Sequential Quantile Estimation Using Continuous Outcomes with Applications in Dose Finding

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Abstract

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We consider dose finding studies where a binary outcome is obtained by dichotomizing a continuous measurement. While the majority of existing dose finding designs work with dichotomized data, two procedures that operate on continuous measurements have been proposed. One is based on stochastic approximation and the other on least square recursion. In both cases, estimating the variance of the continuous measurement is an integral part of the design. In their originally proposed forms, variance estimation is based on data from the most current cohort only. This raises the question of whether performance of the two designs can be improved by incorporating better variance estimators. To this end, we propose estimators that pool data across cohorts. Asymptotic properties of both designs with the proposed estimators are derived. Operating characteristics are also investigated via simulations in the context of a real Phase I trial. Results show that performance of least square recursion based procedure can be substantially improved through pooling data in variance estimation while performance of stochastic approximation based procedure is only marginally improved.

The second problem considered in this dissertation deals with the limitation shared by both designs that complete follow-up of all current patients is required before new patients can be enrolled. This may result in impractically long trial duration. We consider situations where besides the final measurement that the outcome of the study is

defined on, each patient has an additional intermediate continuous measurement. By extending least square recursion through incorporating intermediate measurements, continual patient accrual is allowed. Simulation results show that under reasonable patient accrual rate, the proposed procedure is comparable to the original in terms of accuracy while shortening the trial duration considerably.

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Chapter 1

Introduction

Dose finding in early phase clinical trials is often formulated as a quantile estimation problem. In a study where the primary goal is to evaluate safety of a new drug or treatment, the objective is typically to identify the maximum tolerated dose (MTD), defined as the dose associated with an acceptable level of toxicity rate [29]. When assessment of efficacy is the primary concern, the outcome of interest is therapeutic response (or "success"). In this case, the dose finding objective is to identify the minimum effective dose (MED), defined as the dose associated with a given level of response rate [10].

Designs proposed to address this quantile estimation problem predominantly utilize binary data; that is, the outcome they operate on is the presence or absence of the event of interest. Among such designs are the continual reassessment method (CRM, [21]), escalation with overdose control (EWOC, [2]), biased coin design [12], and logit-MLE [31, 32]. Sometimes, however, the binary outcome is obtained by dichotomizing a continuous measurement. Consider the following two examples.

Several statins have been found to be neuroprotective in rodent acute stroke models in a dose-dependent fashion [13]. The Neuroprotection with Statin Therapy for Acute Recovery Trial (NeuSTART) [13] was a phase 1B dose finding trial of short-

term high-dose lovastatin in acute ischemic stroke patients. Five escalating doses of lovastatin (1, 3, 6, 8, 10 mg/kg/day) were chosen to evaluate safety and determine an optimal dose. Each of the 33 patients was given one of the escalating doses for 3 days within 24 hours of symptom onset. After the initial 3 days, all patients received standard dose (20mg) of lovastatin daily for 27 days. One of the primary safety outcomes was major hepatic toxicity defined by clinical and laboratory criteria. In particular, liver toxicity based on laboratory evidence was defined as elevation in ALT level greater than three times the upper limit of normal (ULN). Toxicity was evaluated up to 30 days after treatment initiation. When any of the safety outcome occurred, the patient was considered to experience dose-limiting toxicity (DLT). The objective of the trial was to determine the MTD of lovastatin, defined as the dose that causes 10% of DLT rate.

The second example is an ongoing trial aimed to determine the MED of a problem-solving therapy (PST) in patients with heart failure. PST is a cognitive-behavioral therapy that helps patients solve their behavioral difficulties systematically and become more physically active. The investigators hypothesize that PST will also improve quality of life (QoL) in heart failure patients through increased physical activity, increased exercise capacity and reduced depression. Five test doses of PST (2, 4, 6, 8 or 12 sessions) administered over an 8 week period are considered in the trial. A planned 48 participants will be enrolled in cohorts of size three and the starting dose is level 3 (6 sessions). Quality of life will be assessed at baseline, 4, 8 and 12 weeks. The objective of the trial is to identify the number of PST sessions that yields a 66% of response, defined as 10-point improvement in QoL between baseline and 8 weeks.

In both examples, the original measurements are continuous and based on which binary outcomes are defined by dichomization. In situations like these, sequential designs that operate on the dichotomized data could be sensitive to the dichotomiza-

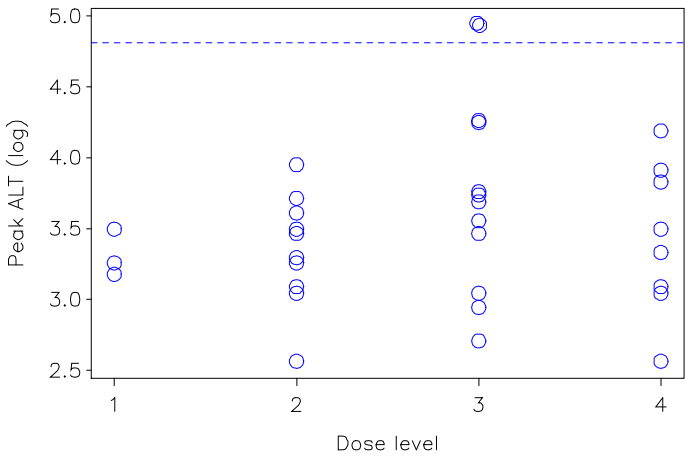

Figure 1.1: Liver function outcomes in the NeuSTART. Each "o" represents an observation and the dashed line the toxicity threshold of 3 times the ULN.

tion threshold and measurement error. This is illustrated by Figure 1.1 which displays the maximum ALT level of the 33 patients from NeuSTART. As can be seen, two DLTs occurred at dose level three. As these two measurements just exceeded the threshold, a slight drop in them could have resulted in a different dose assignment, which was carried out sequentially by a variant of the CRM. Another reason against using dichotomized data is that information may be lost by disregarding the continuous measurements. Motivated by these concerns, Cheung and Elkind [9] proposed a novel variant of the Robbins-Monro stochastic approximation that utilizes continuous outcomes for sequential quantile estimation. The Robbins-Monro procedure was originally developed to estimate the root of an unknown regression function and is well-suited for quantile estimation problems. However, when applied in a dose finding setting, it is not efficient unless the outcomes are continuous [30]. Moreover, it implicitly assumes a continuum of doses is available while in practice the test doses are usually confined to a discrete set. As a result, the Robbins-Monro procedure is rarely used in dose finding applications. The novel procedure, called stochastic ap-

proximation with virtual observations (SAVOR), draws on the strength of stochastic approximation by transforming the dose finding problem into root-finding for continuous variables. At the same time, it introduces a novel concept named virtual observation to overcome the barrier presented by discrete doses.

In a related line of work, Hu and Cheung [14] proposed a design that also utilizes continuous outcomes based on least square recursion (LSR). While the least squares recursion was proposed with the assumption of availability of continuous doses, the idea of virtual observation can be easily incorporated to accommodate discrete doses (see Chapter 3). To the best of our knowledge, SAVOR and LSR are the only designs that tackle sequential quantile estimation problem using continuous outcomes in the dose finding literature. With both designs, estimation of mean and variance of the continuous measurement is an integral part of the design. Estimation of the variance, in particular, plays an important role and can have an sizable impact on the efficiency of the design [14]. In this dissertation, we propose extensions of both SAVOR and LSR through improved variance estimation in the hope of achieving greater efficiency.

So far, the designs mentioned require complete follow-up of all current patients before new patients can be entered into the study. For studies with long observation time this limitation may result in prohibitively long duration. As a case in point, in the PST study, if we have to wait for 8 weeks between cohorts, it will take about 30 months to finish enrolling the planned 16 cohorts. Also, from an ethical point of view, eligible patients may have to be turned away if currently enrolled patients have not reached complete follow-up. With these considerations in mind, the time-to-event continual reassessment method (TITE-CRM, [8]), a variant of the CRM that allows patients to be entered in a staggered fashion is the proposed design for the PST study. With TITE-CRM, the 4-week QoL measurement can be used to aid dose assignment and thereby shortening the inter-cohort time from 8 to 4 weeks.

However, besides the possible loss of efficiency associated with dichotomized data, there is another limitation that comes with TITE-CRM. Namely, the design assumes an observed response at any time during follow-up as a complete observation. Under the current context, this means that if a response, i.e. $\geq$ 10-point improvement in QoL, is observed at 4 weeks, then it is implicitly assumed that the improvement will sustain and a response will also be observed at 8 weeks. This is an unrealistic assumption to make as the change in QoL may fluctuate over time. Despite not being ideal, TITE-CRM was chosen for lack of a better alternative. To fill the gap in the literature, we propose an extension of the LSR to incorporate intermediate continuous outcomes.

This dissertation is structured as follows. In Chapter 2, we shall formally define the dose finding objective and briefly review a few of the designs that utilize binary data. Designs using continuous outcomes are reviewed in Chapter 3. In Chapter 4, SAVOR and LSR are extended to incorporate improved variance estimators. Chapter 5 presents the extension of LSR that accommodates intermediate outcomes.

Chapter 2

Dose Finding Designs Using Binary Outcomes

2.1 Introduction

This chapter reviews some dose finding designs that operate on binary data. As the development of most of these designs was motivated by safety studies, we will present them in this context. Their applications to efficacy studies can be derived analogously. Before presenting the designs, a formal definition of the MTD is given. The MED can be defined in a similar fashion.

2.2 Maximum Tolerated Dose (MTD) as Percentile

Consider a trial in which the patient population is homogeneous. Let T be the binary indicator of dose-limiting toxicity (DLT) for a patient, then the probability of toxicity at dose x is $\pi(x) = P(T = 1|x)$. For now, assume that $\pi(x)$ is strictly increasing in x. Given a level of toxicity of interest p, the dose finding objective is to identify the

MTD, defined as the dose θ such that

$$\pi(\theta) = p. \tag{2.1}$$

When the doses are confined to a discrete set of K levels labelled as $1, \ldots, K$, the MTD can be defined as the dose that has toxicity probability closest to p:

$$\nu_1 = \arg\min_k |\pi(k) - p|. \tag{2.2}$$

This formulation of viewing MTD as a percentile on the dose-toxicity curve is in line with bioassay and statistically appealing in that the MTD is a well-defined quantity (with suitable conditions on π) to be estimated [6]. Also, the target toxicity probability p can be decided on a trial by trial basis to suit the specific application.

For the definition of MED, replace dose-toxicity curve with dose-response curve. That is, let $\pi(x) = P(R = 1|x)$ where R is the binary indicator of response. Then θ in (2.1) and ν_1 in (2.2) become the MED.

2.3 3+3 Algorithm

The 3+3 algorithm is the first algorithm-based design to be widely used in clinical practice and has remained the prevailing method for conducting phase I cancer clinical trial [17]. Generally, an algorithm-based design requires no modelling on the dose-toxicity relationship beyond the assumption that toxicity increases with dose. It prescribes a set of escalation (and/or de-escalation) rules for any given dose without taking outcomes at other doses into account.

The 3+3 algorithm starts at a safe dose (e.g., one tenth of the mouse equivalent LD10) and escalates according to the following rules:

1. Evaluate three patients at current dose
   (a) If zero out of three has DLT, then escalate to the next higher dose and go to step 1;

(b) If one of three has DLT, then go to step 2;

(c) If more than one of three have DLT, then go to step 3.

2. Evaluate an additional three patients at current dose:

   (a) If one of six has DLT, then escalate to next higher dose and go to step 1;

   (b) If more than one of six have DLT then go to step 3.

3. Discontinue dose escalation.

If the trial is stopped then the MTD is estimated by the dose immediately below the terminating dose. If there are only three patients evaluated at that dose level, some protocols add another three patients. In which case, the estimated MTD is the highest level with at most one DLT out of 6 patients.

Similar designs with different cohort sizes and expansion rules have been proposed. The traditional 3+3 algorithm can be viewed as a special case of a class of A+B designs in which an additional cohort of B patients is added if the number of DLT exceeds some threshold in the first cohort of A patients. The key statistical properties of A+B designs were investigated in Lin and Shih [19].

The main advantage of the 3+3 algorithm is its simplicity. However, it has been criticized for involving an excessive number of escalation steps [17]. This is particularly undesirable in trials with therapeutic intent as a large proportion of patients would be treated at low and potentially subtherapeutic doses while few would actually receive doses at or near the recommended MTD. Another criticism is that specification of a target probability of toxicity is not allowed. Thus, the notion of viewing MTD as a percentile on the dose-toxicity curve does not apply. In fact, there is no intrinsic property that yields a good estimate of MTD and the distribution of the estimated MTD depends arbitrarily on the number and actual percentiles of the dose levels examined [5].

Despite its drawbacks, the 3+3 algorithm is still widely used in practice. This is

due mainly to its algorithm-based simplicity in logistics for the clinical investigators to carry out [19].

2.4 The Continual Reassessment Method

The continual reassessment method (CRM), introduced by O'Quigley, Pepe and Fisher [21] was the first Bayesian model-based method proposed for adoption in phase I trial designs. Briefly, a model-based design makes dose decisions based on an assumed dose-toxicity curve and utilizes all accrued data to repeatedly update the curve. The general idea behind the CRM is that a dose-toxicity curve would be fitted to the data and that each patient would be assigned the dose most likely to be associated with the target toxicity level. The process starts with an assumed *a priori* dose-toxicity curve. The estimated dose-toxicity curve is refit after each patient's toxicity outcome was observed. At every stage, the next patient is assigned the current model-based MTD estimate.

2.4.1 The Basic Approach

We consider first a fully sequential version, in which patients are enrolled one at a time. Assuming there are K test doses with numerical labels $d_1, \ldots, d_K$, let T_n be the indicator of toxicity for the nth patient who receives dose $x_n \in \{d_1, \ldots, d_K\}$. It is assumed that T_n is a Bernoulli variable with toxicity probability $\pi(x_n)$ and that $\pi(x)$ is monotone increasing in x. The goal is to estimate ν_1 as defined in (2.2). To achieve this, the CRM assumes a working dose-toxicity model for $\pi(x)$, denoted by $F(x, a)$. It should be noted that the CRM does not require F to be the correct model for π. Among the conditions F needs to satisfy (see [5]), $F(x, a)$ should be monotone increasing in x for all a and monotone in a in the same direction for all x. Also, F

should be flexible enough so that for any given $p \in (0,1)$ and given x, there exists a such that $F(x,a) = p$. The two most commonly choices for F are the empiric function

$$F(x,a) = x^{\exp(a)}, 0 < x < 1, \tag{2.3}$$

and a one-parameter logistic function

$$F(x,a) = \frac{\exp\left(a_0 + \exp(a)x\right)}{1 + \exp(a_0 + \exp(a)x)}, -\infty < x < \infty,$$

where the intercept a_0 is a fixed constant.

The original CRM uses a Bayesian approach in which a is assumed to follow a prior distribution $H(a)$. The trials starts by treating the first patients at the prior MTD, the dose initially believed to have toxicity probability equal or closest to p. Then for $n > 1$, the dose assigned to the nth patient is the model-based MTD estimate:

$$x_n = \arg\min_{d_k} |F(d_k, \hat{a}_{n-1}) - p| \tag{2.4}$$

where

$$\hat{a}_{n-1} = \frac{\int_{-\infty}^{\infty} a L_{n-1}(a) dH(a)}{\int_{-\infty}^{\infty} L_{n-1}(a) dH(a)}$$

is the posterior mean of a and

$$L_{n-1}(a) = \prod_{j=1}^{n-1} \left[F(x_j, a)\right]^{T_j} \left[1 - F(x_j, a)\right]^{1-T_j}.$$

The process is continued until a prespecified number of patients N is reached. The final MTD estimate is x_{N+1}.

One important aspect of CRM is that the dose labels $d_1, \ldots, d_K$ are not the doses administered, but are numerical representation of the risks of toxicity defined on some conceptual scale [5]. More precisely, let p_k be the initial guess of probability of toxicity associated with dose k and $\hat{a}_0$ the prior mean of a, then d_k is obtained by solving $p_k = F(d_k, \hat{a}_0)$. Thus, specification of the initial guesses $p_1, \ldots, p_K$ is an essential part

Table 2.1: Starting dose escalation plan in the NeuSTART

Cohort	Cohort size	Lovastatin dose 0–72 hours (mg/kg/day)	Lovastatin dose days 3–30 (mg/day)
1	3	1	20
2	3	3	20
3	3	6	20
4	3	6	20
5	3	8	20
6	3	8	20
7	3	8	20
8	3	10	20
9	3	10	20
10	3	10	20
11	3	10	20

of a CRM design. A systematic approach to selecting the initial guesses was proposed by Lee and Cheung [18].

Instead of enrolling patients one at a time, cohort accrual can be easily accommodated in the CRM by assigning the same dose to a cohort of $m > 1$ patients. In this case, the MTD estimate (2.4) is updated between cohorts.

2.4.2 Some Variations of CRM

In response to the concern that the use of prior information may be arbitrary and have lingering impact on dose selection, O'Quigley and Shen [22] proposed a version of CRM that is based on likelihood framework. Under this framework, the model-based MTD estimate for the nth patient is

$$x_n = \arg\min_{d_k} |F(d_k, \tilde{a}_{n-1}) - \theta|$$

where $\tilde{a}_{n-1} = \arg\max_a L_{n-1}(a)$ is the maximum likelihood estimate of a. In order to base inference on the likelihood, it is necessary to have a nonmonotone likelihood. In other words, for $\tilde{a}_{n-1}$ to exist, heterogeneity among the toxicity outcomes is needed.

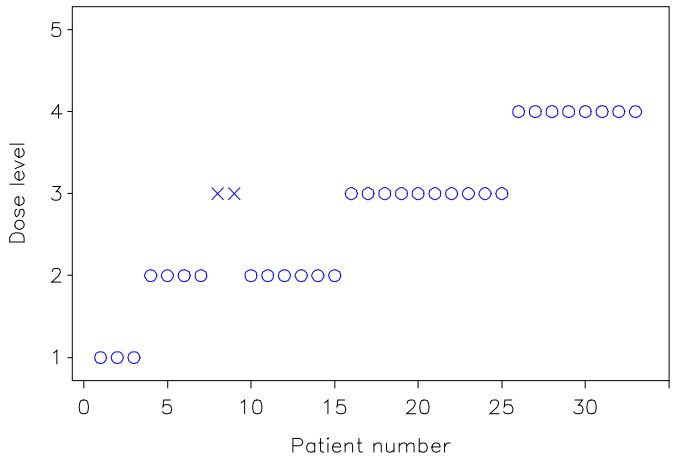

Figure 2.1: Patient flow of NeuSTART. Each point represents a patient, with "o" indicating no toxicity and "x" indicating toxicity.

One way to ensure this is to adopt a two-stage design described as follows. Let $\{x_{n,0}\}$ be a prespecified nondecreasing dose sequence such that $x_{n-1,0} \leq x_{n,0}$. The dose assignments follow this initial sequence until the first observed toxicity. After which the trial will switch to the CRM. As an example, dose escalation for the NeuSTART was done in two stages. The initial escalation plan is shown in Table 2.1 and the trial outcomes in Figure 2.1. After the eighth patient experienced DLT, the trial turned to the CRM. The trial stopped when the planned 33 patients were enrolled and the CRM recommended dose level 4 as the final MTD estimate.

2.4.3 The Time-to-Event CRM

Both 3+3 algorithm and the CRM require all currently enrolled patients be completely followed before the next patient or cohort can be enrolled. An extension of CRM, called time-to-event continual reassessment method (TITE-CRM, [8]) was proposed by Cheung and Chappell to address this limitation by allowing patients to be enrolled in a staggered fashion. Specifically, TITE-CRM allows for incomplete observations

through using weighted likelihood:

$$L_n(a, w) = \prod_{i=1}^{n} \left[w_{i,n+1} F(x_i, a)\right]^{T_{i,n+1}} \left[1 - w_{i,n+1} F(x_i, a)\right]^{1-T_{i,n+1}},$$

where $T_{i,n+1}$ is the indicator of DLT and $w_{i,n+1}$ the weight for patient i prior to the entry of patient $n+1$. The weight $w_{i,n+1}$ reflects the amount of information contributed by patient i and therefore should increase with follow-up time. A simple weight function is the linear weight. Let D be the observation window, that is, the maximum length of follow-up for each patient, then for $t \leq D$,

$$w(t, D) = \begin{cases} \frac{t}{D} & \text{if a patient is in follow-up and has not experienced a DLT at time } t \\ 1 & \text{if a patient has experienced DLT or has been followed for } D. \end{cases}$$

Having defined the weighted likelihood, the estimation of a and the model-based MTD follow in the same manner as in regular CRM, that is,

$$\hat{a}_n^w = \frac{\int_{-\infty}^{\infty} a L_n(a, w) dH(a)}{\int_{-\infty}^{\infty} L_n(a, w) dH(a)}$$

and

$$x_{n+1} = \arg\min_{d_k} |F(d_k, \hat{a}_n^w) - p|.$$

Note that TITE-CRM reduces to regular CRM if new patients are enrolled only after follow-ups are complete for current patients.

Since TITE-CRM does not require suspension of patient accrual in order to wait for toxicity outcomes on previous patients, it can greatly reduce the trial duration compared to regular CRM. However, in situations of fast accrual and late-onset toxicities, TITE-CRM is more likely to assign new patients to doses considered safe at the time but later found otherwise [3]. To reduce the risk of exposing patients to unsafe doses, more complicated weighting schemes can be considered [5].

2.5 Stochastic Approximation

2.5.1 Robbins-Monro Procedure

The 3+3 algorithm and the CRM are representatives of algorithm- and model-based designs, respectively. A third class of design is based on stochastic approximation. Robbins and Monro [25] introduced the subject of stochastic approximation for finding the unique root of a regression equation. The problem they addressed can be stated as follows:

Let $Y = Y(x)$ denote a random variable with expectation $Q(x)$ at level x. The function $Q(x)$ is unknown to the experimenter but Y at different values of x can be observed. The objective is to sequentially approach the root $x = x^*$ of the equation

$$Q(x) = \alpha \tag{2.5}$$

for given α. The Robbins-Monro procedure for finding x^* starts with an prespecified X_1 and defines

$$X_{n+1} = X_n - \frac{1}{nb}(Y_n - \alpha), \tag{2.6}$$

for some $b > 0$.

