) has the same distribution as $\hat{\gamma}^*$, where $\hat{\gamma}^*$ is the maximum likelihood estimator of γ based on a sample from a standard Weibull distribution. Consequently, $\frac{\hat{\gamma}_1}{\gamma_1} \div \frac{\hat{\gamma}_2}{\gamma_2}$ is distributed as $\frac{\hat{\gamma}_1^*}{\hat{\gamma}_2^*}$ where $\hat{\gamma}_1^*$ and $\hat{\gamma}_2^*$ are the maximum likelihood estimators of $\hat{\gamma}_1$ and $\hat{\gamma}_2$, respectively shape parameters, from two independent random samples from the standard Weibull distribution. Thoman and Bain obtained the percentage points of the distribution of $\frac{\hat{\gamma}_1^*}{\hat{\gamma}_2^*}$ by Monte Carlo methods. They computed and tabled the percentage points of l_α such that $P\left[\frac{\hat{\gamma}_1^*}{\hat{\gamma}_2^*} < l_\alpha\right] = \alpha$ as a function of α and a common sample size N.

To test H_0: $\gamma_1 = \gamma_2$ versus H_1: $\gamma_1 = k\gamma_2$ where $k > 1$, Thoman and Bain use the fact that under H_0, $\frac{\hat{\gamma}_1}{\hat{\gamma}_2}$ has the same distribution as $\frac{\hat{\gamma}_1^*}{\hat{\gamma}_2^*}$, i.e., $P\left[\frac{\hat{\gamma}_1}{\hat{\gamma}_2} > l_{1-\alpha} \mid H_0\right] = \alpha$ and a size α test is given by rejecting H_0 if $\frac{\hat{\gamma}_1}{\hat{\gamma}_2} > l_{1-\alpha}$ where $l_{1-\alpha}$ can be obtained from the tabled percentage points. Percentage points for $l_{1-\alpha}$ where $\alpha < 0.50$ can be found by using the fact that $l_\alpha = \frac{1}{l_{1-\alpha}}$. In closing, Thoman and Bain method can be generalized to test H_0: $\gamma_1 = k\gamma_2$ versus H_1: $\gamma_1 = k'\gamma_2$.

APPENDIX P

JOINT ASYMPTOTIC DENSITY OF THE CREDIBILITY LIMITS

In Appendix N, it was shown that $E(\hat{\eta}\,|D) \xrightarrow{d} Y \sim N\left(\mu, \frac{\sigma^2}{n}\right)$ as $n \to \infty$.

Suppose a researcher is interested in computing probabilistic statement such as, $P\left[\left(R_L^{1-\alpha}, R_U^{1-\alpha}\right) \subset (1-\Delta, 1+\Delta)\right]$; then such a computation requires knowledge of the joint of $\left(R_L^{1-\alpha}, R_U^{1-\alpha}\right)$.

To derive the distribution of $\left(R_L^{1-\alpha}, R_U^{1-\alpha}\right)$, let us begin by rewriting $\left(R_L^{1-\alpha}, R_U^{1-\alpha}\right)$ as (L,U) for simplicity. Before proceeding to derive joint of (L,U) it is necessary show that, given a researcher has a random variable, say X, that is distributed as $N(\mu,\sigma^2)$, then the distribution of a random variable $V = X + c$, where c is a constant, is $N(\mu+c, \sigma^2)$. Now this can be shown in the following way:

$$v = x + c \;\Rightarrow\; x = v + c \tag{P.1}$$

hence, $h(v) = v - c \;\rightarrow\; h'(v) = 1$. Thus,

$$\begin{aligned} f_I(v) &= f_X(v-c)\,|h'(v)| = \\ &= \frac{1}{\sqrt{2\pi}\sigma} e^{-\frac{1}{2}\frac{[(v-c)-\mu]^2}{\sigma^2}} |1| \\ &= \frac{1}{\sqrt{2\pi}\sigma} e^{-\frac{1}{2}\frac{[v-(\mu-c)]^2}{\sigma^2}} . \end{aligned} \tag{P.2}$$