Under Conditions A.1, A.2 and A.3 (a) listed in Appendix A, the sequence X_n generated by (2.6) converges to x^* with probability one. If in addition, $b < 2Q'(x^*)$ and Conditions A.3 (b), A.4, A.5 hold then Sacks [27] showed

$$\sqrt{n}(X_n - x^*) \xrightarrow{d} N\left(0,\ \frac{\lim_{x\to x^*} \mathrm{Var}Y(x)}{b\,(2Q'(x^*) - b)}\right).$$

2.5.2 Stochastic Approximation in Dose Finding Setting

The possibility of adapting stochastic approximation to dose finding setting was first discussed by Anbar [5]. If Y is the binary indicator of DLT, x the dose level, $Q(x) = \pi(x) = P(Y = 1|x)$, and $\alpha = p$, then solving for (2.5) is equivalent to estimating the

MTD under definition (2.1). In a trial with N patients, the final estimated MTD can be taken to be the last design point, X_{N+1}. Despite its seemingly suitability, there are some practical considerations that prevent applications of stochastic approximation in dose finding settings. First, the choice of b in (2.6) is of the utmost importance. The asymptotic normality result depends on b being less than an unknown quantity, namely $b < 2Q'(x^*)$. Moreover, considering efficiency in terms of asymptotic variance, the optimal choice would be setting b equal to $Q'(x^*)$. The second issue is that the procedure entails the availability of a continuum of doses which is usually not feasible in practice [9].

The first issue has been addressed by replacing b by a sequence b_n that is strongly consistent for $Q'(x^*)$. Anbar [1] suggested an adaptive procedure that sets b_n to be the truncated least squares estimates of $Q'(x^*)$ from a linear model. That is

$$b_n = \max\left\{c_1, \min\left\{c_2, \frac{\sum_{i=1}^{n}(X_i - \bar{X}_n)(Y_i - \bar{Y}_n)}{\sum_{i=1}^{n}(X_i - \bar{X}_n)^2}\right\}\right\},$$

where $\bar{X}_n = n^{-1}\sum_{i=1}^{n} X_i$, $\bar{Y}_n = n^{-1}\sum_{i=1}^{n} Y_i$ and c_1, c_2 are positive constants such that $c_1 < b < c_2$. The adaptive procedure is theoretically ideal in that $b_n \to Q'(x^*)$ a.s. and the design sequence $\{X_n\}$ achieves minimal asymptotic variance [16]. In applications with small samples, however, estimation of $Q'(x^*)$ could cause numerical instability [6].

One solution to the second issue is to use a discretized version of the stochastic approximation. Suppose there are K doses labelled as $\{1, \ldots, K\}$, then a discretized stochastic approximation that operates on this discrete set of dose levels can be defined as

$$X_{n+1} = C\left\{X_n - \frac{1}{nb}(Y_n - p)\right\}, \tag{2.7}$$

where

$$C(x) = \begin{cases} 1 & \text{if } x < 0.5, \\ [x + 0.5] & \text{if } 0.5 \leq x < K + 0.5, \\ K & \text{if } x \geq K + 0.5. \end{cases} \tag{2.8}$$

While this may seem to be a straightforward solution to accommodate discrete doses, rounding creates a problem called *discrete barrier*, meaning that the output from (2.7) may be confined at a incorrect dose indefinitely. Illustrations of discrete barrier can be found in Cheung [6] and Shen and O'Quigley [28].

The performances of discretized version of both non-adaptive and adaptive Robbins-Monro procedure were compared to a fully sequential CRM in a simulation study carried out by O'Quilgley and Chevret [20]. It was found that in general, CRM performed the best in terms of correctly identifying the MTD.

2.6 Logit-MLE

Wu [31] took a different approach to solve for (2.5). His method is to first specify a parametric model for $Q(x)$ then repeatedly estimate x^* by the maximum likelihood method based on currently accrued data. The design points are set to be the latest estimates of x^*. This method, which was first introduced under the context of binary data and later extended to include data from exponential family, is called maximum likelihood recursion. In particular, when the outcome Y_i is binary and $Q(x) = E(Y_i|X_i = x)$ is assumed to take the form $logit(Q(x)) = logit(\alpha) + \tilde{b}(x - \alpha)$ for some $\tilde{b} > 0$, the resulting recursion, logit-MLE, solves

$$\sum_{i=1}^{n} \left(Y_i - \frac{\alpha e^{\tilde{b}(X_i - \hat{x}_n^*)}}{1 - \alpha + \alpha e^{\tilde{b}(X_i - \hat{x}_n^*)}} \right) = 0, \tag{2.9}$$

at stage n and set $X_{n+1} = \hat{x}_n^*$.

Ying and Wu [33] showed, by first establishing an asymptotic equivalence to an adaptive Robbins-Monro procedure that the design sequence $\{X_n\}$ from (2.9) is strongly consistent for x^* and

$$\sqrt{n}(X_n - x^*) \xrightarrow{d} N\left(0, \frac{1}{\tilde{b}[2Q'(x^*) - \tilde{b}\alpha(1-\alpha)]}\right).$$

Logit-MLE shares similar limitations as stochastic approximation in that it assumes a continuum of doses and $\tilde{b}$ needs to be carefully chosen. In a simulation study of small to moderate sample sizes with binary outcomes and continuous doses, Wu [31] compared logit-MLE, the non-adaptive Robbins-Monro procedure with several choices of b and the adaptive Robbin-Monro procedure with different truncation bounds. It was concluded that logit-MLE is the superior of the three methods in terms of mean squared error.

Chapter 3

Dose Finding Designs Using Continuous Outcomes

3.1 Introduction

In this chapter, we review two dose finding designs that utilize continuous outcomes. The first is a variant of stochastic approximation; the second is based on least square recursion, a versatile framework for sequential percentile estimation. As is the case in chapter 2, the designs are presented in the context of safety trials.

3.2 Problem Formulation

Consider a trial in which patients are enrolled in successive cohorts of size m. Within the ith cohort, let X_i be the dose given and Y_{ij} the observable continuous outcome of the jth patient. A toxicity is said to occur if Y_{ij} is greater than a prespecified threshold t_0, that is, a binary toxicity outcome is defined by dichotomizing Y_{ij}. Throughout the chapter, we assume the following semi-parametric model for Y_{ij}:

$$Y_{ij} = M(X_i) + \sigma(X_i)\epsilon_{ij}, i = 1, \ldots, n, j = 1, \ldots, m, \tag{3.1}$$

where ϵ_{ij}'s are independent and have a common distribution G with mean 0 and variance 1. Notice that the model assumes a homogeneous patient population. Assuming for now that X_i is continuous, the objective of the trial is to estimate dose θ that satisfies (2.1) for some prespecified p, where $\pi(x) = P(Y_{ij} > t_0 | X_i = x)$. Given model (3.1), the toxicity probability at dose x can be written as

$$\pi(x) = 1 - G\left(\frac{t_0 - M(x)}{\sigma(x)}\right). \tag{3.2}$$

With this expression, the target dose θ is the root of

$$f(x) \equiv M(x) + c_p\,\sigma(x) = t_0, \tag{3.3}$$

where c_p denotes the upper pth percentile of G. In words, the dose finding objective (2.1) is now transformed into a root-finding problem for a continuous variable.

When the doses are discrete, that is, $X_i \in \{1, \ldots, K\}$, the working objective can be defined as the identification of $\nu_1 = \arg\min_k |\pi(k) - p|$. Under the current setup, an alternative objective is to identify

$$\nu_2 = \arg\min_k |f(k) - t_0|. \tag{3.4}$$

The two objectives ν_1 and ν_2 represent the closest doses to θ on different scales. To ensure the existence and uniqueness of ν_1 and ν_2, we require that both $\pi(x)$ and $f(x)$ are weakly monotone in x:

Condition 3.1. *For all $k' < \nu_1 - 1$ and $k > \nu_1 + 1$,*

1. $\pi(k') < \pi(\nu_1 - 1) < \pi(\nu_1) < \pi(\nu_1 + 1) < \pi(k)$
2. $f(k') < f(\nu_1 - 1) < f(\nu_1) < f(\nu_1 + 1) < f(k)$

While ν_1 and ν_2 are not necessarily identical, ν_2 is either equal to ν_1 or one of ν_1's immediate neighbours, that is, $\nu_2 \in \{\nu_1 - 1, \nu_1, \nu_1 + 1\}$ [9]. In particular, define c_k

such that $G(c_k) = 1 - \pi(k)$ and let $B_k = 2\sigma(k)|c_k - c_p|$ for $k = 1, \ldots, K$, then $\nu_1 = \nu_2$ if and only if $B_{\nu_1} = \min_k B_k$. Relationship between ν_1 and ν_2 is explored in details in Cheung and Elkind [9]. In accordance with convention, we will focus on estimation of ν_1.

3.3 Stochastic Approximation with Virtual Observations

Having re-formulated the dose finding problem, stochastic approximation can be applied to solve (3.3). For now, assume a continuum of doses is available. Define

$$U_n = \bar{Y}_n + \left[E\left(\frac{S_n}{\sigma(X_n)} \right) \right]^{-1} c_p \, S_n \tag{3.5}$$

where $\bar{Y}_n = m^{-1} \sum_{j=1}^{m} Y_{nj}$ and $S_n^2 = (m-1)^{-1} \sum_{j=1}^{m} (Y_{nj} - \bar{Y}_n)^2$. Then $E(U_n | X_n) = f(X_n)$ and U_n's can be used to generate a Robbins-Monro recursion:

$$X_{n+1} = X_n - \frac{1}{nb} (U_n - t_0) \text{ for some } b > 0. \tag{3.6}$$

In particular, when G is standard normal,

$$U_n = \bar{Y}_n + z_p \sqrt{\lambda_m} S_n, \tag{3.7}$$

where z_p is the pth upper percentile of $N(0,1)$, and

$$\lambda_m = \frac{(m-1)\Gamma^2((m-1)/2)}{2\Gamma^2(m/2)} \tag{3.8}$$

with $\Gamma(\cdot)$ being the gamma function.

Assume the following conditions are satisfied:

Condition 3.2. *$f(\theta) = t_0$ and $(x - \theta)(f(x) - t_0) > 0$ for all $x \neq \theta$.*

Condition 3.3. *For all x and some positive constant D, $|f(x)-t_0| \leq D|x-\theta|$. And for every c_1, c_2 such that $0 < d_1 < d_2 < \infty$,*

$$\inf_{d_1 \leq |x-\theta| \leq d_2} |f(x) - t_0| > 0.$$

Condition 3.4. *$f(x) = t_0 + \alpha(x-\theta) + \delta(x,\theta)$ where $\delta(x,\theta) = o(|x-\theta|)$ as $x \to \theta$ and $\alpha > 0$.*

The sequence generated by (3.6) with (3.7) converges to θ a.s. and if $b < 2f'(\theta)$ then

$$\sqrt{n}(X_n - \theta) \xrightarrow{d} N\left(0, \sigma^2(\theta)\frac{1 + mz_p^2(\lambda_m - 1)}{mb(2f'(\theta) - b)}\right). \tag{3.9}$$

To examine the advantage of using continuous outcomes as opposed to dichotomized outcomes under the current setting, Cheung [6] compared recursion (3.6) assuming normal noises to logit-MLE in terms of optimal asymptotic efficiency. The former was found to be substantially more efficient when cohort sizes are larger than 2, especially when p is extreme. In particular, when $m = 3$, the relative efficiency has a minimum of 1.238 when $p = 0.12$ or 0.88 [6].

As mentioned in the previous chapter, one of the reasons that has impeded the application of stochastic approximation in practice is that doses are usually confined to a discrete set. To overcome this hurdle, Cheung and Elkind [9] introduced the novel notion of virtual observation. Specifically, the virtual observation of the nth cohort is

$$V_n = U_n + \beta(X_n^* - X_n),$$

where $\beta > 0$ and X_n^* is called the assigned dose of cohort n that takes values on a continuous conceptual scale, and $X_n = C(X_n^*)$ is the actual dose given with C defined in (2.8). Setting $X_1^* = X_1 \in \{1, \ldots, K\}$, then stochastic approximation based

on virtual observation (SAVOR) is

$$X_{n+1}^* = X_n^* - \frac{1}{nb}\left(V_n - t_0\right). \tag{3.10}$$

Instead of solving for θ, the solution to (3.3), recursion (3.10) solves for θ_β, the solution to

$$h(x) \equiv E(V_n | X_n^* = x) = t_0. \tag{3.11}$$

Using previously defined notations, $h(x) = f(C(x)) + \beta(x - C(x))$. The existence and uniqueness of the root to (3.11) depend on the choice of β. Cheung and Elkind showed that

1. If $B_{\nu_1} = \min_k B_k$ and $B_{\nu_1} < \beta < \min_{k \neq \nu_1} B_k$ then $h(\theta_\beta) = t_0$ for some unique θ_β with $C(\theta_\beta) = \nu_1$ and $X_n = \nu_1$ eventually with probability one. If in addition, $b < 2\beta$, then

$$\sqrt{n}(X_n^* - \theta_\beta) \xrightarrow{d} N\left(0, \frac{Var(V_i | X_i^* = \theta_\beta)}{b(2\beta - b)}\right). \tag{3.12}$$

   In particular, if G is standard normal, that is, if $V_n = \bar{Y}_n + z_p\sqrt{\lambda_m} S_n + \beta(X_n^* - X_n)$, then the asymptotic variance in (3.12) is

$$\sigma^2(\nu_1)\frac{1 + m z_p^2(\lambda_m - 1)}{mb(2\beta - b)}.$$

2. If $0 < \beta < \min_k B_k$ then the root of $h(x) = t_0$ does not exist. In this case, if

   (a) $\pi(\nu_1) < p$ then $h(\nu_1 + 0.5-) < t_0$, $h(\nu_1 + 0.5) > t_0$ and $P(X_n \in (\nu_1, \nu_1 + 1)$ eventually$) = 1$.

   (b) $\pi(\nu_1) > p$ then $h(\nu_1 - 0.5-) < t_0$, $h(\nu_1 - 0.5) > t_0$ and $P(X_n \in (\nu_1, \nu_1 - 1)$ eventually$) = 1$.

A point worth emphasizing is that by the construction of virtual observations, the objective function $h(\cdot)$ has a known local slope β at the root θ_β. This feature makes stochastic approximation stable and reliable in small-sample settings [9].

In view of minimizing asymptotic variance in (3.12), it would be ideal to set $b = \beta$ and β as large as consistency condition would allow. However, the condition depends on B_k's, which are unknown quantities. Guidelines on calibration of β were provided by Cheung and Elkind [9] under scenarios where the following two conditions are met:

Condition 3.5. *$\pi(\nu_1) = \pi(\nu_2) = p$, $\pi(k) \leq p_L < p < p_U \leq \pi(k')$ for $k < \nu_1 < k'$ and some prespecified limits p_L, p_U.*

Condition 3.6. *$\sigma(k)$ depends on dose k only via $M(k)$ as follows: $s(\sigma(k)) = s(\sigma(\theta)) + \phi(M(k) - M(\theta))$ for some $\phi \geq 0$ and some smooth function $s(\sigma)$ with $s(\sigma) \geq 0$ and $s'(\sigma) > 0$*

Under Condition 3.5, there is an unambiguous target $\theta = \nu_1 = \nu_2 = \theta_\beta$. Together with Condition 3.6, X_n is consistent for θ if

$$0 < \frac{\beta}{2\sigma(\theta)} < \omega \equiv \min\left\{c_p - \frac{c_p^2}{c_L}, c_p - c_U\right\}, \tag{3.13}$$

where $c_L = G^{-1}(1 - p_L)$ and $c_U = G^{-1}(1 - p_U)$. The authors suggested that the unknown quantity $\sigma(\theta)$ be estimated by σ_0, the estimated standard deviation of the safety measurement in a comparable untreated population.

In a redesign of NeuSTART, Cheung and Elkind compared SAVOR to CRM via simulations and found the former superior in terms of probability of selecting the MTD. They also demonstrated that SAVOR is robust to misspecification of distribution in model (3.1) and the superiority over CRM maintains under several different distributions.

3.4 Least Square Recursion with Virtual Observations

Another framework of designs for sequential estimation of θ using continuous data was proposed by Hu and Cheung [14]. For any n, let U_{in} be equal to U_i as defined in (3.5) for $i = 1, \ldots, n$. With outcomes from the first n cohorts, θ is estimated by $\hat{\theta}_n$ where

$$\sum_{i=1}^{n} \left\{ U_{in} - \left[t_0 + b(X_i - \hat{\theta}_n) \right] \right\} = 0, \text{ for some } b > 0. \tag{3.14}$$

Equation (3.14) comes from assuming the working model $f(x) = t_0 + b(x - \theta)$ then estimating θ by method of least squares. Setting the design point for the next cohort to

$$X_{n+1} = \hat{\theta}_n$$

then the least square recursion (LSR) based on U_{in} is

$$X_{n+1} = \bar{X}_n - \frac{1}{nb} \sum_{i=1}^{n} (U_{in} - t_0) . \tag{3.15}$$

A direct application of Lemma 1 in Lai and Robbins [15] shows that recursions (3.15) and (3.6) are equivalent. Thus, standard asymptotic results from stochastic approximation can be applied if appropriate conditions are satisfied.

Similar to traditional stochastic approximation, recursion (3.15) assumes availability of continuum of doses. The idea of virtual observation can easily be incorporated into least square recursion to accommodate discrete doses. Let

$$V_{in} = U_{in} + \beta(X_i^* - X_i), i = 1, \ldots, n,$$

then least square recursion with virtual observations (LSRVO) is defined as

$$X_{n+1}^* = \bar{X}_n^* - \frac{1}{nb} \sum_{i=1}^{n} (V_{in} - t_0) , \tag{3.16}$$

where $b > 0$ and $\bar{X}_n^* = n^{-1}\sum_{i=1}^n X_i^*$. Results from SAVOR apply since (3.16) is equivalent to (3.10).

A few comments on recursions (3.10) and (3.16) are in order. First, since the update is done on the continuous X^* without rounding, discrete barrier problem is circumvented. Second, both the use of continuous outcome and the distribution assumption in model (3.1) contribute to the efficiency gain over procedure using dichotomized data $1\{Y_{ij} > t_0\}$. In contrast, no distributional assumption is required in logit-MLE and CRM. While robustness against misspecification in G has been established under Conditions 3.5 and 3.6 in Cheung and Elkind [9], further investigation needs to be done for more general scenarios. Third, due to the need to estimate variance function $\sigma(\cdot)$, only group accrual are permitted in SAVOR and LSRVO as opposed to the possibility of individual enrolment in CRM and logit-MLE. Lastly, while (3.16) and (3.10) are equivalent under the current formulation, it is not hard to see that as a general framework, (3.16) is the more versatile of the two. This is mainly because (3.16) works with triangle arrays and therefore has the potential to accommodate more complicated situations. This last observation will become clear in subsequent chapters.

3.5 Efficiency and Variance Assumptions

3.5.1 Variance Assumptions

Under the current setting, a correct specification of the standard deviation function $\sigma(\cdot)$ in model (3.1) is important. So far, we have left $\sigma(\cdot)$ unspecified and estimated it nonparametrically. While putting additional assumption on $\sigma(\cdot)$ may improve efficiency, such endeavour should be proceeded with caution. With sequential designs, any assumption on $\sigma(\cdot)$ will be directly involved in the generation of design points

and hence sensitivity analysis may not be performed after data are collected. In this section, we look into how much information can be retrieved by placing additional parametric assumptions in model (3.1) while keeping the mean $M(x)$ unspecified. Since the goal is to investigate the impact of variance assumption on efficiency, doses are assumed to be continuous and the objective is to identify θ, the root to (3.3). Both stochastic approximation (3.6) and least square recursion (3.15) are considered. It is also assumed that G follows standard normal; Conditions 3.2, 3.3, and 3.4 are met and that $b < 2f'(\theta)$.

We consider three sets of assumptions on $\sigma(\cdot)$:

Case 1 (known variance): Assume $\sigma(x)$ is completely known. It is natural to define $U_n = \bar{Y}_n + z_p\sigma(X_n)$ for stochastic approximation , and $U_{in} = \bar{Y}_i + z_p\sigma(X_i)$ for least square recursion.

Case 2 (heteroscedasticity): $\sigma(x)$ is unknown and unspecified. This is the case considered in Sections 3.3 and 3.4. We let $U_n = \bar{Y}_n + z_p\sqrt{\lambda_m}S_n$ and $U_{in} = \bar{Y}_i + z_p\sqrt{\lambda_m}S_i$.

Case 3 (homoscedasticity): Assume $\sigma(x) \equiv \sigma$, where σ is unknown. In this case, a natural estimator of σ^2 is $n^{-1}\sum_{i=1}^{n} S_i^2$ and we may let $U_n = \bar{Y}_n + z_p\sqrt{n^{-1}\sum_{i=1}^{n} S_i^2}$ and $U_{in} = \bar{Y}_i + z_p\sqrt{n^{-1}\sum_{i=1}^{n} S_i^2}$.

We note that homoscedasticity may not be a viable assumption in many practical situations, and it is arguably the strongest parametric assumption one can impose on $\sigma(x)$ besides complete knowledge assumed under case 1. The consideration of case 3 is intended to serve as a reference for case 2, so as to shed light on how much efficiency one may lose due to nonparametric estimation of $\sigma(x)$.

Table 3.1 summarizes the procedures being considered by recursion and variance assumption. The equivalence of LSR-c2 and SA-c2 and their asymptotic properties have been discussed. Under case 1, the equivalence between stochastic approximation and least square recursion also holds and standard asymptotic results can be applied

Table 3.1: Summary of procedures

Assumption on $\sigma(x)$	Least Square Recursion $X_{n+1} = \bar{X}_n - \frac{1}{nb}\sum_{i=1}^{n}(U_{in} - t_0)$	Stochastic Approximation $X_{n+1} = X_n - \frac{1}{nb}(U_n - t_0)$
Case 1 (known variance)	LSR-c1 $U_{in} = \bar{Y}_i + z_p\sigma(X_i)$	SA-c1 $U_n = \bar{Y}_n + z_p\sigma(X_n)$
Case 2 (heteroscedasticity)	LSR-c2 $U_{in} = \bar{Y}_i + z_p\sqrt{\lambda_m}S_i$	SA-c2 $U_n = \bar{Y}_n + z_p\sqrt{\lambda_m}S_n$
Case 3 (homoscedasticity)	LSR-c3 $U_{in} = \bar{Y}_i + z_p\sqrt{\frac{1}{n}\sum_{i=1}^{n}S_i^2}$	SA-c3 $U_n = \bar{Y}_n + z_p\sqrt{\frac{1}{n}\sum_{i=1}^{n}S_i^2}$

to show that $X_n \to \theta$ a.s. and

$$\sqrt{n}(X_n - \theta) \xrightarrow{d} N\left(0, \frac{\sigma^2(\theta)}{mb(2f'(\theta) - b)}\right). \tag{3.17}$$

The equivalence of stochastic approximation and least square recursion breaks down under case 3. Moreover, standard asymptotic results can be applied to neither SA-c3 nor LSR-c3 because the summands are correlated in a complex way via U_i and U_{in}. To establish asymptotic property of LSR-c3 under homoscedasticity, Hu and Cheung [14] first showed LSR-c3 can be seen as a Robbins-Monro procedure with some small bias that does not affect the asymptotic properties.

Lemma 3.1. *The design sequence $\{X_n\}$ generated by LSR-c3 under homoscedasticity can be represented as*

$$X_{n+1} = X_n - \frac{1}{nb}\left[\bar{Y}_n + \frac{z_p}{2\sigma}\left(S_n^2 - \sigma^2\right) + z_p\sigma - t_0\right] + \xi_n.$$

where $\sum_{n=1}^{\infty} E\left(|\xi_n||\mathcal{F}_{n-1}\right) < \infty$ a.s. and $\mathcal{F}_{n-1}$ denotes the σ-field generated by $(X_i, \epsilon_{i1}, \epsilon_{i2}, \ldots, \epsilon_{im})$ for $i = 1, \ldots, n-1$.

Note that $E\left(\bar{Y}_n + \frac{z_p}{2\sigma}\left(S_n^2 - \sigma^2\right) + z_p\sigma|X_n\right) = f(X_n)$. It can then be shown that

when homoscedasticity in fact holds, the sequence $\{X_n\}$ generated by LSR-c3 converges to θ with probability one and if $b < 2f'(\theta)$,

$$\sqrt{n}(X_n - \theta) \xrightarrow{d} N\left(0, \frac{\sigma^2}{mb(2f'(\theta) - b)}\left(1 + \frac{z_p^2}{2}\frac{m}{m-1}\right)\right). \tag{3.18}$$

Analogous arguments can be used to obtain the properties of SA-c3 under homoscedasticity. In an unpublished manuscript, Cheung [4] showed that design sequence generated under SA-c3 is indeed strongly consistent for θ and $\sqrt{n}(X_n - \theta)$ converges weakly to a normal distribution with mean 0 and variance

$$\frac{\sigma^2}{mb(2f'(\theta) - b)}\left(1 + \frac{b}{f'(\theta)}z_p^2\frac{m}{m-1}\right), \tag{3.19}$$

which is minimized at

$$b = \frac{2}{1 + \sqrt{1 + 2z_p^2\frac{m}{m-1}}}f'(\theta).$$

3.5.2 Asymptotic Efficiency Comparisons

As a consequence of (3.17), (3.9), (3.18) and (3.19), we can study the asymptotic relative efficiencies of the procedures in Table 3.1 when homoscedasticity in truth holds, i.e. $\sigma(x) \equiv \sigma$. To investigate the efficiency gain in using continuous instead of dichotomized outcomes, logit-MLE is included in the comparisons. The logit-MLE recursion based on dichotomised data solves

$$\sum_{i=1}^{n}\left[\sum_{j=1}^{m} 1\{Y_{ij} > t_0\} - \frac{mpe^{\tilde{b}(\tilde{X}_i - \tilde{\theta}_n)}}{1 - p + pe^{\tilde{b}(\tilde{X}_i - \tilde{\theta}_n)}}\right] = 0$$

and set $\tilde{X}_{n+1} = \tilde{\theta}_n$. In practice, to ensure the existence and uniqueness of $\tilde{\theta}_n$, we can adopt a two-stage approach that assigns doses initially via the stochastic approximation based on the dichotomizes data: $\tilde{X}_{n+1} = \tilde{X}_n - (n\tilde{b})^{-1}\left(m^{-1}\sum_{j=1}^{m} 1\{Y_{ij} > t_0\} - p\right)$. Applying results in Ying and Wu [33] gives that $\tilde{X}_n \to \theta$ a.s. and that if $\tilde{b} <$

$2\phi(z_p)\left(\sigma p(1-p)\right)^{-1} f'(\theta)$, then $\sqrt{n}(\tilde{X}_n - \theta)$ converges weakly to a normal distribution with mean 0 and variance

$$\frac{\sigma}{m\tilde{b}\left[2f'(\theta)\phi(z_p) - \sigma\tilde{b}p(1-p)\right]}, \tag{3.20}$$

where $\phi(\cdot)$ is the standard normal pdf. The asymptotic variance in (3.20) achieves its minimum when $\tilde{b} = \phi(z_p)\left[\sigma p(1-p)\right]^{-1} f'(\theta)$.

The comparisons are based on minimum asymptotic variances. Figures 3.1 (a), (b) and (c) display the asymptotic efficiencies of case 2 and case 3 relative to case 1 with different cohort sizes. The ratios are uniformly less than 1 and all go to 0 as $p \to 0$ or 1. When $m = 3$ and $p = (0.10, 0.20)$, the relative efficiencies against case 1 are $(0.43, 0.63)$, $(0.45, 0.65)$ and $(0.34, 0.52)$ for case 2, LSR-c3 and SA-c3, respectively. The substantial efficiency loss is not surprising due to complete knowledge of σ under case 1. In contrast, the efficiency loss from assuming homoscedasticity to assuming heteroscedasticity using least square recursion is much smaller. Figure 3.1(d) shows relative efficiency of LSR-c3 versus LSR-c2 under different cohort sizes. The efficiency converges to $[2(m-1)(\lambda_m - 1)]^{-1}$ as $p \to 0$ or 1 where the ratio reaches a minimum of 0.88 when $m = 2$. The efficiency improves as the cohort size m increases, and always stays above 0.90 with $m \geq 3$. The asymptotic efficiency of LSR-c2 relative to logit-MLE is depicted in Figure 3.1 (e). When $p = 0.10$ and $m = 3$, the ratio is 1.25. As the plot shows, the efficiency gain can be considerable, especially when p is extreme.

From these comparisons, we observe that stochastic approximation seems to be making poor use of the data when U_i are correlated as is evident in the fact that SA-c3 has worse efficiency then SA-c2 even when homoscedasticity holds. In contrast, LSR-c3 uses the data much more efficiently. Another observation is that, in the context of least square recursion, efficiency loss from parametric to nonparametric variance estimation is small. This modest advantage of parametric estimation and

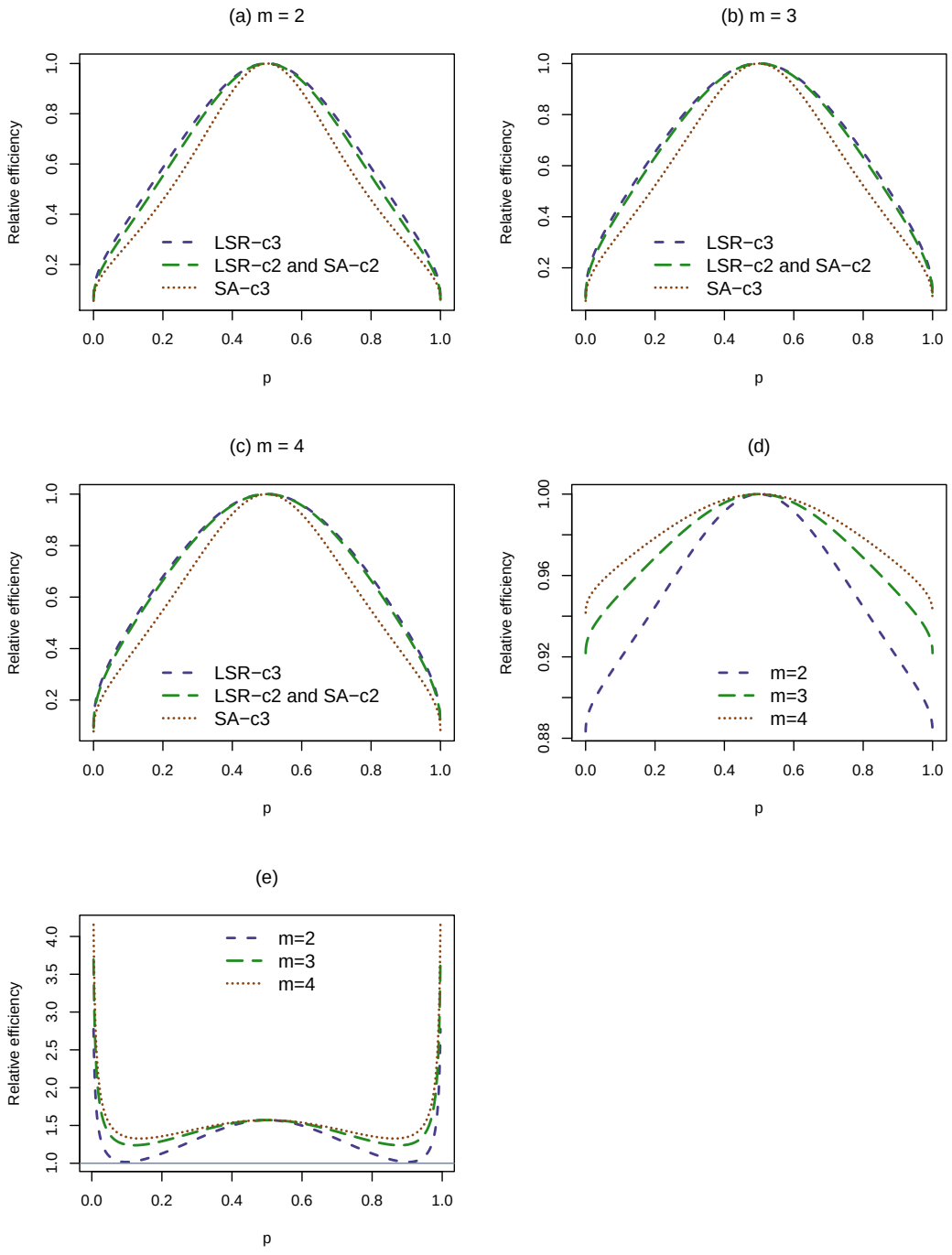

Figure 3.1: Asymptotic relative efficiencies under homoscedasticity with various cohort sizes. (a), (b) and (c): case 2 and case 3 relative to case 1 (d): LSR-c2 relative to LSR-c3 (e) LSR-c2 relative to logit-MLE.

the irreversible effect misspecification on $\sigma(\cdot)$ can have on the final estimate lead to the conclusion that, unless there are compelling reasons, parametric assumptions on $\sigma(\cdot)$ should be avoided. Nonparametric estimation of variance seems to be a reasonable choice when using continuous data.

3.5.3 Simulation Studies

We conducted a series of simulation studies to compare efficiency in finite-sample settings. The outcomes are generated with mean

$$M(x) = \frac{2\left[-c_p + 2\log(x-\theta+1) + 1.5(x-\theta)^3\right]}{1+e^{\theta-x}}, \tag{3.21}$$

variance $\sigma^2(x) \equiv 1$ for $x \in [0,1]$. We set $t_0 = 0$ so that θ as specified in (3.21) is the root to (3.3). We consider $p = 0.1, 0.2$ and $\theta = 0.25, 0.50, 0.75$. All procedures in the simulation make the working assumption that ϵ_{ij} arises from a standard normal, even though noises may be generated from other distributions to evaluate the impact of violation of normality assumption.

To restrict the doses to $[0,1]$, we apply truncation to the design points. Specifically, if $\hat{\theta}_n$ is the current design point generated by a procedure, then the next dose is set at $X_{n+1} = \max\{\min(\hat{\theta}_n, 1), 0\}$ instead of $X_{n+1} = \hat{\theta}_n$. Such truncation does not affect the asymptotic properties of a procedure (see [14]), and is often done in practice. However, with truncation, the sequences generated by least square recursion and stochastic approximation may no longer be identical even under cases 1 and 2. Thus, the simulation include all procedures in Table 3.1 as well as logit-MLE based on dichotomized data, to which truncation was also applied. In order to investigate the relative performance of the procedures when the tuning parameters b (for least square recursion and stochastic approximation) and $\tilde{b}$ (for logit-MLE) are both well and poorly chosen, we set b and $\tilde{b}$ at their respective optimal value that minimizes the asymptotic variance as well as half of the optimal value.

In the first set of simulations, we ran the procedures with $m = 3$, $n = 15$, and also considered the fully sequential version of logit-MLE (denoted as logit-MLE(f)), i.e., $m = 1$ and $n = 45$. Each simulated trial has starting dose $X_1 = 0.25$ or 0.50. Table 3.2 summarizes the results of the first simulation study with optimal b and $\tilde{b}$. Overall, the biases are small when compared to the variances for all procedures. In line with the asymptotic comparison, the efficiency against case 1 (assuming known σ) is quite low for cases 2 and 3, especially when the target percentile is extreme, i.e., $p = 0.1$. For least square recursion, assuming heteroscedasticity instead of homoscedasticity yields further slight drop in efficiency; while with stochastic approximation efficiency improves noticeably. Stochastic approximation seems to have comparable bias but smaller variance to its least square recursion counterpart under cases 1 and 2. The logit-MLE shows a marked efficiency loss when compared to either stochastic approximation or least square recursion, with the exception of SA-c3 under some scenarios. The fully sequential logit-MLE retrieves some information loss from the small-group logit-MLE, but the gain in efficiency does not completely recover the loss due to the use of dichotomised data. The impact of the starting dose X_1 on the operating characteristics is comparatively nuanced, although the logit-MLE tends to have smaller variance when the starting dose X_1 is closer to the target dose θ.

Results from the first set of simulations when b and $\tilde{b}$ are set at half the optimal values are displayed in Table 3.3. In line with the asymptotic theory, setting the tuning parameter to be optimal generally yields better bias and variance. The only exception is when $p = 0.1$ and $\theta = 0.75$, the logit-MLE with a low starting dose ($X_1 = 0.25$) has worse mean squared error when compared to Table 3.2. It is known that logit-MLE with a large $\tilde{b}$ corresponds to small changes in subsequent doses; therefore, with a finite sample size, it will have difficulty climbing to a high θ if the starting dose is low, and can be improved with the use of a smaller $\tilde{b}$. Interestingly,

using a suboptimal b improves the relative performance of SA-c3. While still inferior to SA-c2, SA-c3 now generally has slightly smaller mean squared error than LSR-c3.

Tables 3.4 and 3.5 displays results from the second set of simulations where we further study the effects of group sizes. Specifically, we consider designs with a bigger group size, $m = 5$ and set $n = 9$ so that the total sample size remains 45. We also consider random group sizes generated by permuting $\{2, 2, 2, 3, 3, 3, 4, 4, 5, 5, 6, 6\}$ so that there are $n = 12$ groups and a total of 45 subjects in each simulated trial.

Generally, the relative performance between stochastic approximation and least square recursion and the relative performance among the cases within the method follow the same patterns as in Tables 3.2 and 3.3. A bigger group size seems to have a slightly negative effect on logit-MLE. Specifically, logit-MLE(f) seems to outperform the small-group logit-MLE in finite sample size. Note that the asymptotic variance of logit-MLE does not depend on group size as long as the total sample size nm is the same. In contrast, the impact of group size on least squares recursion is relatively small. There is in fact slight improvement in relative efficiency of case 2 and case 3 against case 1 when $m = 5$: this is in line with the fact that bigger group size improves asymptotic efficiency of the least squares recursion with unknown variance.

The third simulation study aims to examine the robustness of least squares recursion and stochastic approximation when ϵ_{ij} is non-normal. While the procedures use normality as the working assumption, we generated noises from other distributions with mean 0 and unit variance. Tables 3.6 and 3.7 summarize the results under logistic distribution with mean 0 and scale 0.55, and t-distribution with 6 degrees of freedom (scaled to have unit variance).

Overall, both least squares recursion procedure and stochastic approximation induce larger biases under misspecified distribution, except for SA-c2 and SA-c3 with $p = 0.10$ and $\theta = 0.25$. The increased biases are still generally small when compared

to the variances. Interestingly, assuming heteroscedasticity (case 2) seems to mitigate the increase in bias due to misspecification, and as a result, LSR-c2 now has smaller mean squared error then LSR-c3. It is also important to note that least squares recursion and stochastic approximation are generally superior to the logit-MLE in terms of mean squared error, even though the latter did not require normality to be valid. This suggests that variability, rather than bias, is the limiting factor of performance when sample size ranges from small to moderate. In other words, the information retrieved via the use of continuous data outweighs the potential bias induced by misspecification.

Table 3.2: Properties of least square recursion, stochastic approximation and logit-MLE with $m = 3$, $n = 15$ and the fully sequential logit-MLE(f) ($m = 1$, $n = 45$). Tuning parameters b and $\tilde{b}$ equal optimal values that minimize asymptotic variances.

p	θ		$X_1 = 0.25$				$X_1 = 0.50$			
			bias	var	rmse_{LSR}	rmse_{SA}	bias	var	rmse_{LSR}	rmse_{SA}
0.10	0.25	LSR-c1	-0.05	1.05	—	0.90	-0.06	1.05	—	0.90
		LSR-c2	-0.09	2.11	0.50	0.45	-0.09	2.11	0.50	0.45
		LSR-c3	-0.04	2.03	0.52	0.47	-0.05	2.03	0.52	0.47
		SA-c1	0.05	0.95	1.11	—	0.05	0.95	1.11	—
		SA-c2	0.19	1.79	0.58	0.52	0.18	1.79	0.58	0.52
		SA-c3	0.23	2.22	0.46	0.42	0.23	2.22	0.46	0.42
		logit-MLE	-0.04	2.71	0.39	0.35	-0.12	2.38	0.44	0.40
		logit-MLE(f)	-0.02	2.59	0.41	0.37	-0.11	2.41	0.44	0.39
	0.50	LSR-c1	0.00	1.03	—	0.99	-0.01	1.03	—	0.99
		LSR-c2	-0.01	2.25	0.46	0.45	-0.01	2.25	0.46	0.45
		LSR-c3	0.04	2.14	0.48	0.48	0.03	2.14	0.48	0.48
		SA-c1	-0.00	1.02	1.01	—	-0.01	1.02	1.01	—
		SA-c2	0.01	2.14	0.48	0.48	0.01	2.14	0.48	0.48
		SA-c3	0.12	2.63	0.39	0.38	0.12	2.63	0.39	0.38
		logit-MLE	-0.11	3.60	0.29	0.28	-0.09	3.13	0.33	0.32
		logit-MLE(f)	-0.09	3.39	0.30	0.30	-0.09	3.09	0.33	0.33
	0.75	LSR-c1	0.10	1.04	—	0.90	0.04	1.03	—	0.92
		LSR-c2	0.13	2.12	0.49	0.44	0.09	2.12	0.49	0.45
		LSR-c3	0.18	2.02	0.51	0.46	0.13	2.02	0.51	0.47
		SA-c1	-0.03	0.94	1.11	—	-0.05	0.95	1.09	—
		SA-c2	-0.15	1.84	0.57	0.51	-0.16	1.84	0.56	0.51
		SA-c3	-0.01	2.20	0.48	0.43	-0.01	2.20	0.47	0.43
		logit-MLE	-1.35	4.96	0.15	0.14	-0.19	3.11	0.33	0.30
		logit-MLE(f)	-0.98	4.32	0.20	0.18	-0.15	2.96	0.35	0.32
0.20	0.25	LSR-c1	-0.03	0.81	—	0.92	-0.04	0.81	—	0.92
		LSR-c2	-0.05	1.23	0.66	0.61	-0.06	1.23	0.66	0.61
		LSR-c3	-0.02	1.19	0.68	0.63	-0.02	1.19	0.68	0.63
		SA-c1	0.04	0.75	1.08	—	0.03	0.74	1.09	—
		SA-c2	0.08	1.09	0.74	0.68	0.08	1.09	0.74	0.68
		SA-c3	0.13	1.30	0.61	0.57	0.13	1.30	0.61	0.56
		logit-MLE	-0.04	1.59	0.51	0.47	-0.06	1.53	0.53	0.49
		logit-MLE(f)	-0.04	1.57	0.51	0.48	-0.07	1.58	0.51	0.47
	0.50	LSR-c1	0.00	0.79	—	0.99	-0.00	0.79	—	0.99
		LSR-c2	0.00	1.22	0.65	0.64	-0.00	1.22	0.65	0.64
		LSR-c3	0.03	1.18	0.67	0.66	0.02	1.18	0.67	0.66
		SA-c1	0.00	0.79	1.01	—	-0.00	0.79	1.01	—
		SA-c2	0.00	1.20	0.66	0.65	0.00	1.20	0.66	0.66
		SA-c3	0.09	1.42	0.56	0.55	0.09	1.42	0.56	0.55
		logit-MLE	-0.00	1.84	0.43	0.43	-0.05	1.65	0.48	0.48
		logit-MLE(f)	0.00	1.81	0.44	0.44	-0.05	1.68	0.47	0.47
	0.75	LSR-c1	0.08	0.80	—	0.92	0.03	0.80	—	0.94
		LSR-c2	0.10	1.23	0.66	0.60	0.05	1.22	0.65	0.61
		LSR-c3	0.13	1.19	0.67	0.62	0.08	1.18	0.67	0.63
		SA-c1	-0.01	0.74	1.09	—	-0.03	0.75	1.07	—
		SA-c2	-0.05	1.10	0.74	0.68	-0.07	1.10	0.72	0.68
		SA-c3	0.04	1.28	0.63	0.58	0.04	1.28	0.62	0.58
		logit-MLE	0.11	2.09	0.39	0.35	0.00	1.77	0.45	0.42
		logit-MLE(f)	0.09	1.90	0.42	0.39	0.00	1.75	0.46	0.43

bias: bias $\times 10$; var: variance $\times 10^2$; rmse_{LSR}: mean squared error ratio relative to LSR-c1; rmse_{SA}: mean squared error ratio relative to SA-c1

Table 3.3: Properties of least square recursion, stochastic approximation and logit-MLE with $m = 3$, $n = 15$ and the fully sequential logit-MLE(f) ($m = 1$, $n = 45$). Tuning parameters b and $\tilde{b}$ equal half the optimal values that minimize asymptotic variances.