Similarly, it can be illustrated to show that $W = X + c$ is distributed as $N(\mu - c, \sigma^2)$. Subsquently, it follows that

$$L \sim N(\hat{\mu} - c, \sigma_{\hat{\mu}}^2) \tag{P.3}$$

and

$$U \sim N(\hat{\mu} + c, \sigma_{\hat{\mu}}^2) \tag{P.4}$$

where $\hat{\mu} = E(\hat{\eta})$, $c = z_{1-\alpha}\hat{\sigma}_{E(\hat{\eta})}$, and $\hat{\sigma}_{\hat{\mu}}^2 = \hat{\sigma}_{E(\hat{\eta})}^2$. Hence, by definition, it follows that

$$L = E(\hat{\eta}) - z_{1-\alpha}\hat{\sigma}_{E(\eta)} \tag{P.5}$$

then rewriting in terms of $E(\hat{\eta})$,

$$E(\hat{\eta}) = L + z_{1-\alpha}\hat{\sigma}_E(\hat{\eta}) \ . \tag{P.6}$$

Thus,

$$U|L \sim N\left(L + 2z_{1-\alpha}\hat{\sigma}_{E(\eta)},\ \hat{\sigma}^2_{E(\hat{\eta})}\right) \tag{P.7}$$

and continuing by definition,

$$f_{U|L}(u|l) = \frac{f(u,l)}{f(l)} \ . \tag{P.8}$$

Note that

$$f(l) = \frac{1}{\hat{\sigma}_{E(\eta)}\sqrt{2\pi}} e^{-\frac{1}{2}\frac{[l-(E(\hat{\eta})-z_{1-\alpha}\hat{\sigma}_{E(\eta)})]^2}{\hat{\sigma}^2_{E(\eta)}}} \tag{P.9}$$

where $-\infty < l < \infty$, $\hat{\sigma}^2_{E(\hat{\eta})} > 0$, and $-\infty < E(\hat{\eta}) - z_{1-\alpha}\hat{\sigma}_{E(\hat{\eta})} < \infty$, and

$$\begin{aligned} f_{U|L}(u|l) &= \frac{1}{\hat{\sigma}_{E(\hat{\eta})}\sqrt{2\pi}} e^{-\frac{1}{2}\frac{[u-(l-z_{1-\alpha}\hat{\sigma}_{E(\hat{\eta})}-z_{1-\alpha}\hat{\sigma}_{E(\hat{\eta})})]^2}{\hat{\sigma}^2_{E(\hat{\eta})}}} \\ &= \frac{1}{\hat{\sigma}_{E(\hat{\eta})}\sqrt{2\pi}} e^{-\frac{1}{2}\frac{[u-(l-2z_{1-\alpha}\hat{\sigma}_{E(\hat{\eta})})]^2}{\hat{\sigma}^2_{E(\hat{\eta})}}} \end{aligned} \tag{P.10}$$

where $-\infty < u < \infty$, $-\infty < L + z_{1-\alpha}\hat{\sigma}_{E(\hat{\eta})} < \infty$, and $-\infty < l + 2z_{1-\alpha}\hat{\sigma}_{E(\hat{\eta})} < \infty$. Therefore from eq. P.8, it follows

$$f(u,l) = f_{U|L}(u|l)f(l) \ . \tag{P.11}$$

As a result,

$$f(u,l) = \frac{1}{\hat{\sigma}_{E(\hat{\eta})}\sqrt{2\pi}} e^{-\frac{1}{2}\left(\frac{[u-(l+2z_{1-\alpha}\hat{\sigma}_{E(\hat{\eta})})]^2}{\hat{\sigma}^2_{E(\hat{\eta})}}\right)}$$

$$\times \frac{1}{\hat{\sigma}_{E(\hat{\eta})}\sqrt{2\pi}} e^{-\frac{1}{2}\left(\frac{[l-(E(\hat{\eta})-z_{1-\alpha}\hat{\sigma}_{E(\hat{\eta})})]^2}{\hat{\sigma}^2_{E(\hat{\eta})}}\right)} \qquad \text{(P.12)}$$

$$= \frac{1}{2\pi\hat{\sigma}^2_{E(\hat{\eta})}} e^{-\frac{1}{2}\left(\frac{[u-(l+2z_{1-\alpha}\hat{\sigma}_{E(\hat{\eta})})]^2+[l-(E(\hat{\eta})-z_{1-\alpha}\hat{\sigma}_{E}(\hat{\eta})]^2}{\hat{\sigma}^2_{E(\hat{\eta})}}\right)} .$$

Therefore, $P[(L,U)\in(1-\Delta, 1+\Delta)]$ can be computed from the joint asymptotic density $f(l,u)$, that is,

$$P[(L,U)\in(1-\Delta, 1+\Delta)] = \int_{1-\Delta}^{\infty}\int_{-\infty}^{1-\Delta} f(l,u)\,du\,dl \ . \qquad \text{(P.13)}$$