p	θ		$X_1 = 0.25$				$X_1 = 0.50$			
			bias	var	rmse_{LSR}	rmse_{SA}	bias	var	rmse_{LSR}	rmse_{SA}
0.10	0.25	LSR-c1	-0.10	1.51	—	0.90	-0.10	1.52	—	0.90
		LSR-c2	-0.20	2.99	0.50	0.45	-0.21	2.99	0.50	0.45
		LSR-c3	-0.18	2.88	0.52	0.47	-0.19	2.88	0.52	0.47
		SA-c1	0.06	1.37	1.11	—	0.06	1.37	1.11	—
		SA-c2	0.25	2.59	0.57	0.52	0.25	2.59	0.58	0.52
		SA-c3	0.23	2.75	0.54	0.49	0.23	2.75	0.54	0.49
		logit-MLE	-0.44	3.09	0.46	0.42	-0.54	3.01	0.46	0.42
		logit-MLE(f)	-0.35	3.19	0.46	0.41	-0.43	3.11	0.46	0.42
	0.50	LSR-c1	0.00	1.48	—	1.00	0.00	1.48	—	1.00
		LSR-c2	-0.01	3.33	0.45	0.45	-0.01	3.33	0.45	0.44
		LSR-c3	-0.00	3.15	0.47	0.47	-0.01	3.15	0.47	0.47
		SA-c1	0.00	1.48	1.00	—	0.00	1.48	1.00	—
		SA-c2	0.02	3.20	0.46	0.46	0.02	3.20	0.46	0.46
		SA-c3	0.08	3.35	0.44	0.44	0.08	3.35	0.44	0.44
		logit-MLE	-0.20	4.88	0.30	0.30	-0.43	4.27	0.33	0.33
		logit-MLE(f)	-0.21	4.58	0.32	0.32	-0.40	4.17	0.34	0.34
	0.75	LSR-c1	0.12	1.49	—	0.91	0.09	1.48	—	0.91
		LSR-c2	0.23	3.01	0.49	0.44	0.19	3.01	0.49	0.45
		LSR-c3	0.24	2.88	0.51	0.46	0.20	2.88	0.51	0.47
		SA-c1	-0.05	1.36	1.10	—	-0.05	1.36	1.09	—
		SA-c2	-0.19	2.70	0.55	0.50	-0.19	2.70	0.54	0.50
		SA-c3	-0.08	2.76	0.54	0.49	-0.08	2.76	0.54	0.49
		logit-MLE	-0.29	4.74	0.31	0.28	-0.04	4.11	0.36	0.33
		logit-MLE(f)	-0.09	4.24	0.35	0.32	-0.11	4.04	0.37	0.34
0.20	0.25	LSR-c1	-0.06	1.16	—	0.93	-0.07	1.16	—	0.93
		LSR-c2	-0.11	1.77	0.65	0.61	-0.12	1.78	0.65	0.60
		LSR-c3	-0.10	1.72	0.67	0.62	-0.11	1.73	0.67	0.62
		SA-c1	0.04	1.08	1.08	—	0.04	1.08	1.08	—
		SA-c2	0.09	1.58	0.73	0.68	0.09	1.58	0.73	0.68
		SA-c3	0.12	1.70	0.68	0.63	0.12	1.70	0.68	0.63
		logit-MLE	-0.24	2.13	0.53	0.49	-0.27	2.17	0.52	0.48
		logit-MLE(f)	-0.21	2.13	0.54	0.50	-0.24	2.14	0.53	0.49
	0.50	LSR-c1	0.01	1.13	—	1.00	0.00	1.13	—	1.00
		LSR-c2	0.00	1.77	0.64	0.64	0.00	1.77	0.64	0.64
		LSR-c3	0.01	1.70	0.66	0.66	0.00	1.70	0.66	0.66
		SA-c1	0.00	1.13	1.00	—	0.01	1.13	1.00	—
		SA-c2	0.01	1.76	0.64	0.64	0.01	1.76	0.64	0.64
		SA-c3	0.06	1.88	0.60	0.60	0.06	1.88	0.60	0.60
		logit-MLE	-0.15	2.37	0.47	0.47	-0.19	2.32	0.48	0.48
		logit-MLE(f)	-0.16	2.32	0.48	0.48	-0.17	2.33	0.48	0.48
	0.75	LSR-c1	0.09	1.15	—	0.92	0.07	1.14	—	0.93
		LSR-c2	0.14	1.77	0.65	0.60	0.11	1.76	0.65	0.60
		LSR-c3	0.15	1.71	0.67	0.62	0.11	1.70	0.67	0.63
		SA-c1	-0.03	1.07	1.08	—	-0.03	1.07	1.07	—
		SA-c2	-0.07	1.60	0.72	0.67	-0.07	1.60	0.71	0.67
		SA-c3	-0.01	1.69	0.69	0.63	-0.01	1.69	0.68	0.63
		logit-MLE	0.19	2.52	0.45	0.42	-0.01	2.34	0.49	0.46
		logit-MLE(f)	0.06	2.44	0.47	0.44	-0.06	2.33	0.49	0.46

bias: bias $\times 10$; var: variance $\times 10^2$; rmse_{LSR}: mean squared error ratio relative to LSR-c1; rmse_{SA}: mean squared error ratio relative to SA-c1

Table 3.4: Properties of least square recursion, stochastic approximation and logit-MLE with $X_1 = 0.25$. Tuning parameters b and $\tilde{b}$ equal optimal values that minimize asymptotic variances.

p	θ		$m = 5$, $n = 9$				Varying group sizes			
			bias	var	rmse_{LSR}	rmse_{SA}	bias	var	rmse_{LSR}	rmse_{SA}
0.10	0.25	LSR-c1	-0.04	1.04	—	0.91	-0.04	1.17	—	0.90
		LSR-c2	-0.06	1.94	0.53	0.48	-0.05	2.42	0.48	0.43
		LSR-c3	-0.02	1.90	0.55	0.50	-0.00	2.30	0.51	0.46
		SA-c1	0.04	0.94	1.10	—	0.06	1.05	1.11	—
		SA-c2	0.13	1.67	0.62	0.56	0.23	2.01	0.57	0.51
		SA-c3	0.15	2.09	0.49	0.45	0.29	2.55	0.44	0.40
		logit-MLE	-0.02	2.65	0.39	0.36	-0.03	2.71	0.43	0.39
	0.50	LSR-c1	0.01	1.03	—	0.99	0.02	1.16	—	0.98
		LSR-c2	0.02	2.03	0.50	0.50	0.02	2.68	0.43	0.42
		LSR-c3	0.06	1.98	0.52	0.51	0.08	2.52	0.46	0.45
		SA-c1	0.01	1.01	1.01	—	0.01	1.14	1.02	—
		SA-c2	0.02	1.94	0.53	0.52	0.05	2.48	0.47	0.46
		SA-c3	0.08	2.43	0.42	0.42	0.16	3.11	0.37	0.36
		logit-MLE	-0.09	3.71	0.28	0.27	-0.07	3.73	0.31	0.31
	0.75	LSR-c1	0.15	1.04	—	0.88	0.14	1.18	—	0.87
		LSR-c2	0.19	1.97	0.53	0.47	0.18	2.45	0.48	0.42
		LSR-c3	0.23	1.92	0.54	0.48	0.23	2.32	0.51	0.44
		SA-c1	0.02	0.94	1.14	—	-0.01	1.05	1.15	—
		SA-c2	-0.06	1.70	0.63	0.55	-0.13	2.12	0.56	0.49
		SA-c3	-0.00	2.09	0.51	0.45	0.01	2.57	0.47	0.41
		logit-MLE	-1.57	5.26	0.14	0.12	-1.49	5.16	0.16	0.14
0.20	0.25	LSR-c1	-0.02	0.80	—	0.93	-0.02	0.91	—	0.92
		LSR-c2	-0.03	1.15	0.70	0.64	-0.03	1.42	0.64	0.58
		LSR-c3	0.00	1.13	0.71	0.66	0.01	1.36	0.67	0.61
		SA-c1	0.03	0.74	1.08	—	0.05	0.83	1.09	—
		SA-c2	0.06	1.03	0.77	0.72	0.11	1.24	0.72	0.66
		SA-c3	0.08	1.23	0.65	0.60	0.16	1.50	0.59	0.54
		logit-MLE	-0.04	1.60	0.50	0.46	-0.02	1.57	0.58	0.53
	0.50	LSR-c1	0.01	0.79	—	0.99	0.02	0.90	—	0.98
		LSR-c2	0.02	1.15	0.69	0.68	0.03	1.43	0.63	0.62
		LSR-c3	0.04	1.13	0.70	0.70	0.06	1.37	0.65	0.64
		SA-c1	0.01	0.78	1.01	—	0.02	0.88	1.02	—
		SA-c2	0.02	1.13	0.70	0.70	0.03	1.39	0.65	0.64
		SA-c3	0.07	1.33	0.59	0.59	0.12	1.67	0.53	0.53
		logit-MLE	0.01	1.85	0.43	0.42	0.03	1.84	0.49	0.48
	0.75	LSR-c1	0.13	0.81	—	0.90	0.12	0.92	—	0.89
		LSR-c2	0.15	1.16	0.69	0.62	0.14	1.43	0.64	0.57
		LSR-c3	0.17	1.14	0.70	0.63	0.18	1.37	0.66	0.59
		SA-c1	0.04	0.74	1.11	—	0.01	0.83	1.12	—
		SA-c2	0.02	1.03	0.80	0.72	-0.03	1.26	0.74	0.66
		SA-c3	0.05	1.22	0.67	0.60	0.05	1.49	0.62	0.55
		logit-MLE	0.09	2.37	0.35	0.31	0.09	2.23	0.42	0.37

bias: bias $\times 10$; var: variance $\times 10^2$; rmse_{LSR}: mean squared error ratio relative to LSR-c1; rmse_{SA}: mean squared error ratio relative to SA-c1

Table 3.5: Properties of least square recursion, stochastic approximation and logit-MLE with $X_1 = 0.25$. Tuning parameters b and $\tilde{b}$ equal half the optimal values that minimize asymptotic variances.

p	θ		$m = 5$, $n = 9$				Varying group sizes			
			bias	var	rmse_{LSR}	rmse_{SA}	bias	var	rmse_{LSR}	rmse_{SA}
0.10	0.25	LSR-c1	-0.15	1.55	—	0.90	-0.11	1.73	—	0.89
		LSR-c2	-0.22	2.80	0.55	0.50	-0.20	3.40	0.51	0.45
		LSR-c3	-0.21	2.74	0.57	0.51	-0.17	3.24	0.54	0.48
		SA-c1	0.02	1.41	1.11	—	0.07	1.56	1.12	—
		SA-c2	0.16	2.46	0.63	0.57	0.31	2.93	0.58	0.52
		SA-c3	0.16	2.77	0.56	0.50	0.31	3.34	0.51	0.45
		logit-MLE	-0.56	3.12	0.46	0.41	-0.48	3.32	0.49	0.44
	0.50	LSR-c1	-0.01	1.53	—	1.00	0.01	1.72	—	0.99
		LSR-c2	0.00	3.03	0.50	0.50	-0.00	4.04	0.43	0.42
		LSR-c3	0.01	2.96	0.52	0.51	0.01	3.81	0.45	0.45
		SA-c1	-0.02	1.52	1.00	—	0.01	1.71	1.01	—
		SA-c2	0.01	2.94	0.52	0.52	0.04	3.74	0.46	0.46
		SA-c3	0.05	3.30	0.46	0.46	0.13	4.17	0.41	0.41
		logit-MLE	-0.22	5.17	0.29	0.29	-0.22	5.26	0.32	0.32
	0.75	LSR-c1	0.18	1.57	—	0.89	0.17	1.75	—	0.88
		LSR-c2	0.30	2.80	0.55	0.49	0.28	3.48	0.50	0.44
		LSR-c3	0.31	2.74	0.56	0.50	0.30	3.33	0.52	0.46
		SA-c1	-0.05	1.42	1.13	—	-0.05	1.56	1.14	—
		SA-c2	-0.13	2.52	0.63	0.56	-0.21	3.15	0.56	0.49
		SA-c3	-0.07	2.78	0.58	0.51	-0.07	3.39	0.52	0.46
		logit-MLE	-0.48	5.25	0.29	0.26	-0.34	5.05	0.34	0.30
0.20	0.25	LSR-c1	-0.10	1.19	—	0.92	-0.08	1.35	—	0.91
		LSR-c2	-0.13	1.70	0.70	0.65	-0.12	2.07	0.65	0.59
		LSR-c3	-0.13	1.68	0.71	0.66	-0.11	1.99	0.67	0.62
		SA-c1	0.01	1.11	1.08	—	0.05	1.23	1.09	—
		SA-c2	0.05	1.53	0.78	0.72	0.12	1.80	0.74	0.68
		SA-c3	0.08	1.72	0.70	0.64	0.17	2.05	0.65	0.60
		logit-MLE	-0.34	2.16	0.53	0.49	-0.29	2.18	0.60	0.55
	0.50	LSR-c1	-0.01	1.16	—	1.00	0.01	1.31	—	1.00
		LSR-c2	0.01	1.67	0.69	0.69	0.01	2.13	0.62	0.62
		LSR-c3	0.01	1.65	0.71	0.70	0.01	2.04	0.64	0.64
		SA-c1	-0.02	1.16	1.00	—	0.01	1.31	1.00	—
		SA-c2	-0.00	1.66	0.70	0.70	0.01	2.09	0.63	0.63
		SA-c3	0.03	1.86	0.62	0.62	0.09	2.34	0.56	0.56
		logit-MLE	-0.19	2.51	0.46	0.46	-0.18	2.54	0.51	0.51
	0.75	LSR-c1	0.14	1.21	—	0.90	0.14	1.36	—	0.89
		LSR-c2	0.20	1.71	0.70	0.63	0.20	2.11	0.64	0.57
		LSR-c3	0.21	1.69	0.71	0.64	0.20	2.04	0.66	0.59
		SA-c1	-0.03	1.11	1.11	—	-0.03	1.23	1.12	—
		SA-c2	-0.05	1.53	0.80	0.72	-0.08	1.88	0.73	0.65
		SA-c3	-0.01	1.70	0.72	0.65	-0.00	2.06	0.67	0.60
		logit-MLE	0.28	2.66	0.45	0.41	0.22	2.67	0.51	0.45

bias: bias $\times 10$; var: variance $\times 10^2$; rmse_{LSR}: mean squared error ratio relative to LSR-c1; rmse_{SA}: mean squared error ratio relative to SA-c1

Table 3.6: Properties of least square recursion, stochastic approximation and logit-MLE ($m = 3$, $n = 15$) and the fully sequential logit-MLE(f) ($m = 1$, $n = 45$) with $X_1 = 0.25$. Tuning parameters b and $\tilde{b}$ equal the optimal values.

p	θ		Logistic				t_6			
			bias	var	rmse_{LSR}	rmse_{SA}	bias	var	rmse_{LSR}	rmse_{SA}
0.10	0.25	LSR-c1	-0.50	1.00	—	0.82	-0.74	0.90	—	0.80
		LSR-c2	-0.30	2.11	0.57	0.46	-0.40	2.02	0.67	0.53
		LSR-c3	-0.40	2.10	0.55	0.45	-0.54	2.02	0.62	0.50
		SA-c1	-0.37	0.88	1.22	—	-0.60	0.79	1.25	—
		SA-c2	0.02	1.75	0.71	0.58	-0.07	1.66	0.87	0.69
		SA-c3	-0.10	2.23	0.56	0.46	-0.24	2.17	0.65	0.52
		logit-MLE	-0.04	2.74	0.46	0.37	-0.08	2.57	0.56	0.45
		logit-MLE(f)	-0.06	2.64	0.47	0.39	-0.11	2.56	0.56	0.45
	0.50	LSR-c1	-0.45	1.01	—	0.99	-0.69	0.93	—	0.98
		LSR-c2	-0.25	2.40	0.49	0.48	-0.36	2.36	0.57	0.55
		LSR-c3	-0.37	2.49	0.46	0.46	-0.55	2.58	0.49	0.48
		SA-c1	-0.45	0.99	1.02	—	-0.68	0.91	1.02	—
		SA-c2	-0.19	2.23	0.53	0.53	-0.28	2.16	0.63	0.62
		SA-c3	-0.27	2.92	0.40	0.40	-0.43	3.00	0.44	0.43
		logit-MLE	-0.18	3.71	0.32	0.32	-0.19	3.68	0.38	0.37
		logit-MLE(f)	-0.18	3.62	0.33	0.33	-0.16	3.47	0.40	0.40
	0.75	LSR-c1	-0.36	1.03	—	0.99	-0.60	0.95	—	1.03
		LSR-c2	-0.09	2.30	0.50	0.50	-0.20	2.31	0.56	0.58
		LSR-c3	-0.21	2.40	0.47	0.47	-0.39	2.57	0.48	0.50
		SA-c1	-0.45	0.95	1.01	—	-0.69	0.88	0.97	—
		SA-c2	-0.32	2.02	0.55	0.54	-0.40	2.05	0.59	0.61
		SA-c3	-0.37	2.61	0.42	0.42	-0.53	2.82	0.42	0.44
		logit-MLE	-1.19	4.89	0.18	0.18	-1.22	4.89	0.21	0.21
		logit-MLE(f)	-0.90	4.38	0.22	0.22	-0.95	4.36	0.25	0.26
0.20	0.25	LSR-c1	-0.47	0.78	—	0.85	-0.62	0.72	—	0.84
		LSR-c2	-0.35	1.23	0.74	0.63	-0.43	1.17	0.82	0.69
		LSR-c3	-0.42	1.24	0.71	0.60	-0.53	1.20	0.75	0.63
		SA-c1	-0.39	0.70	1.18	—	-0.53	0.65	1.19	—
		SA-c2	-0.19	1.05	0.92	0.78	-0.26	0.99	1.05	0.88
		SA-c3	-0.25	1.28	0.75	0.63	-0.35	1.25	0.81	0.68
		logit-MLE	-0.08	1.47	0.68	0.58	-0.11	1.35	0.82	0.68
		logit-MLE(f)	-0.09	1.46	0.68	0.58	-0.11	1.34	0.82	0.69
	0.50	LSR-c1	-0.44	0.78	—	0.99	-0.58	0.72	—	0.99
		LSR-c2	-0.31	1.27	0.71	0.70	-0.39	1.22	0.77	0.76
		LSR-c3	-0.38	1.30	0.67	0.66	-0.50	1.33	0.67	0.66
		SA-c1	-0.43	0.77	1.01	—	-0.58	0.71	1.02	—
		SA-c2	-0.29	1.23	0.73	0.73	-0.36	1.17	0.82	0.80
		SA-c3	-0.32	1.53	0.59	0.59	-0.43	1.56	0.61	0.60
		logit-MLE	-0.05	1.72	0.56	0.55	-0.05	1.58	0.67	0.66
		logit-MLE(f)	-0.08	1.67	0.58	0.57	-0.10	1.52	0.69	0.68
	0.75	LSR-c1	-0.36	0.79	—	1.00	-0.51	0.74	—	1.02
		LSR-c2	-0.22	1.28	0.69	0.70	-0.29	1.23	0.76	0.77
		LSR-c3	-0.28	1.31	0.66	0.66	-0.40	1.33	0.67	0.68
		SA-c1	-0.43	0.74	1.00	—	-0.57	0.69	0.98	—
		SA-c2	-0.32	1.18	0.72	0.72	-0.39	1.14	0.77	0.79
		SA-c3	-0.35	1.45	0.59	0.59	-0.46	1.51	0.58	0.59
		logit-MLE	0.04	2.06	0.45	0.45	0.04	1.98	0.50	0.52
		logit-MLE(f)	0.05	1.85	0.50	0.50	0.04	1.76	0.57	0.58

bias: bias $\times 10$; var: variance $\times 10^2$; rmse_{LSR}: mean squared error ratio relative to LSR-c1; rmse_{SA}: mean squared error ratio relative to SA-c1

Table 3.7: Properties of least square recursion, stochastic approximation, logit-MLE ($m = 3$, $n = 15$) and the fully sequential logit-MLE(f) ($m = 1$, $n = 45$) with $X_1 = 0.25$. Tuning parameters b and $\tilde{b}$ equal half the optimal values.

p	θ		Logistic				t_6			
			bias	var	rmse_{LSR}	rmse_{SA}	bias	var	rmse_{LSR}	rmse_{SA}
0.10	0.25	LSR-c1	-0.56	1.43	—	0.79	-0.81	1.29	—	0.77
		LSR-c2	-0.40	2.87	0.58	0.46	-0.50	2.78	0.64	0.50
		LSR-c3	-0.53	2.79	0.57	0.45	-0.68	2.70	0.62	0.48
		SA-c1	-0.36	1.26	1.26	—	-0.58	1.16	1.30	—
		SA-c2	0.11	2.42	0.72	0.57	0.02	2.37	0.82	0.63
		SA-c3	-0.09	2.74	0.64	0.50	-0.21	2.69	0.71	0.55
		logit-MLE	-0.49	3.16	0.51	0.41	-0.52	3.12	0.58	0.44
		logit-MLE(f)	-0.43	3.11	0.53	0.42	-0.46	3.04	0.60	0.46
	0.50	LSR-c1	-0.46	1.45	—	0.99	-0.70	1.40	—	0.99
		LSR-c2	-0.26	3.51	0.46	0.46	-0.38	3.53	0.51	0.51
		LSR-c3	-0.43	3.63	0.44	0.43	-0.62	3.75	0.46	0.45
		SA-c1	-0.45	1.45	1.01	—	-0.70	1.39	1.01	—
		SA-c2	-0.17	3.25	0.51	0.50	-0.27	3.23	0.57	0.57
		SA-c3	-0.30	3.64	0.44	0.44	-0.46	3.75	0.48	0.47
		logit-MLE	-0.31	5.06	0.32	0.32	-0.36	4.91	0.38	0.37
		logit-MLE(f)	-0.37	4.76	0.34	0.34	-0.35	4.61	0.40	0.40
	0.75	LSR-c1	-0.37	1.50	—	0.99	-0.63	1.43	—	1.02
		LSR-c2	-0.02	3.29	0.50	0.49	-0.15	3.36	0.54	0.55
		LSR-c3	-0.18	3.42	0.47	0.47	-0.39	3.71	0.47	0.48
		SA-c1	-0.48	1.38	1.01	—	-0.72	1.35	0.98	—
		SA-c2	-0.36	2.91	0.54	0.53	-0.43	3.03	0.57	0.58
		SA-c3	-0.43	3.20	0.48	0.48	-0.58	3.45	0.48	0.49
		logit-MLE	-0.27	4.92	0.33	0.32	-0.35	4.90	0.36	0.37
		logit-MLE(f)	-0.12	4.50	0.36	0.36	-0.15	4.46	0.41	0.42
0.20	0.25	LSR-c1	-0.52	1.12	—	0.83	-0.68	1.05	—	0.81
		LSR-c2	-0.43	1.73	0.72	0.60	-0.51	1.66	0.78	0.64
		LSR-c3	-0.52	1.72	0.70	0.58	-0.64	1.67	0.72	0.59
		SA-c1	-0.38	1.00	1.21	—	-0.53	0.95	1.23	—
		SA-c2	-0.16	1.47	0.93	0.77	-0.23	1.41	1.03	0.84
		SA-c3	-0.25	1.66	0.81	0.67	-0.35	1.63	0.86	0.70
		logit-MLE	-0.30	1.98	0.67	0.55	-0.32	1.92	0.74	0.61
		logit-MLE(f)	-0.28	1.94	0.69	0.57	-0.28	1.90	0.76	0.62
	0.50	LSR-c1	-0.44	1.11	—	1.00	-0.60	1.07	—	1.00
		LSR-c2	-0.32	1.83	0.68	0.67	-0.40	1.81	0.72	0.72
		LSR-c3	-0.42	1.87	0.64	0.64	-0.56	1.95	0.63	0.63
		SA-c1	-0.44	1.11	1.00	—	-0.60	1.07	1.00	—
		SA-c2	-0.29	1.79	0.70	0.69	-0.37	1.76	0.75	0.75
		SA-c3	-0.36	1.99	0.62	0.61	-0.47	2.05	0.63	0.63
		logit-MLE	-0.23	2.26	0.56	0.56	-0.25	2.18	0.64	0.64
		logit-MLE(f)	-0.23	2.15	0.59	0.59	-0.25	2.04	0.68	0.68
	0.75	LSR-c1	-0.38	1.14	—	1.00	-0.54	1.10	—	1.02
		LSR-c2	-0.20	1.85	0.68	0.68	-0.30	1.84	0.72	0.74
		LSR-c3	-0.30	1.89	0.65	0.65	-0.45	1.96	0.64	0.66
		SA-c1	-0.46	1.08	1.00	—	-0.61	1.05	0.98	—
		SA-c2	-0.34	1.71	0.70	0.70	-0.41	1.73	0.73	0.75
		SA-c3	-0.40	1.88	0.63	0.63	-0.51	1.98	0.62	0.64
		logit-MLE	0.10	2.47	0.52	0.52	0.07	2.39	0.58	0.59
		logit-MLE(f)	-0.04	2.29	0.56	0.56	-0.06	2.20	0.63	0.64

bias: bias $\times 10$; var: variance $\times 10^2$; rmse_{LSR}: mean squared error ratio relative to LSR-c1; rmse_{SA}: mean squared error ratio relative to SA-c1

Chapter 4

Improved Variance Estimation

4.1 Introduction

We have seen that in sequential dose finding designs based on continuous data, there is strong reason for nonparametric estimation of $\sigma(\cdot)$. In the last chapter, $\sigma(x_n)$ is estimated by $[E\left(S_n/\sigma(X_n)\right)]^{-1} S_n$, which utilizes data from cohort n only. In this chapter, we propose better estimates by pooling observations across cohorts in hopes of improving upon the current designs.

We retain the setting and notations defined in Section 3.2. The objective remains to identify, from a set of discrete doses labelled $\{1, \ldots, K\}$, either ν_1 or ν_2, defined in (2.2) and (3.4), respectively. In this chapter, the procedure with recursion (3.10) and $V_n = U_n + \beta(X_n^* - X_n) = \bar{Y}_n + c_p \left[E\left(S_n/\sigma(X_n)\right)\right]^{-1} S_n + \beta(X_n^* - X_n)$ is referred to as SAVOR and the procedure with recursion (3.16) and $V_{in} = V_i$ as LSRVO. Note that under this definition, the two procedures are equivalent.

4.2 The Procedures

Before introducing the estimators, it is necessary to introduce a few more notations first. Let $n_{kn} = \sum_{l=1}^{n} 1\{X_l = k\}$, $\tilde{Y}_{kn} = (mn_{kn})^{-1} \sum_{l=1}^{n} 1\{X_l = k\} \sum_{j=1}^{m} Y_{lj} = n_{kn}^{-1} \sum_{l=1}^{n} 1\{X_l = k\} \bar{Y}_l$. In words, after inclusion of n cohorts, n_{kn} is the number of cohorts assigned to dose level k and $\tilde{Y}_{kn}$ the average of the all continuous outcomes from those cohorts. To incorporate all available data in estimation of $\sigma(\cdot)$, a natural extension of the current estimator is to pool the sample standard deviations from cohorts given the same dose. It turns out, however, that this approach provides no improvement at all.

Proposition 4.1. *Define* $V_{in} = \bar{Y}_i + c_p \sum_{k=1}^{K} \check{\sigma}_{kn} 1\{X_i = k\} + \beta\,(X_i^* - X_i)$, *where*

$$\check{\sigma}_{kn} = \left[E\left(\frac{S_n}{\sigma(X_n)} \right) \right]^{-1} \frac{\sum_{l=1}^{n} 1\{X_l = k\} S_l}{n_{kn}}. \tag{4.1}$$

Then the sequence $\{X_n^*\}$ *generated by recursion* (3.16) *is equivalent to LSRVO.*

It can be inferred from Proposition 4.1 that pooling sample standard deviations is not an efficient way of utilizing the data and better estimators need to be proposed. To this end, we define the following three estimators for each dose level $k \in \{1, \ldots, K\}$:

$$\tilde{\sigma}_{kn}^2 \equiv \frac{\sum_{l=1}^{n} 1\{X_l = k\} S_l^2}{n_{kn}} \tag{4.2}$$

$$\bar{\sigma}_{kn}^2 \equiv \frac{\sum_{l=1}^{n} 1\{X_l = k\} \sum_{j=1}^{m} (Y_{lj} - \tilde{Y}_{kn})^2}{mn_{kn} - 1} \tag{4.3}$$

$$\hat{\sigma}_{kn}^2 \equiv \frac{\sum_{l=1}^{n} 1\{X_l = k\} \sum_{j=1}^{m} (Y_{lj} - \tilde{Y}_{kn})^2}{mn_{kn}} \tag{4.4}$$

Table 4.1: Summary of virtual observation recursions

	Least Square Recursion $X^*_{n+1} = \bar{X}^*_n - \frac{1}{nb}\sum_{i=1}^{n}(V_{in} - t_0)$ $V_{in} = U_{in} + \beta(X^*_i - X_i)$	Stochastic Approximation $X^*_{n+1} = X^*_n - \frac{1}{nb}(V_n - t_0)$ $V_n = U_n + \beta(X^*_n - X_n)$
single cohort sample standard deviation: $\left[E\left(\frac{S_n}{\sigma(X_n)}\right)\right]^{-1} S_n$	LSRVO $U_{in} = \bar{Y}_i + c_p\left[E\left(\frac{S_i}{\sigma(X_i)}\right)\right]^{-1} S_i$	SAVOR $U_n = \bar{Y}_n + c_p\left[E\left(\frac{S_n}{\sigma(X_n)}\right)\right]^{-1} S_n$
pooled sample standard deviation: $\check{\sigma}_{kn} = \left[E\left(\frac{S_n}{\sigma(X_n)}\right)\right]^{-1} \frac{\sum_{l=1}^{n} 1\{X_l=k\} S_l}{n_{kn}}$	LSRVO-A $U_{in} = \bar{Y}_i + c_p \sum_{k=1}^{K} \check{\sigma}_{kn} 1\{X_i = k\}$	SAVOR-A $U_n = \bar{Y}_n + c_p \sum_{k=1}^{K} \check{\sigma}_{kn} 1\{X_n = k\}$
pooled sample variance: $\tilde{\sigma}^2_{kn} = \frac{\sum_{l=1}^{n} 1\{X_l=k\} S_l^2}{n_{kn}}$	LSRVO-B $U_{in} = \bar{Y}_i + c_p \sum_{k=1}^{K} \tilde{\sigma}_{kn} 1\{X_i = k\}$	SAVOR-B $U_n = \bar{Y}_n + c_p \sum_{k=1}^{K} \tilde{\sigma}_{kn} 1\{X_n = k\}$
sample variance across cohorts: $\bar{\sigma}^2_{kn} = \frac{\sum_{l=1}^{n} 1\{X_l=k\} \sum_{j=1}^{m} (Y_{lj} - \tilde{Y}_{kn})^2}{mn_{kn}-1}$	LSRVO-C $U_{in} = \bar{Y}_i + c_p \sum_{k=1}^{K} \bar{\sigma}_{kn} 1\{X_i = k\}$	SAVOR-C $U_n = \bar{Y}_n + c_p \sum_{k=1}^{K} \bar{\sigma}_{kn} 1\{X_n = k\}$
MLE across cohorts: $\hat{\sigma}^2_{kn} = \frac{\sum_{l=1}^{n} 1\{X_l=k\} \sum_{j=1}^{m} (Y_{lj} - \tilde{Y}_{kn})^2}{mn_{kn}}$	LSRVO-D $U_{in} = \bar{Y}_i + c_p \sum_{k=1}^{K} \hat{\sigma}_{kn} 1\{X_i = k\}$	SAVOR-D $U_n = \bar{Y}_n + c_p \sum_{k=1}^{K} \hat{\sigma}_{kn} 1\{X_n = k\}$

The estimator $\tilde{\sigma}^2_{kn}$ estimates $\sigma^2(k)$ by averaging sample variances from cohorts given dose k, while $\bar{\sigma}^2_{kn}$ and $\hat{\sigma}^2_{kn}$ view all patients with dose k as if they belong to one cohort then estimate $\sigma^2(k)$ by the sample variance and maximum likelihood estimator, respectively. Each of the new estimators can be incorporated into SAVOR by changing the definition of the virtual observation V_n in recursion (3.10). The procedures using estimators (4.1), (4.2), (4.3), (4.4) will be respectively denoted as SAVOR-A, -B, -C and -D. Similarly, through redefining V_{in} in (3.16), LSRVO can be extended to accommodate these estimators. LSRVO with estimators (4.1), (4.2), (4.3), (4.4) will be denoted as LSRVO-A, -B, -C and -D, respectively. Table 4.1 summarizes the virtual observation recursions and the name they shall be referred to.

To illustrate how the new estimators operate, Table 4.2 displays the dose assignment, continuous outcomes, estimates of $\sigma(\cdot)$ and virtual observations of a simulated trial using LSRVO-D. In this example, $K = 5$, $p = 0.1$, $t_0 = 4.81$, $m = 3$, $n = 11$ and dose assignment follows a two-stage design with initial dose sequence $\{1, 2, 3, 3, 4, 4, 4, 5, 5, 5, 5\}$. The tuning parameters are $b = \beta = 0.30$. Noises are assumed to be standard normal so $c_p = 1.282$. As can be seen, no outcome exceeds t_0 in the first 5 cohorts thus dose assignment up to cohort 6 are dictated by the initial dose sequence and $X^*_i = X_i$ for $i = 1, \ldots, 6$. After the occurrence of the first toxicity in cohort 6, ($Y_{61} = 5.883 > 4.81$), dose assignment switches to LSRVO-D and

$$X^*_7 = \frac{1 + 2 + \cdots + 4}{6} - \frac{(4.076 - 4.81) + (4.691 - 4.81) + \cdots + (5.669 - 4.81)}{6 \times 0.30} = 2.711.$$

This gives $X_7 = C(X^*_7) = 3$. Throughout the trial, estimates of $\sigma(k)$ and virtual observation of a cohort assigned dose level k change every time a new cohort is assigned dose k. For example, at the time of the switch (after inclusion of 6 cohorts), only cohorts 3 and 4 are given dose level 3 and the estimate of $\sigma(3)$ is

$$\hat{\sigma}_{36} = \sqrt{\frac{\sum_{l=3}^{4} \sum_{j=1}^{3} (Y_{lj} - \tilde{Y}_{36})^2}{6}} = 0.762,$$

Table 4.2: A simulated trial using LSRVO-D with two-stage design

n	1	2	3	4	5	6	7	8	9	10	11	12
X_n	1	2	3	3	4	4	3	3	3	4	3	3
X_n^*	1	2	3	3	4	4	2.711	3.011	3.463	3.535	3.364	3.317
Y_{n1}	2.391	3.321	4.055	3.219	4.549	5.883	4.277	3.429	3.053	4.311	4.023	-
Y_{n2}	2.668	3.373	2.463	4.759	4.270	4.642	3.194	2.684	2.074	3.068	3.358	-
Y_{n3}	4.168	4.781	2.996	3.962	3.628	2.271	2.645	2.958	4.403	5.370	4.456	-
$\bar{Y}_n$	3.076	3.825	3.172	3.980	4.149	4.265	3.372	3.023	3.177	4.249	3.946	-
$\hat{\sigma}_{1n}$	0.781	0.781	0.781	0.781	0.781	0.781	0.781	0.781	0.781	0.781	0.781	-
$\hat{\sigma}_{2n}$	-	0.676	0.676	0.676	0.676	0.676	0.676	0.676	0.676	0.676	0.676	-
$\hat{\sigma}_{3n}$	-	-	0.662	0.762	0.762	0.762	0.741	0.693	0.757	0.757	0.749	-
$\hat{\sigma}_{4n}$	-	-	-	-	0.385	1.095	1.095	1.095	1.095	1.047	1.047	-
$\hat{\sigma}_{5n}$	-	-	-	-	-	-	-	-	-	-	-	-
V_{1n}	4.076	4.076	4.076	4.076	4.076	4.076	4.076	4.076	4.076	4.076	4.076	-
V_{2n}	-	4.691	4.691	4.691	4.691	4.691	4.691	4.691	4.691	4.691	4.691	-
V_{3n}	-	-	4.020	4.148	4.148	4.148	4.121	4.059	4.142	4.142	4.132	-
V_{4n}	-	-	-	4.956	4.956	4.956	4.930	4.868	4.950	4.950	4.940	-
V_{5n}	-	-	-	-	4.643	5.553	5.553	5.553	5.553	5.490	5.490	-
V_{6n}	-	-	-	-	-	5.669	5.669	5.669	5.669	5.607	5.607	-
V_{7n}	-	-	-	-	-	-	4.235	4.173	4.255	4.255	4.246	-
V_{8n}	-	-	-	-	-	-	-	3.914	3.997	3.997	3.987	-
V_{9n}	-	-	-	-	-	-	-	-	4.286	4.286	4.276	-
$V_{10,n}$	-	-	-	-	-	-	-	-	-	5.451	5.451	-
$V_{11,n}$	-	-	-	-	-	-	-	-	-	-	5.015	-
$V_{12,n}$	-	-	-	-	-	-	-	-	-	-	-	-

where $\tilde{Y}_{36} = \sum_{l=3}^{4} \sum_{j=1}^{3} Y_{lj}/6$.

This estimate is used in the calculation of the virtual observations for both cohorts 3 and 4. For instance, $V_{36} = \bar{Y}_3 + c_p\hat{\sigma}_{36} + \beta(X_3^* - X_3) = 3.172 + 1.282 \times 0.762 + 0 = 4.148$. At the end of the trial, outcomes from all cohorts assigned dose level 3 are used in estimating $\sigma(3)$ which is now $\hat{\sigma}_{3,11} = 0.749$. This estimator in turn is used in the calculation of virtual observations $V_{3,11}$, $V_{4,11}$, $V_{7,11}$, $V_{8,11}$, $V_{9,11}$, and $V_{11,11}$. Similarly, the final estimate of $\sigma(4)$ is based on all cohorts given dose level 4 (cohorts 5, 6 and 10) and $\hat{\sigma}_{4,11}$ is used to form virtual observations from these cohorts. Notice that only one cohort each is assigned to dose levels 1 and 2. Therefore estimates for these two dose levels remain the same throughout the trial as are the virtual observations. The final recommended dose is dose level 3 since $X_{12}^* = 3.317$.

As a comparison, Table 4.3 a trial using SAVOR-D simulated under the same

Table 4.3: A simulated trial using SAVOR-D with a two-stage design

n	1	2	3	4	5	6	7	8	9	10	11	12
X_n	1	2	3	3	4	4	3	3	4	4	3	3
X_n^*	1	2	3	3	4	4	3.288	3.480	3.796	3.716	3.479	3.431
Y_{n1}	2.391	3.321	4.055	3.219	4.549	5.883	4.277	3.429	3.562	4.311	4.023	-
Y_{n2}	2.668	3.373	2.463	4.759	4.270	4.642	3.194	2.684	2.540	3.068	3.358	-
Y_{n3}	4.168	4.781	2.996	3.962	3.628	2.271	2.645	2.958	4.969	5.370	4.456	-
$\bar{Y}_n$	3.076	3.825	3.172	3.980	4.149	4.265	3.372	3.023	3.690	4.249	3.946	-
$\hat{\sigma}_{1n}$	0.781	0.781	0.781	0.781	0.781	0.781	0.781	0.781	0.781	0.781	0.781	-
$\hat{\sigma}_{2n}$	-	0.676	0.676	0.676	0.676	0.676	0.676	0.676	0.676	0.676	0.676	-
$\hat{\sigma}_{3n}$	-	-	0.662	0.762	0.762	0.762	0.741	0.693	0.693	0.693	0.689	-
$\hat{\sigma}_{4n}$	-	-	-	-	0.385	1.095	1.095	1.095	1.091	1.059	1.059	-
$\hat{\sigma}_{51n}$	-	-	-	-	-	-	-	-	-	-	-	-
V_n	4.076	4.691	4.020	4.956	4.643	5.669	4.408	4.055	5.027	5.522	4.972	-

settings. Now the virtual observations are a single sequence instead of triangle arrays. The estimators of $\sigma(k)$ are still based on all available data. However, the most current estimator is used to calculate virtual observation of the latest cohort only. For example, at the end of the trial, the estimate for $\sigma(3)$ is $\hat{\sigma}_{3,11} = 0.689$ which is based on outcomes from cohorts 3, 4, 7, 8 and 11. This estimator is used to form $V_{11} = \bar{Y}_{11} + c_p\hat{\sigma}_{3,11} + \beta(X_{11}^* - X_{11}) = 3.946 + 1.282 \times 0.689 + 0.30(3.479 - 3) = 4.972$. The final recommended dose is also level 3.

Some comments are in order. First, it is not difficult to imagine that for procedures using the same estimator, the performance of least square recursion based procedure will be superior to its stochastic approximation based counterpart. As was demonstrated in the above examples, at any time during the trial and for every cohort, $\sigma(\cdot)$ is always estimated by the most up-to-date estimators in LSR-based procedures. In contrast, in SA-based procedures, only the most recent cohort benefits from the latest estimate. This feature of more efficient use of data is shared by all LSR-based methods and was manifested in the superiority of LSR-c3 over SA-c3 in Section 3.5.

Second, within the cohorts of procedures using the same recursion, we can conjecture on the relative performances of the four estimators. It would be reasonable

to expect that procedure with $\check{\sigma}_{kn}$ will have the worst and the ones with $\bar{\sigma}_{kn}$ and $\hat{\sigma}_{kn}$ the best performances with the latter two having equivalent asymptotic properties. Combined with the first observation means that we would expect LSRVO-B, LSRVO-C and LSRVO-D all to improve upon LSRVO. On the other hand, SAVOR-A will be inferior to SAVOR and while we can speculate on the the relative performances of SAVOR-B, SAVOR-C and SAVOR-D among themselves, their relative performances to SAVOR are more difficult to predict.

4.3 Theoretical Properties

This section states some large sample properties of the proposed procedures. The proofs are collected in Appendix B.1. Let $\bar{\epsilon}_n = m^{-1}\sum_{j=1}^{m}\epsilon_{nj}$ and $\mathcal{F}_{n-1}$ be the σ-field generated by $(X_i^*, \epsilon_{i1}, \epsilon_{i2}, \ldots, \epsilon_{im})$ for $i = 1, \ldots, n-1$.

Convergence properties under the new estimators do not trivially inherit those under the original estimator. To establish convergence results when using the new estimators, we start with a key transformation:

Lemma 4.1. *The sequences $\{X_n^*\}$ generated by LSRVO-B, LSRVO-C, LSRVO-D, SAVOR-A, SAVOR-B, SAVOR-C and SAVOR-D can be represented by the following form*

$$X_{n+1}^* = X_n^* - \frac{1}{nb}\left(h(X_n^*) + e_n - t_0\right) + \xi_n, \tag{4.5}$$

where $E(e_n \mid \mathcal{F}_{n-1}) = 0$ and $\sum_{n=1}^{\infty} E(|\xi_n| \mid \mathcal{F}_{n-1}) < \infty$ a.s.

Recursion (4.5) can be viewed as a Robbins-Monro recursion with mean function $h(\cdot)$, target t_0, errors e_n's and biases ξ_n's.

The next result shows that under the same conditions on β as stated in Cheung and Elkind [9], recursion (4.5) has the similar convergence properties as SAVOR and LSRVO (recall $G(c_k) = 1 - \pi(k)$ and $B_k = 2\sigma(k)|c_k - c_p|$).

Theorem 4.1. *Let* $\{X_n\}$ *be the design sequence generated by* (4.5).
(i) If $B_{\nu_1} < \beta < \min_{k \neq \nu_1} B_k$ *then* $X_n = \nu_1$ *eventually with probability one*
(ii) If $\beta < \min_k B_k$ *then* $P(X_n \in \{\nu_1 - 1, \nu_1, \nu_1 + 1\}$ *eventually*$) = 1$.

If consistency condition in Theorem 4.1 (i) holds, then the sequence of assigned doses $\{X_n^*\}$ generated by (4.5) can be shown to be asymptotically normal. Admittedly, the assigned doses exist only on a conceptual scale. However, as we shall see later, knowing the asymptotic variance of $\{X_n^*\}$ can facilitate the calibration of the tuning parameter b.

Theorem 4.2. *Assume the consistency conditions in Theorem 4.1 (i) hold and* $b < 2\beta$. *Let* θ_β *the unique root to* $h(x) = t_0$, $u_1 = Var\left(S_n^2/\sigma^2(X_n)\right)$, $u_2 = Var(\bar{\epsilon}_n^2)$, $u_3 = E\left(\bar{\epsilon}_n S_n^2/\sigma^2(X_n)\right)$, $u_4 = E\bar{\epsilon}_n^3$, $u_5 = Cov\left(\bar{\epsilon}_n^2, S_n^2/\sigma^2(X_n)\right)$ *and* $u_6 = E\left(\bar{\epsilon}_n S_n/\sigma(X_n)\right)$.

(i) For LSR-based procedures

$$\sqrt{n}\left(X_n^* - \theta_\beta\right) \xrightarrow{d} N\left(0, \frac{\sigma^2(\nu_1)}{mb(2\beta - b)}\left(1 + \kappa\right)\right),$$

where $\kappa = mc_p^2 u_1/4 + mc_p u_3$ *with LSRVO-B, and*

$$\kappa = \frac{c_p^2}{4}\left(\frac{(m-1)^2}{m}u_1 + mu_2 + 2(m-1)u_5\right) + c_p\left((m-1)u_3 + mu_4\right)$$

with LSRVO-C and LSRVO-D.