APPENDIX Q

WEIBULL AND LINEAR-EXPONENTIAL RESULTS

Table 1. Weibull Model Results

$\hat{\mu}_\eta$
(90% Credibility Region)
(95% Credibility Region)

t_o		n_o = 1.7	n_o = 4	n_o = 6	n_o = 9.5
10		1.00365	0.99271	0.98105	1.03805
	90%	(0.8936, 1.1137)	(0.8834, 1.1020)	(0.8733, 1.0888)	(0.9265, 1.1496)
	95%	(0.8726, 1.1347)	(0.8625, 1.1230)	(0.8526, 1.1095)	(0.9052, 1.1710)
17		0.99920	1.00607	0.99952	1.02424
	90%	(0.8900, 1.1084)	(0.8959, 1.1162)	(0.8896, 1.1095)	(0.9141, 1.1344)
	95%	(0.8691, 1.1293)	(0.8748, 1.1373)	(0.8685, 1.1305)	(0.8930, 1.1555)
24		0.98335	0.98258	0.98747	1.00998
	90%	(0.8740, 1.0927)	(0.8740, 1.0912)	(0.8779, 1.0971)	(0.9002, 1.1198)
	95%	(0.8530, 1.1137)	(0.8532, 1.1120)	(0.8569, 1.1180)	(0.8792, 1.1408)
33		1.00037	0.98778	1.01231	0.99385
	90%	(0.8905, 1.1102)	(0.8774, 1.0982)	(0.9033, 1.1214)	(0.8849, 1.1028)
	95%	(0.8695, 1.1313)	(0.8562, 1.1193)	(0.8824, 1.1422)	(0.8640, 1.1237)

Table 2. Linear-Exponential Results for Treatment 1

$$\lambda_1^* = E(\lambda_1)$$

$$n_o$$

t_o	1.7	4	6	9.5
10	0.1010	0.0995	0.0990	0.0977
17	0.1261	0.1227	0.1267	0.1234
24	0.1448	0.1445	0.1421	0.1419
33	0.1687	0.1667	0.1672	0.1659

Table 3. Linear-Exponential Results for Treatment 2

$$\lambda_2^* = E(\lambda_2)$$

$$n_o$$

t_o	1.7	4	6	9.5
10	0.0939	0.0931	0.0923	0.0911
17	0.1181	0.1165	0.1165	0.1145
24	0.1371	0.1365	0.1362	0.1350
33	0.1591	0.1583	0.1574	0.1561

Table 4. Linear-Exponential Results for $-2\log(k_i)$

	$-2\log(k_1)$ $-2\log(k_2)$	n_o		
	1.7	4	6	9.5
t_o				
10	1.8058	1.8163	1.8198	1.8291
	1.8570	1.8630	1.8690	1.8781
17	1.6491	1.6684	1.6457	1.6644
	1.6954	1.7050	1.7050	1.7173
24	1.5515	1.5530	1.5648	1.5658
	1.5952	1.5933	1.5944	1.6009
33	1.4447	1.4529	1.4509	1.4563
	1.4855	1.4890	1.4930	1.4988

Table 5. Linear-Exponential Model Results

$\hat{\mu}_\eta$
(90% Credibility Region)
(95% Credibility Region)

t_o		n_o = 1.7	n_o = 4	n_o = 6	n_o = 9.5
10		1.01586	0.99635	0.93210	1.00906
	90%	(0.9035, 1.1283)	(0.8876, 1.1051)	(0.8242, 1.0400)	(0.8971, 1.1210)
	95%	(0.8819, 1.1498)	(0.8668, 1.1259)	(0.8035, 1.0607)	(0.8757, 1.1424)
17		1.03510	1.01845	0.99202	1.03438
	90%	(0.9257, 1.1445)	(0.9070, 1.1299)	(0.8815, 1.1026)	(0.9247, 1.1440)
	95%	(0.9048, 1.1654)	(0.8857, 1.1512)	(0.8603, 1.1237)	(0.9037, 1.1650)
24		0.97751	0.96017	1.01327	1.02109
	90%	(0.8687, 1.0863)	(0.8501, 1.0702)	(0.9003, 1.1263)	(0.9119, 1.1303)
	95%	(0.8479, 1.1072)	(0.8291, 1.0913)	(0.8786, 1.1479)	(0.8910, 1.1512)
33		1.05063	0.97425	0.99604	1.01763
	90%	(0.9397,1.1615)	(0.8658, 1.0827)	(0.8865, 1.1056)	(0.9097, 1.1256)
	95%	(0.9185, 1.1828)	(0.8451, 1.1035)	(0.8656, 1.1265)	(0.8890, 1.1463)

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