(ii) For SA-based procedures,

$$\sqrt{n}\left(X_n^* - \theta_\beta\right) \xrightarrow{d} N\left(0, \frac{\sigma^2(\nu_1)}{mb(2\beta - b)}\left(1 + \frac{b}{\beta}\kappa\right)\right),$$

where

$$\kappa = 2mc_p^2\left(\left[E\left(\frac{S_n}{\sigma(X_n)}\right)\right]^{-2} - 1\right) + 2mc_p\left[E\left(\frac{S_n}{\sigma(X_n)}\right)\right]^{-1} u_6$$

with SAVOR-A; $\kappa = mc_p^2 u_1/2 + mc_p u_3$ *with SAVOR-C, and*

$$\kappa = \frac{c_p^2}{2}\left(\frac{(m-1)^2}{m}u_1 + mu_2 + 2(m-1)u_5\right) + c_p\left((m-1)u_3 + mu_4\right)$$

with SAVOR-C and SAVOR-D.

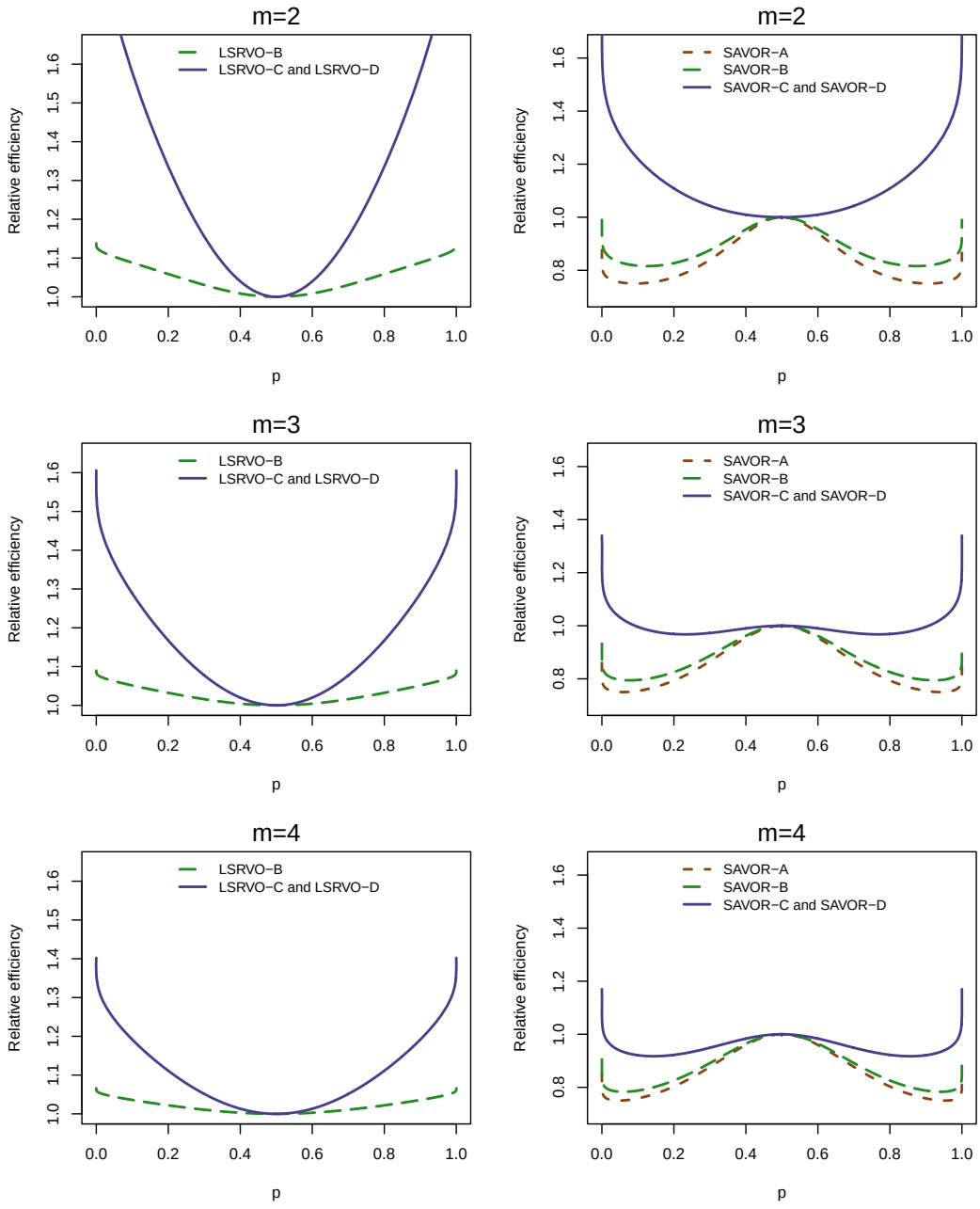

Figure 4.1: Left panel: asymptotic efficiency of LSRVO-B, LSRVO-C and LSRVO-D relative to LSRVO under standard normal noise. Right panel: Asymptotic efficiency of SAVOR-A, SAVOR-B, SAVOR-C and SAVOR-D relative to SAVOR under standard normal noise.

The asymptotic variances are minimized at $b = \beta$ for LSR-based procedures and at $b = 2/(1 + \sqrt{1 + 2\kappa})\beta$ for SA-based procedures. If G is standard normal then, $u_1 = \frac{2}{m-1}$, $u_2 = \frac{2}{m^2}$, $u_3 = u_4 = u_5 = u_6 = 0$ and $[E(S_n/\sigma(X_n))]^{-1} = \sqrt{\lambda_m}$, where λ_m is defined in (3.8). Table C.1 summarizes the asymptotic variances of the procedures when G is standard normal.

The asymptotic efficiencies of LSRVO-B, LSRVO-C and LSRVO-D relative to LSRVO are shown in left panel of Figure 4.1, assuming standard normal noise and the same b for all procedures. The ratios are uniformly greater than 1. Using $\bar{\sigma}_{kn}$ or $\hat{\sigma}_{kn}$ offers marked improvement over the original estimator that increases as p becomes more extreme. In contrast, the efficiency gain from $\tilde{\sigma}_{kn}$ is in general much more modest. When $p = 0.1$ and $m = 3$, as is the case in NeuSTART, efficiency is 1.288 for LSRVO-C and LSRVO-D, compared to LSRVO-B's 1.051.

Retaining the assumption of standard normal noise, the asymptotic efficiencies of SAVOR-A, SAVOR-B, SAVOR-C and SAVOR-D relative to SAVOR are depicted in right panel of Figure 4.1. The comparison are based on minimum asymptotic variances, that is, we assume $b = \beta$ for SAVOR and $b = 2/(1 + \sqrt{1 + 2\kappa})\beta$ for the other four procedures. Except with SAVOR-C and SAVOR-D when $m = 2$, the ratios only become larger 1 when p becomes extreme. When $p = 0.1$ and $m = 3$, the efficiencies are 0.755 for SAVOR-A, 0.796 for SAVOR-B, and 0.996 for SAVOR-C and SAVOR-D.

4.4 Application

We conducted a series of simulations in the context of NeuSTART to compare the operating characteristics of the procedures listed in Table 4.1. To emphasize the advantage of utilizing continuous outcomes, results from the CRM are also presented.

4.4.1 Simulation Setup

Five toxicity scenarios were considered. In the ith scenario, dose level i has DLT probability of 10% and is therefore the target dose (cf. Table C.2). With this setup, $\theta = \nu_1 = \nu_2$ and Condition 3.5 is satisfied. The trial size is $m = 3$ and $n = 11$. The same two-stage design adopted in NeuSTART was implemented (cf. Table 2.1). Virtual observations recursions (or the CRM) took over dose assignment in the second stage either after occurrence of the first toxicity or after inclusion of 11 cohorts in the event that no toxicity occurred during the first stage. Thus, the final estimate was always procedure based. Restriction on dose skipping in escalation and dose escalation immediately after a toxicity was enforced. For virtual observation recursions, restriction on dose escalation was done by setting the next assigned dose to be $\min\left\{X^*_{n+1}, \max_{1\leq i\leq n} X_i + 1.49\right\}$ instead of X^*_{n+1}. Dose de-escalation was unrestricted. One important implication of the two-stage design and the dose escalation restriction is that sequences generated by SAVOR and LSRVO are no longer identical. Thus, results from both recursions are presented.

For the CRM, dose-toxicity model was assumed to be empiric (2.3). Thus for dose k, the toxicity probability was modeled as $d_k^{exp(a)}$, where d_k is the numeric label and a is a priori normal with mean 0 and variance 1.34. Calibration of initial guesses of probabilities of DLT in the CRM was done according to the approach proposed by Lee and Cheung [18]. Finally, all simulations were done in R [24] and simulations of the CRM was carried out with the 'dfcrm' package [7].

4.4.2 Generating Continuous Outcomes

Table 4.4 displays the liver function data of each dose level from NeuSTART. The data suggest a monotone mean-variance relationship, that is, the variance increases with dose as the mean increases. To estimate the relationship, the standard deviations

Table 4.4: Summary of liver function data in NeuSTART

Dose level	Number of patients	Number of toxicity patients	log(peak ALT) Mean	log(peak ALT) STD
1	3	0	3.24	0.23
2	10	0	3.25	0.42
3	12	2	3.78	0.72
4	8	0	3.42	0.54
5	0	–	–	–

were transformed by the function $s(x) = e^{x^4}$ then regressed against sample means. The fitted line has a slope of 0.55. Left panel of Figure 4.2 shows that this particular mean-variance relationship fits the data well. Finally, Q–Q plot (right panel of Figure 4.2) suggests that assuming the noises ϵ_{ij} to be standard normal is reasonable.

To generate continuous outcomes, in each scenario, $M(\theta)$ was fixed to be 3.63, the estimated mean log(ALT) for dose levels 3 and 4 from isotonic regression [9]. The standard deviation at the target dose was determined by solving for $f(\nu) = log(123)$. The mean function $M(k)$ and $\sigma(k)$ at the other dose levels were then determined by solving simultaneously for

$$e^{\sigma^4(k)} = e^{\sigma^4(\theta)} + 0.55(M(k) - M(\theta))$$

and

$$\Phi\left(\frac{t_0 - M(k)}{\sigma(k)}\right) = 1 - \pi(k),$$

where Φ is the distribution function of standard normal. Table C.2 displays the probability of DLT, $M(k)$ and $\sigma(k)$ at each dose level of the five scenarios used in the simulations.

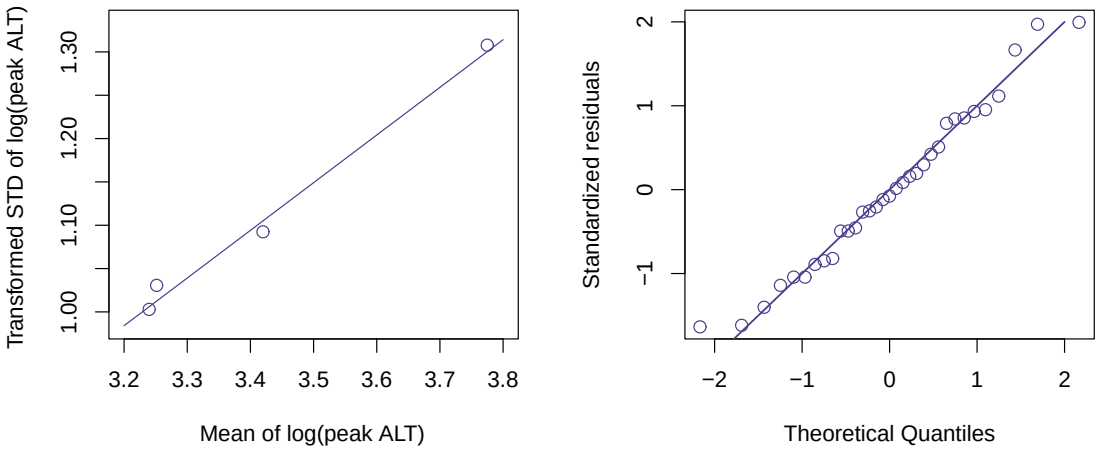

Figure 4.2: Left: Sample standard deviation of log(peak ALT) transformed by function $s(\cdot)$ against sample mean. Right: Normal Q-Q plot of standardized residuals

4.4.3 Design Calibration

Having specified the model for the continuous outcomes, we next consider the choice of β and b. To simplify the process, b was fixed at the optimal value in terms of minimizing the asymptotic variance and we focused on calibration of β. Based on our setup, consistency condition in Theorem 4.1 (i) stipulates that β should be between 0 and 0.83. For each virtual observation recursion, we calibrated β in the following manner:

1. Iterate β from 0.08 to 0.83 with a grid of 0.01. For all LSR-based procedures and SAVOR, set $b = \beta$; for the other SA-based procedures, set $b = 2/(1+\sqrt{1+2\kappa})\beta$.

2. For each β, perform simulations 5000 times under each scenario and obtain the proportion of correct selection (PCS).

3. Choose the β that maximizes the average PCS across the 5 scenarios.

Figure 4.3 displays the calibration results. For LSR-based procedures, LSRVO-C offers consistent and marked improvement over LSRVO in terms of correctly selecting

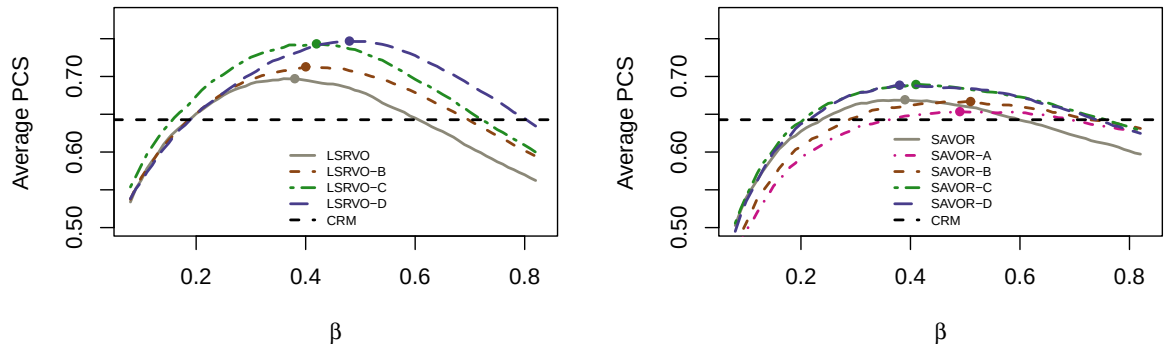

Figure 4.3: Average proportion of selecting ν_1 against β. The dot on each line indicates maximum average PCS. The average PCS of the continual reassessment method is indicated.

ν_1 on average. In contrast, LSRVO-B and LSRVO-D are superior to the original only when β becomes larger. The maximum average selection probabilities are 0.70, 0.71, 0.74, 0.75 and the corresponding β are 0.38, 0.40, 0.42, 0.48 for LSRVO, LSRVO-B, LSRVO-C and LSRVO-D, respectively. As a comparison, the average PCS of the continual reassessment method is 0.64.

Calibration results of the SA-based procedures show that, compared to SAVOR, SAVOR-C and SAVOR-D perform slightly better overall while SAVOR-B is worse. The maximum average selection probabilities are 0.67, 0.65, 0.67, 0.69, 0.69 at $(\beta, b) = (0.39, 0.39)$, $(0.49, 0.28)$, $(0.51, 0.30)$, $(0.41, 0.27)$, and $(0.38, 0.25)$ for SAVOR, SAVOR-A, SAVOR-B, SAVOR-C and SAVOR-D, respectively.

4.4.4 Results

Table 4.5 shows the selection proportions, average number of patients treated at each dose, average number of patients treated at doses above the target dose ν_1, and the average number of toxicity when each virtual observation recursion is run at its respective optimal β. Among the four LSR-based procedures, none of the

new estimators outperforms the original under scenario 1 in terms of PCS. However, the probabilities are all well over 0.80. The patterns under scenarios 2 to 4 are similar in that LSRVO-B does marginally better than the original while LSRVO-C and LSRVO-D both provide appreciably higher selection proportion. Under scenario 5, the new estimators offer a noticeable improvement. In terms of safety, LSRVO-D is more aggressive with a higher number of patients treated above the target and more frequent recommendations of an unsafe dose than both LSRVO and LSRVO-C. However, this aggressiveness is limited to no more than one level above the target and the number of total toxicities are comparable for all estimators across scenarios.

Among the five SA-based procedures, none of the new estimators improves upon the original under scenario 1 and all do under scenario 5 with SAVOR-D having the most extreme performance. Under scenarios 2 to 4, the four estimators are comparable. A comparison between SAVOR-C and SAVOR-D, the two with the highest average PCS shows that SAVOR-C is the safer of the two with SAVOR-D recommending an unsafe dose at least 23% of the time.

For each estimator, the procedure based on least square recursion is consistently superior to the its stochastic approximation based counterpart in both accuracy and safety. Except for scenario 1, all virtual observation recursions have higher PCS then the continual reassessment method. All in all, LSRVO-C seems to be the procedure of choice given that it improves accuracy and preserves safety at the same time. The same conclusion can be reached under a two-stage design with more aggressive initial dose sequence and one-stage designs with starting doses at level 1 or 3 (cf. Tables C.3, C.4, and C.5).

Table 4.5: Operating characteristics of virtual observation recursions and the CRM under a two stage design with $n = 11$, $m = 3$ and initial sequence $\{1, 2, 3, 3, 4, 4, 4, 5, 5, 5, 5\}$

	% Recommendation					# Treated						
	1	2	3	4	5	1	2	3	4	5	N_{ν_1+}	N_{DLT}
Scenario 1												
P(DLT)	0.10	0.25	0.30	0.35	0.40	0.10	0.25	0.30	0.35	0.40		
LSRVO	85.7	13.7	0.6	0.0	0.0	24.2	6.8	1.8	0.2	0.0	8.8	4.8
LSRVO-B	82.7	16.5	0.8	0.0	0.0	23.0	7.8	2.1	0.2	0.0	10.0	4.9
LSRVO-C	85.6	13.9	0.5	0.0	0.0	23.5	7.4	1.9	0.2	0.0	9.5	4.8
LSRVO-D	80.7	18.1	1.1	0.0	0.0	21.4	9.1	2.4	0.2	0.0	11.6	5.2
SAVOR	83.1	15.4	1.3	0.1	0.0	23.3	7.3	2.1	0.2	0.0	9.7	4.9
SAVOR-A	81.5	17.0	1.4	0.2	0.0	23.2	7.4	2.1	0.2	0.0	9.8	4.9
SAVOR-B	77.5	20.6	1.7	0.2	0.0	21.9	8.4	2.4	0.3	0.0	11.1	5.1
SAVOR-C	79.7	19.0	1.2	0.1	0.0	22.7	7.9	2.2	0.2	0.0	10.3	5.0
SAVOR-D	73.9	24.0	1.9	0.2	0.0	20.6	9.4	2.7	0.3	0.0	12.4	5.4
CRM	84.9	13.9	1.1	0.1	0.0	23.9	6.9	2.0	0.2	0.0	9.1	4.8
Scenario 2												
P(DLT)	0.04	0.10	0.25	0.30	0.35	0.04	0.10	0.25	0.30	0.35		
LSRVO	22.1	63.8	13.6	0.5	0.0	11.0	14.3	6.9	0.8	0.0	7.7	3.9
LSRVO-B	17.1	65.7	16.5	0.7	0.0	9.2	15.0	7.9	0.8	0.0	8.8	4.1
LSRVO-C	15.6	70.3	13.7	0.4	0.0	8.9	15.9	7.4	0.7	0.0	8.2	4.0
LSRVO-D	10.2	71.3	17.9	0.6	0.0	6.9	16.2	9.1	0.8	0.0	9.9	4.5
SAVOR	20.4	63.5	15.1	1.0	0.0	10.3	14.8	7.0	0.9	0.0	7.9	3.9
SAVOR-A	21.6	61.4	15.9	1.0	0.1	10.8	14.4	6.9	0.9	0.0	7.8	3.9
SAVOR-B	16.3	63.1	19.2	1.3	0.1	9.2	14.9	7.9	1.0	0.1	9.0	4.2
SAVOR-C	15.8	64.7	18.6	0.7	0.1	9.5	15.0	7.6	0.9	0.0	8.5	4.1
SAVOR-D	10.9	62.9	24.7	1.3	0.1	7.7	14.7	9.3	1.2	0.1	10.6	4.5
CRM	25.6	60.5	12.9	1.0	0.1	11.4	14.2	6.5	0.8	0.0	7.4	3.8
Scenario 3												
P(DLT)	0.01	0.04	0.10	0.25	0.30	0.01	0.04	0.10	0.25	0.30		
LSRVO	0.6	19.0	64.3	15.7	0.4	4.1	8.0	14.9	5.7	0.3	6.0	3.4
LSRVO-B	0.3	14.5	65.4	19.2	0.5	3.6	6.9	15.5	6.6	0.3	6.9	3.6
LSRVO-C	0.1	13.5	70.5	15.7	0.3	3.6	6.9	16.3	6.0	0.2	6.2	3.5
LSRVO-D	0.0	8.9	70.7	20.0	0.3	3.3	5.7	16.6	7.1	0.2	7.3	3.8
SAVOR	0.5	19.9	64.2	14.4	1.1	4.2	8.5	14.7	5.3	0.3	5.6	3.3
SAVOR-A	0.8	21.0	61.8	15.4	1.0	4.4	8.5	14.6	5.2	0.3	5.5	3.2
SAVOR-B	0.4	16.5	63.9	18.0	1.2	4.0	7.7	15.1	5.9	0.3	6.2	3.4
SAVOR-C	0.3	15.9	66.5	16.3	1.0	4.0	7.7	15.3	5.7	0.3	6.0	3.4
SAVOR-D	0.1	10.9	64.6	23.0	1.4	3.6	6.4	15.5	7.0	0.4	7.4	3.7
CRM	1.4	25.9	58.5	13.2	1.0	4.5	9.1	14.3	4.8	0.3	5.0	3.1
Scenario 4												
P(DLT)	0.01	0.01	0.04	0.10	0.25	0.01	0.01	0.04	0.10	0.25		
LSRVO	0.1	1.0	20.6	62.3	16.1	3.4	3.8	9.9	12.7	3.3	3.3	2.6
LSRVO-B	0.0	0.5	15.7	64.1	19.7	3.3	3.5	9.2	13.3	3.7	3.7	2.7
LSRVO-C	0.0	0.4	15.5	69.1	15.0	3.3	3.5	9.3	13.8	3.1	3.1	2.6
LSRVO-D	0.0	0.2	11.6	71.1	17.1	3.2	3.3	8.6	14.6	3.3	3.3	2.7
SAVOR	0.1	0.9	23.9	58.8	16.3	3.4	4.1	10.6	11.9	2.9	2.9	2.4
SAVOR-A	0.2	1.3	25.4	56.8	16.2	3.5	4.2	10.7	11.7	2.8	2.8	2.4
SAVOR-B	0.1	1.0	20.9	59.0	19.0	3.4	3.9	10.2	12.4	3.1	3.1	2.5
SAVOR-C	0.0	0.6	19.6	62.8	17.0	3.4	3.9	10.2	12.6	3.0	3.0	2.5
SAVOR-D	0.0	0.2	12.9	63.6	23.3	3.2	3.5	9.2	13.2	3.8	3.8	2.7
CRM	0.1	2.7	27.8	52.0	17.4	3.6	4.6	10.9	11.1	2.8	2.8	2.4
Scenario 5												
P(DLT)	0.01	0.01	0.01	0.04	0.10	0.01	0.01	0.01	0.04	0.10		
LSRVO	0.1	0.3	1.8	25.3	72.5	3.3	3.3	6.5	11.0	8.8		1.5
LSRVO-B	0.0	0.2	1.3	20.1	78.4	3.3	3.3	6.3	10.8	9.3		1.5
LSRVO-C	0.0	0.2	1.2	22.5	76.1	3.2	3.3	6.4	11.1	9.0		1.5
LSRVO-D	0.0	0.1	0.9	19.4	79.6	3.2	3.3	6.3	10.9	9.3		1.5
SAVOR	0.1	0.3	2.4	32.2	65.0	3.4	3.4	7.0	11.6	7.6		1.4
SAVOR-A	0.2	0.5	2.9	31.2	65.3	3.4	3.4	6.9	11.5	7.7		1.4
SAVOR-B	0.1	0.4	1.8	27.9	69.8	3.4	3.3	6.7	11.6	8.1		1.4
SAVOR-C	0.0	0.2	1.3	27.6	70.9	3.3	3.3	6.7	11.6	8.1		1.4
SAVOR-D	0.0	0.0	0.4	20.4	79.1	3.2	3.2	6.3	11.1	9.1		1.5
CRM	0.1	1.3	7.7	25.4	65.5	3.6	3.9	7.3	11.0	7.2		1.3

N_{ν_1+}: number treated above ν_1; N_{DLT}: total number of DLT

Chapter 5

Incorporating Intermediate Measurements

5.1 Introduction

So far, designs using continuous outcomes require all current patients to have completed follow-up before a new cohort can be enrolled. Using the PST study as motivating example, we extend least square recursion to allow continual patient accrual through incorporating intermediate measurements.

5.2 The Procedure

We build on the setting and notations in Section 3.2. Consider a trial in which patients are enrolled sequentially in small cohorts of size m. Each patient has two continuous measurements taken at time points that are predetermined and identical for all patients. The first measurement will be referred to as intermediate and the second as final. The event of interest is said to occur if the final measurement exceeds

threshold t_0. For patient j in cohort i, the final measurement is

$$Y_{ij} = M(X_i) + \sigma(X_i)\epsilon_{ij}, \tag{5.1}$$

and the intermediate measurement is

$$Z_{ij} = \phi^{-1}M(X_i) + \tau^{-1}\sigma(X_i)e_{ij}, \tag{5.2}$$

where ϕ, $\tau > 0$ and (ϵ_{ij}, e_{ij}) has a joint distribution G with mean 0, variance 1 and correlation ρ. In these models, ϕ, τ and ρ are constant across doses and we define the following estimators for ϕ and τ^2:

$$\hat{\phi}_n = \frac{\sum_{i=1}^n \bar{Y}_i}{\sum_{i=1}^n \bar{Z}_i}, \quad \hat{\tau}_n^2 = \frac{\sum_{i=1}^n S_i^2}{\sum_{i=1}^n R_i^2},$$

where $\bar{Z}_i$ and R_i^2 are the sample mean and sample variance of the intermediate measurements in cohort i and $\bar{Y}_i$ and S_i^2 are those for the final measurements. In order to keep track of follow-up status of each cohort, let $n_c = n_c(n)$ be the number of cohorts with complete follow-up prior to the entry of the first subject of cohort $n+1$, and $n_I = n_I(n)$ be that with only intermediate measurements.

Now, to incorporate intermediate outcomes into least square recursion

$$X_{n+1}^* = \bar{X}_n^* - \frac{1}{nb}\sum_{i=1}^n (V_{in} - t_0), \tag{5.3}$$

we first define a variable that is analogous to $U_i = \bar{Y}_i + c_p \left[E\left(S_i/\sigma(X_i)\right)\right]^{-1} S_i$ but based on intermediate measurements:

$$W_{in} = \hat{\phi}_{n_c}\bar{Z}_i + c_p\hat{\tau}_{n_c}\left[E\left(S_i/\sigma(X_i)\right)\right]^{-1} R_i \tag{5.4}$$

for $i = n_c + 1, \ldots, n_c + n_I$. Next, define the virtual observation of cohort i just prior to the entry of cohort $n+1$ as

$$V_{in} = \begin{cases} V_i \equiv U_i + \beta(X_i^* - X_i) & \text{for } i = 1, \ldots, n_c, \\ W_{in} + \beta(X_i^* - X_i) & \text{for } i = n_c + 1, \ldots, n_c + n_I, \\ t_0 & \text{for } i = n_c + n_I + 1, \ldots, n. \end{cases} \tag{5.5}$$

Note that we need $n_c \geq 1$ for $\hat{\phi}_n$ and $\hat{\tau}_n$ to exist and the proposed recursion to work. One way to initiate the recursion is to use TITE-CRM as the initial design until the first cohort is completely followed. With this definition of V_{in} patients can be continually enrolled as they become available. Contribution of each cohort to the proposed recursion depends on and changes with its follow-up status. Thus, performance of the recursion hinges on patient accrual process. We first consider the following cases:

1. Enroll the next cohort only when all current cohorts have been completely followed.

2. Compress the enrollment process so that the intermediate outcomes from the most recent cohort and complete outcomes from all other cohorts are available.

Under the first case, $n_I = 0$, $n_c = n$, $V_{in} = V_i$ for all n and the propose recursion reduces to LSRVO. The following result shows that under the second case, the proposed recursion has the same consistency properties as LSRVO (recall that $G(c_k) = 1 - \pi(k)$ and $B_k = 2\sigma(k)|c_k - c_p|$):

Theorem 5.1. *Let* $\{X_n\}$ *be the design sequence generated by recursion* (5.3) *with* (5.5) *under an accrual process such that* $n_c(n) = n - 1$ *and* $n_I(n) = 1$ *for all* n.
(i) If $B_{\nu_1} < \beta < \min_{k \neq \nu_1} B_k$ *then* $X_n = \nu_1$ *eventually with probability one*
(ii) If $\beta < \min_k B_k$ *then* $P(X_n \in \{\nu_1 - 1, \nu_1, \nu_1 + 1\}$ *eventually*$) = 1$.

The proof of Theorem 5.1 is presented in Appendix B.2. We now turn our attention to the case where no restriction is placed on the accrual process. A simulated trial in the context of the PST study is presented in Table 5.1 to illustrate how the proposed recursion operates under this general case. Recall that the objective of the study is to identify, out of five test doses, the one associated with 66% of at least 10 point improvement in quality of life (QoL) score over 8 weeks. In addition to the

Table 5.1: Dose assignments, patients enrollment time, sample means, sample standard deviations, virtual observations and parameters estimates of a simulated trial

n	1	2	3	4	5	6	7	8	9	10
X_n	1	2	3	1	1	2	3	3	3	4
X_n^*	1.00	2.00	3.00	1.00	1.00	2.00	2.50	3.03	3.16	3.54
T_{n1}	0.95	1.85	4.03	6.65	9.12	10.61	12.81	18.73	20.49	24.65
T_{n2}	1.31	2.25	4.71	6.97	9.62	12.25	15.92	18.85	24.12	26.70
T_{n3}	1.82	3.88	6.19	8.80	10.29	12.31	16.76	18.99	24.51	27.40
n_c	0	0	0	0	1	2	5	6	6	-
n_I	0	0	1	2	2	2	1	0	2	-
$\bar{Z}_n$	19.46	5.74	16.75	-1.96	4.19	-5.12	11.75	-5.73	-2.55	11.23
$\bar{Y}_n$	20.75	5.00	4.10	-1.62	15.01	-15.64	23.72	4.85	-0.97	18.07
R_n	20.96	9.26	5.88	19.00	16.47	10.63	14.10	5.60	26.96	13.46
S_n	50.51	28.78	20.00	33.95	38.93	31.45	20.16	35.86	27.35	15.69
V_{1n}	-	-	-	-	-2.76	-2.76	-2.76	-2.76	-2.76	-2.76
V_{2n}	-	-	-	-	-4.26	-8.39	-8.39	-8.39	-8.39	-8.39
V_{3n}	-	-	-	-	11.27	10.18	-5.21	-5.21	-5.21	-5.21
V_{4n}	-	-	-	-	10.00	-24.43	-17.43	-17.43	-17.43	-17.43
V_{5n}	-	-	-	-	10.00	10.00	-3.11	-3.11	-3.11	-3.11
V_{6n}	-	-	-	-	-	10.00	-16.57	-30.32	-30.32	-30.32
V_{7n}	-	-	-	-	-	-	10.00	10.00	-13.81	7.90
V_{8n}	-	-	-	-	-	-	-	10.00	-9.84	-11.41
V_{9n}	-	-	-	-	-	-	-	-	10.00	-11.56
$V_{10,n}$	-	-	-	-		-	-	-	-	4.77
$\hat{\phi}_{n_c}$	-	-	-	-	1.07	1.02	0.98	0.71	0.71	1.36
$\hat{\tau}_{n_c}$	-	-	-	-	2.41	2.54	2.33	2.39	2.39	2.04

measurement of QoL score at 8 weeks, each patient also has a planned intermediate measurement at 4 weeks. In this example, we set $X_1 = 1$, $m = 3$, $n = 10$, $b = \beta = 13$ and changes in QoL scores at 4 and 8 weeks are assumed to follow bivariate normal distribution thus $c_p = \Phi^{-1}(1 - 0.66) = -0.412$ and $[E\left(S_i/\sigma(X_i)\right)]^{-1} = 1.128$. The entry time of the jth patient in cohort n is denoted as T_{nj} in Table 5.1.

Doses for cohorts 2 to 5 are assigned by TITE-CRM as the second and third patients in cohort 1 have not completed follow-up at the time the first patient in cohort 5 arrives. When the first patient in cohort 6 is enrolled, week 8 outcomes from cohort 1 are completely observed and dose assignment switched to the proposed recursion with $\hat{\phi}_{n_c(5)} = (20.75)/(19.46) = 1.07$, $\hat{\tau}_{n_c(5)} = 50.51/20.96 = 2.41$, $V_{15} = V_1 = -2.76$,

$V_{25} = W_{25} = -4.26$, $V_{35} = W_{35} = 11.27$ and $V_{45} = V_{55} = t_0 = 10$. By the time patient 1 in cohort 7 arrives, cohort 2 has completed follow-up thus estimates for ϕ and τ are updated:

$$\hat{\phi}_{n_c(6)} = \frac{20.75 + 5.00}{19.46 + 5.74} = 1.02 \text{ and } \hat{\tau}_{n_c(6)} = \sqrt{\frac{50.51^2 + 28.78^2}{20.96^2 + 9.26^2}} = 1.02.$$

The new estimates are used to update virtual observations for cohorts 2 to 4. The process continues until week 8 outcomes are collected from all patients. At this point, X_{11}^* is calculated to be 3.59, making dose level 4 the final MED estimate.

5.3 Applications

5.3.1 Simulation Setup

Having seen how the proposed procedure operates, its operating characteristics are examined and compared to that of TITE-CRM via simulations. Again, the context is PST study. Four dose-response scenarios were considered (Table 5.2). Throughout the simulations, $m = 3$, $n = 16$ and the starting dose level is 3 (6 sessions of therapy), the prior MED. Doses were assigned by TITE-CRM before the first cohort reached week 8 follow-up. Afterwards, the proposed procedure took over dose assignment. Skipping an untested dose in both escalation and de-escalation was restricted by setting the next assigned dose to be $\max\{\min\{X_{n+1}^*, \max_{1\le i\le n} X_i + 1.49\}, \min_{1\le i\le n} X_i - 1.50\}$. In the current context, dose-skipping in escalation is undesirable because of financial considerations. On the other hand, dose-skipping in de-escalation could result in patient drop-outs due to unsatisfactory therapy results. Truncations were applied to the estimators of ϕ and τ in order to restrict them to a reasonable range. Specifically, the estimators were set to be $\max\{\min\{\hat{\phi}_{n_c}, 5\}, 0\}$ and $\min\{\hat{\tau}_{n_c}, 5\}$.

To generate continuous outcomes, the final 8-week outcome and intermediate 4-week outcome were assumed to be jointly normal with mean 0 and variance 1. We

Table 5.2: Simulation scenarios used in the PST study protocol

	Dose level				
Scenario	1	2	3	4	5
1	0.50	0.66	0.75	0.80	0.85
2	0.40	0.50	0.66	0.75	0.80
3	0.35	0.40	0.50	0.66	0.75
4	0.25	0.35	0.40	0.50	0.66

set $\sigma(k)$, the standard deviation of 8-week outcome at dose level k, to be 32 for all scenarios based on an internal pilot. The mean function $M(k)$ was determined by solving $\pi(k) = 1 - \Phi\left((t_0 - M(k))/\sigma(k)\right)$ (cf. Table C.6). Different values were considered for the model parameters ϕ, τ and ρ (see details below).

5.3.2 Accrual Process

Two types of process and various rates ξ were considered for patients accrual process. The first type of accrual process is fixed, meaning that inter-patient arrival time is constant. Under fixed accrual process, accrual rate ξ is the number of patient(s) enrolled in 8 weeks and $8/\xi$ is the fixed inter-patient arrival time. In particular, when $\xi \leq 1$, the proposed procedure reduces to LSRVO. The second and more realistic type of accrual process assumes inter-patient arrival to follow an exponential distribution. In this case, ξ is the average number of patient(s) enrolled in 8 weeks. We will refer to this second type as the Poisson accrual process. Regardless of the type of process and rate, the final MED estimate is always based on week 8 outcomes; that is, MED is estimated after every patient has completed follow-up .

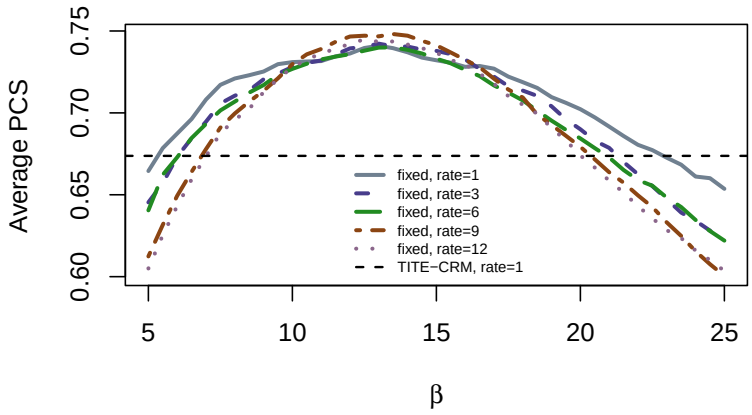

Figure 5.1: Average PCS versus β under several patient accrual scenarios.

5.3.3 Design Calibration

The calibration process closely follows the approach in Section 4.4. Fixing $b = \beta$, β is calibrated β under the fixed accrual process with $\xi = 1$. Under this particular process, only measurements from 8 weeks were used thus the performance of the procedure does not depend on model parameters ϕ, τ and ρ. The calibration steps are

1. Iterate β from 5 to 25 with a grid of 0.5.
2. Perform simulations 2000 times under each scenario and obtain PCS.
3. Choose the β that maximizes the average PCS across the 4 scenarios.

The maximum average PCS is 0.74 at $\beta = 13$. To put things into perspective, average PCS of TITE-CRM under the same accrual process is 0.67 (see below for specifications of the TITE-CRM). We also repeated the calibration steps under both accrual types with several different ξ (1 to 12 with grid of 1) while setting $\phi = \tau = 2$ and $\rho = 0.8$. Optimal β from these accrual scenarios ranges from 12.5 to 13.5 with maximum average PCS oscillating between 0.74 and 0.75. These results suggest that 13 is indeed a reasonable choice of β. The average PCS against β from some of the accrual scenarios are plotted in Figure 5.1.

5.3.4 Specifications of TITE-CRM

The empiric function was used as dose response model. Specifically, for dose k with label d_k, the probability of response was assumed to be $d_k^{exp(a)}$, where a is a priori normal with mean 0 and variance 1.34. The following weight function was adopted:

$$w(t) = \begin{cases} 0 & \text{if } t < 4 \\ 0.5 & \text{if } 4 \leq t < 8 \\ 1 & \text{if } t \geq 8. \end{cases}$$

Restrictions on dose skipping in escalation and de-escalation were enforced. Calibration of initial guesses of response probability followed the approach of Lee and Cheung [18].

5.3.5 Results

We first investigate the impact of accrual process on the performance of the proposed procedure. In this set of simulation, the model parameters are fixed at $\phi = 2$, $\tau = 2$ and $\rho = 0.8$ and ξ ranges from 1 to 12 with grid of 1. Operating characteristics of the proposed procedure and TITE-CRM are plotted in Figure 5.2 and tabulated in Tables C.7 and C.8. While results from both accrual processes are presented in the figure and tables, the discussion below focuses on the fixed process as results from the two processes lead to similar conclusions.

In terms of accuracy, PCS from both the proposed procedure and TITE-CRM exhibit similar patterns in that it increases slightly with ξ under the first three scenarios, and drops more markedly under scenario 4. In particular, for the proposed procedure, PCS at $\xi = 1, 3, 6, 9, 12$ are 0.67, 0.68, 0.68, 0.70 , 0.69 under scenario 1; 0.69, 0.71, 0.70, 0.73, 0.73 under scenario 2 and 0.72, 0.73, 0.73, 0.73, 0.73 under scenario 3 and 0.89, 0.86, 0.86, 0.83, 0.82 under scenario 4.

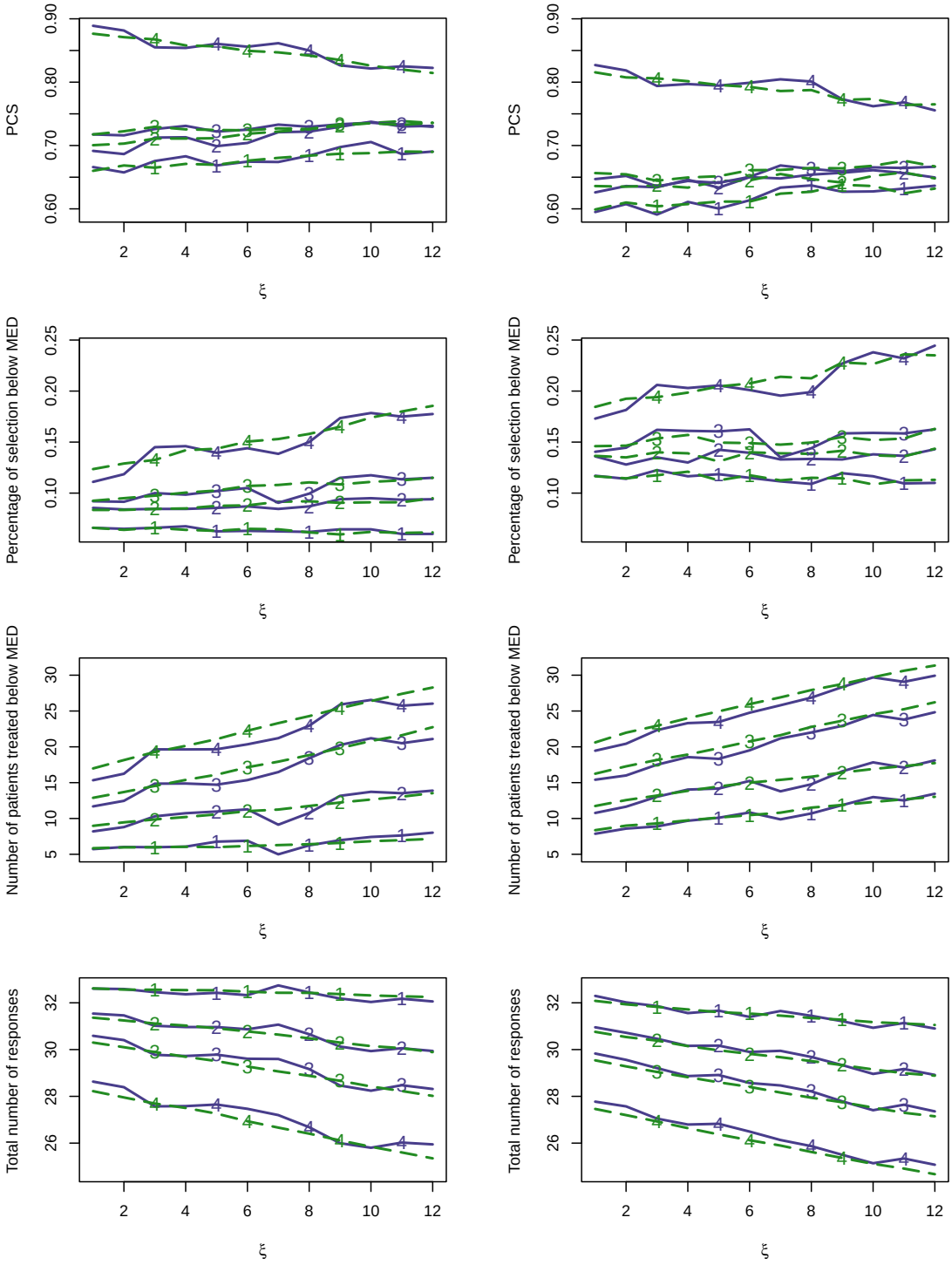

Figure 5.2: Operating characteristics of the proposed procedure (left panel) and TITE-CRM (right panel) against accrual rate ξ. Solid lines indicate fixed accrual process. Dashed lines indicate Poisson accrual process. The numbers on the lines denote scenario.

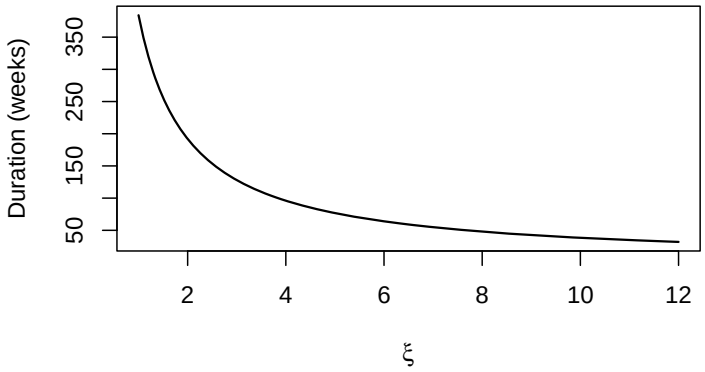

Figure 5.3: Average accrual duration against accrual rate ξ.

While percentage of correct selection suggests that compressing accrual process does not seem to take its toll on accuracy, the adverse impact of fast accrual can be seen in the increase number of patients treated below MED. Between the two designs, TITE-CRM seems to be more susceptible to this negative impact under scenarios 1 and 2. The numbers increase from 7.9 at $\xi = 1$ to 16.4 at $\xi = 12$ under scenario 1 and from 10.8 to 18.1 under scenario 2 for TITE-CRM. In comparison, the increase is more modest for the proposed procedure: from 5.7 to 8.0 under scenario 1 and from 8.2 to 13.9 under scenario 2. The increases under scenarios 3 and 4 are more pronounced but comparable for both designs. In particular, the numbers increase from 11.7 at $\xi = 1$ to 21.1 at $\xi = 12$ under scenario 3; from 15.3 to 26.0 under scenario 4 for the proposed procedure. Another undesirable feature due to compressed accrual is decreased number of responses. However, the decreases are slight with a worst drop of 2.7 responses from $\xi = 1$ to 12 under scenario 4 for both designs.

When compared to the TITE-CRM, the proposed procedure is uniformly superior in that it identifies the correct MED more often, selects an ineffective dose less frequently, treats fewer patients at ineffective doses and results in higher number or responses. Although its performance deteriorates as ξ increases, the drop in performance is moderate when compared to the considerably shortened trial duration as ξ

gets larger (Figure 5.3).

So far, we have looked at the operating characteristics of the proposed procedure under one particular set of model parameters. To evaluate the impact of these parameters on the procedure's performance, we ran simulations with different values of ϕ, τ and ρ. While different ξ were considered, only results with $\xi = 6$ are shown (Figure 5.4) as similar conclusions can be reached with other values of ξ. The top panel of Figure 5.4 shows PCS and number of patients treated below MED of the procedure with $\xi = 6$, $\tau = 2$, $\rho = 0.8$ and ϕ ranges from 0.1 to 4. As can be seen, except for very slight drops under scenario 4 when ϕ is small and under scenarios 1 to 3 when ϕ is extreme, the procedure's performance does not seem to depend on true value of ϕ. In contrast, when ϕ is fixed at 2 and τ allowed to vary (second panel of Figure 5.4), the drop in performance with small τ under scenarios 1 to 3 becomes more pronounced. This is because a small τ/ϕ ratio corresponds to large variation in the week 4 outcomes and as a result, less accurate ϕ estimates due to truncation. When τ/ϕ is fixed to be 1, the patterns are similar to those in the first panel. Finally, results when ρ ranges from 0.05 to 0.95 and both ϕ and τ are fixed at 2 show that ρ does not affect the performance of the procedure (bottom panel). These results show that the procedure is fairly consistent under a wide range and combination of model parameters even when the tuning parameters are chosen irrespective of these parameters.

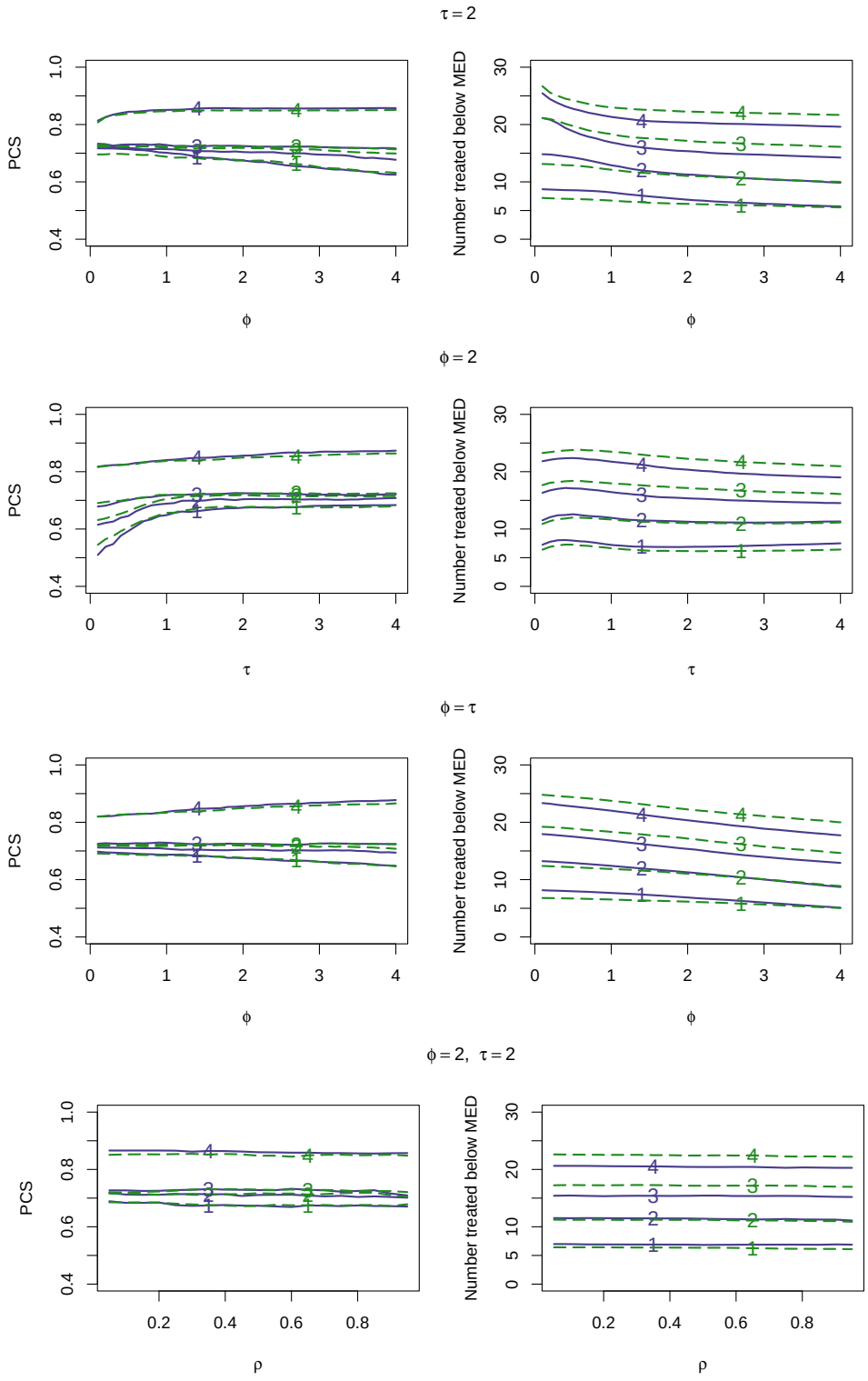

Figure 5.4: Operating characteristics of the proposed recursion with $b = \beta = 13$, $\xi = 6$ and various combinations of ϕ, τ and ρ. Solid line: fixed accrual process. Dashed line: Poisson accrual process. The numbers on the lines denote scenario.

Chapter 6

Concluding Remarks

This dissertation considers dose finding studies where a binary outcome is obtained by dichotomizing a continuous measurement and has two major contributions. The first contribution is that we improved the performance of virtual observation recursions through pooling data in variance estimation. In accordance with the conclusion reached in Section 3.5 that parametric assumption on variance should be avoided, $\sigma(x)$ is left unspecified in model (3.1) and only nonparametric methods were considered. Asymptotic and simulation results show that least square recursion can benefit substantially from the proposed estimators, especially when an extreme quantile is targeted. In particular, $\bar{\sigma}_{kn}$ strikes the best balance between accuracy and safety. In contrast, asymptotic performance of stochastic approximation seems to be burdened by the use of more data. Empirically, the proposed estimators tend to be too aggressive and offer only marginal improvement in accuracy. The second contribution of this dissertation is in extending least square recursion to incorporate intermediate outcomes. This is accomplished by taking advantage of least square recursion's ability to work with a triangle array of virtual observations V_{in}. Theoretical results of the proposed procedure under a simplified accrual scenario is provided. Results on more general accrual process need to be developed. Also, the estimator $\bar{\sigma}_{kn}$ can be

incorporated to improve performance.

It is natural to ask the question whether the idea of pooling data across cohorts can be applied to estimation of mean function $M(k)$ as well. For example, we can define

$$U_{in} = \sum_{k=1}^{K} \tilde{Y}_{kn} 1\{X_i = k\} + c_p \left[E\left(\frac{S_i}{\sigma(X_i)} \right) \right]^{-1} S_i \tag{6.1}$$

and

$$U_n = \sum_{k=1}^{K} \tilde{Y}_{kn} 1\{X_n = k\} + c_p \left[E\left(\frac{S_n}{\sigma(X_n)} \right) \right]^{-1} S_n. \tag{6.2}$$

Just like using $\check{\sigma}_{kn}$ makes no difference, using $\tilde{Y}_{kn}$ provides no advantage for LSR-based procedures. Arguments analogous to those in the proof of Proposition 4.1 can show that recursion (3.16) with (6.1) is equivalent to LSRVO. On the other hand, (3.10) with (6.2) generates different design sequence from that of SAVOR. Preliminary simulation results show that using (6.2) worsens the performance of recursion (3.10).

Another important comment is that in order to implement virtual observation recursion, it is necessary to specify β and b. Instead of calibrating both parameters in a two dimensional space, we choose b based on asymptotic consideration and restrict attention to calibrating β in both Chapters 4 and 5. In particular, in Section 4.4, the upper bound 0.83 used in the calibration of β depends on $\pi(k)$ and $\sigma(k)$, quantities that are typically unknown. To address this issue, we note that with both Conditions 3.5 and 3.6 satisfied, a upper bound for β can be obtained from (3.13). Letting $p_L = 0.04$ and $p_U = 0.25$, then this new upper bound is 0.63 under all scenario using true $\sigma(\nu)$. An estimate of the upper bound can be obtained by approximating $\sigma(\nu)$ by 0.59, the 80% lower confidence limit based on the 20 observations in the combined dose levels 3 and 4 from NeuSTART. The resulting estimated upper bound, 0.41, while conservative, still allows a wide enough range for calibration.

Throughout the dissertation, we consider the case when the binary outcome is obtained by dichotomizing a single continuous measurement. It is common however,

that a binary outcome is defined on several continuous measurements. It would be of both theoretical and practical importance to extend virtual observation recursions to such situations.

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Appendix A

Conditions

A.1 Conditions for Stochastic Approximation

Condition A.1. *$Q(x^*) = \alpha$ and $(x - x^*)(Q(x) - \alpha) > 0$ for all $x \neq x^*$*

Condition A.2. *For all x and some positive constants D_1 and D_2,*

$$D_1|x - x^*| \leq |Q(x) - \alpha| \leq D_2|x - x^*|$$

Condition A.3. *(a) $\sup_x VarY(x) < \infty$ (b) $\lim_{x \to x^*} VarY(x)$ exists.*

Condition A.4. *$Q(x) = \alpha + \alpha_1(x - x^*) + \delta(x, x^*)$ where $\delta(x, x^*) = o(|x - x^*|)$ as $x \to x^*$ and $\alpha_1 > 0$.*

Condition A.5. *For some $\epsilon_1 > 0$ and some $\epsilon_2 > 0$, $\sup_{|x-x^*|<\epsilon_1} E|Y(x)|^{2+\epsilon_2} < \infty$.*

A.2 Conditions for SAVOR

The following condition on $h(x)$ is extracted from Cheung and Elkind [9].

Condition A.6. *One and only one of the following statements is true:*

1. *The equation $h(x) = t_0$ has a unique root, denoted by θ_b, not among the jump points $\{l_2, \ldots, l_K\}$.*

2. *The root of $h(x) = t_0$ does not exist.*

3. *The equation $h(x) = t_0$ has multiple roots, with the smallest root denoted by θ' and the largest root by θ''. Both θ' and θ'' are not among the jump points.*

Appendix B

Proofs

B.1 Chapter 4

Proof of Proposition 4.1. The result follows immediately by observing that

$$\begin{aligned}\sum_{i=1}^{n}\sum_{k=1}^{K}\check{\sigma}_{kn}1\{X_i=k\} &= \sum_{k=1}^{K}\sum_{i=1}^{n}\check{\sigma}_{kn}1\{X_i=k\}\\ &= \sum_{k=1}^{K} n_{kn}\check{\sigma}_{kn}\\ &= \sum_{k=1}^{K}\sum_{i=1}^{n}\left\{E\left[S_i/\sigma(X_i)\right]\right\}^{-1}S_i 1\{X_i=k\}\\ &= \sum_{i=1}^{n}\left\{E\left[S_i/\sigma(X_i)\right]\right\}^{-1}S_i.\end{aligned}$$

□

Proof of Lemma 4.1 for LSR-based procedures. We first prove the results for LSRVO-B. From (3.16), we have

$$nX^*_{n+1} = \sum_{i=1}^{n} X^*_i - \frac{1}{b}\sum_{i=1}^{n}\left(V_{in}-t_0\right)$$

and

$$(n-1)X^*_n = \sum_{i=1}^{n-1} X^*_i - \frac{1}{b}\sum_{i=1}^{n-1}\left(V_{i,n-1}-t_0\right).$$

Subtracting the above equations gives

$$X^*_{n+1} = X^*_n - \frac{1}{nb}\left[V_{nn} - t_0 + \sum_{i=1}^{n-1}(V_{in} - V_{i,n-1})\right]. \tag{B.1}$$

Under LSRVO-B,

$$\begin{aligned} V_{nn} + \sum_{i=1}^{n-1}(V_{in} - V_{i,n-1}) &= V_{nn} + c_p \sum_{i=1}^{n-1}\sum_{k=1}^{K}(\tilde{\sigma}_{kn} - \tilde{\sigma}_{k,n-1})\, 1\{X_i = k\} \\ &= \bar{Y}_n + c_p \sum_{k=1}^{K} \tilde{\sigma}_{kn} 1\{X_n = k\} + \beta\,(X^*_n - X_n) \\ &\quad + c_p \sum_{k=1}^{K} n_{k,n-1}\,(\tilde{\sigma}_{kn} - \tilde{\sigma}_{k,n-1}) \\ &= h(X^*_n) + \sigma(x_n)(\bar{\epsilon}_n - c_p) + c_p \sum_{k=1}^{K}\left(n_{kn}\tilde{\sigma}_{kn} - n_{k,n-1}\tilde{\sigma}_{k,n-1}\right). \end{aligned} \tag{B.2}$$

Next, expanding $\tilde{\sigma}_{kn}$ around $\sigma(k)$ gives

$$\tilde{\sigma}_{kn} - \sigma(k) = \frac{1}{2\sigma(k)}\left(\tilde{\sigma}^2_{kn} - \sigma^2(k)\right) - \tilde{\eta}_{kn},$$

with

$$\tilde{\eta}_{kn} = \frac{1}{8\sigma^3(k)}\left(\tilde{\sigma}^2_{kn} - \sigma^2(k)\right)^2 - \frac{1}{16\tilde{\tau}^5_{kn}}\left(\tilde{\sigma}^2_{kn} - \sigma^2(k)\right)^3 \tag{B.3}$$

for some $\tilde{\tau}_{kn}$ between $\sigma(k)$ and $\tilde{\sigma}_{kn}$.

Substituting $n_{kn}\tilde{\sigma}_{kn} - n_{k,n-1}\tilde{\sigma}_{k,n-1}$

$$\begin{aligned} &= n_{kn}\left(\tilde{\sigma}_{kn} - \sigma(k)\right) - n_{k,n-1}\left(\tilde{\sigma}_{k,n-1} - \sigma(k)\right) + \sigma(k) 1\{X_n = k\} \\ &= n_{kn}\left(\frac{\tilde{\sigma}^2_{kn} - \sigma^2(k)}{2\sigma(k)} - \tilde{\eta}_{kn}\right) - n_{k,n-1}\left(\frac{\tilde{\sigma}^2_{k,n-1} - \sigma^2(k)}{2\sigma(k)} - \tilde{\eta}_{k,n-1}\right) + \sigma(k) 1\{X_n = k\} \\ &= \frac{1}{2\sigma(k)}\left(n_{kn}\tilde{\sigma}^2_{kn} - n_{k,n-1}\tilde{\sigma}^2_{k,n-1}\right) - \left(n_{kn}\tilde{\eta}_{kn} - n_{k,n-1}\tilde{\eta}_{k,n-1}\right) + \frac{1}{2}\sigma(k) 1\{X_n = k\}, \end{aligned}$$

and (B.2) into (B.1) yields

$$X^*_{n+1} = X^*_n - \frac{1}{nb}\left[h(X^*_n) + \sigma(X_n)\bar{\epsilon}_n + \frac{c_p}{2}\sum_{k=1}^{K}\frac{1}{\sigma(k)}\left(n_{kn}\tilde{\sigma}^2_{kn} - n_{k,n-1}\tilde{\sigma}^2_{k,n-1}\right) - \frac{c_p}{2}\sigma(X_n) - t_0\right]$$

$$+ \frac{c_p}{nb} \sum_{k=1}^{K} \left(n_{kn} \tilde{\eta}_{kn} - n_{k,n-1} \tilde{\eta}_{k,n-1} \right). \tag{B.4}$$

Since

$$n_{kn} \tilde{\sigma}^2_{kn} = n_{k,n-1} \tilde{\sigma}^2_{k,n-1} + S_n^2 1\{X_n = k\}, \tag{B.5}$$

(B.4) can be written as representation (4.5) with

$$e_n = \sigma(X_n) \left[\bar{\epsilon}_n + \frac{c_p}{2} \left(\frac{S_n^2}{\sigma^2(X_n)} - 1 \right) \right]$$

and

$$\xi_n = \frac{c_p}{nb} \sum_{k=1}^{K} \left(n_{kn} \tilde{\eta}_{kn} - n_{k,n-1} \tilde{\eta}_{k,n-1} \right).$$

It is easy to verify that $\sum_{n=1}^{\infty} E(e_n \mid \mathcal{F}_{n-1}) = 0$ a.s. We next show that $\sum_{n=1}^{\infty} E(|\xi_n| \mid \mathcal{F}_{n-1}) < \infty$ a.s. Let $\tilde{D}_{kn} = \tilde{\sigma}^2_{kn} - \sigma^2(k)$, then $\tilde{D}_{kn}$ has the following properties:

$$\tilde{D}_{kn} = \frac{n_{k,n-1}}{n_{kn}} \tilde{D}_{k,n-1} + \frac{1}{n_{kn}} (S_n^2 - \sigma^2(k)) 1\{X_n = k\} \tag{B.6}$$

$$\text{Given } \delta > 0, n_{kn}^{1/2-\delta} \tilde{D}_{kn} \to 0 \text{ on } \{n_{kn} \to \infty\} \tag{B.7}$$

Property (B.7) can be obtained by applying Corollary 5 of Chow (1965) [11] (with $p = 2$) and Kronecker's lemma to the martingale $\{\sum_{i=1}^{n} n_{ki}^{-(1/2+\delta)} (S_i^2 - \sigma^2(k)) 1\{X_i = k\}, \mathcal{F}_n, n \geq 1\}$. Note that (B.7) implies

$$\tilde{\sigma}^2_{kn} \to \sigma^2(k) \text{ on } \{n_{kn} \to \infty\}. \tag{B.8}$$

Now, from (B.3) and (B.6),

$$\begin{aligned} n_{kn} \tilde{\eta}_{kn} - n_{k,n-1} \tilde{\eta}_{k,n-1} = & \left\{ \left[-\frac{n_{kn}}{16 \tilde{\tau}^5_{kn}} \left(\frac{n_{k,n-1}}{n_{kn}} \right)^3 + \frac{n_{k,n-1}}{16 \tilde{\tau}^5_{k,n-1}} \right] \tilde{D}^3_{k,n-1} \right. \\ & - \frac{n_{k,n-1}}{n_{kn}} \left[\frac{1}{8\sigma^3(k)} + \frac{3}{16 \tilde{\tau}^5_{kn}} \left(\frac{n_{k,n-1}}{n_{kn}} \right) \left(S_n^2 - \sigma^2(k) \right) \right] \tilde{D}^2_{k,n-1} \\ & \left. + \frac{n_{k,n-1}}{n_{kn}} \left[\frac{S_n^2 - \sigma^2(k)}{4\sigma^3(k)} - \frac{3 \left(S_n^2 - \sigma^2(k) \right)^2}{16 \tilde{\tau}^5_{kn} n_{kn}} \right] \tilde{D}_{k,n-1} \right. \end{aligned}$$

$$+\frac{1}{n_{kn}}\left[\frac{\left(S_n^2-\sigma^2(k)\right)^2}{8\sigma^3(k)}-\frac{\left(S_n^2-\sigma^2(k)\right)^3}{16\tilde{\tau}_{kn}^5 n_{kn}}\right]\Bigg\}1\{X_n=k\}.$$

Fixing $0<\delta<1/2$, then from (B.7) we have $\sum_{n=1}^{\infty}E\left(|\xi_n|\mid\mathcal{F}_{n-1}\right)$

$$\begin{aligned}&=\sum_{n=1}^{\infty}n^{-1}\sum_{k=1}^{K}O\left(n_{k,n-1}|\tilde{D}_{k,n-1}^3|+\tilde{D}_{k,n-1}^2+|\tilde{D}_{k,n-1}|+n_{kn}^{-1}\right)1\{X_n=k\}\\&=\sum_{n=1}^{\infty}\sum_{k=1}^{K}O\left(n^{-1}n_{kn}^{-1/2+\delta}\right)1\{X_n=k\}<\infty\text{ a.s.}\end{aligned}$$

This finishes the proof for LSRVO-B.

We next move on to LSRVO-D. Following the algebraic steps up to (B.4) gives

$$\begin{aligned}X_{n+1}^*=X_n^*-\frac{1}{nb}\Bigg[&h(X_n^*)+\sigma(X_n)\bar{\epsilon}_n+\frac{c_p}{2}\sum_{k=1}^{K}\frac{1}{\sigma(k)}\left(n_{kn}\hat{\sigma}_{kn}^2-n_{k,n-1}\hat{\sigma}_{k,n-1}^2\right)-\frac{c_p}{2}\sigma(X_n)-t_0\Bigg]\\&+\frac{c_p}{nb}\sum_{k=1}^{K}\left(n_{kn}\hat{\eta}_{kn}-n_{k,n-1}\hat{\eta}_{k,n-1}\right),\end{aligned}\tag{B.9}$$

with

$$\hat{\eta}_{kn}=\frac{1}{8\sigma^3(k)}\left(\hat{\sigma}_{kn}^2-\sigma^2(k)\right)^2-\frac{1}{16\hat{\tau}_{kn}^5}\left(\hat{\sigma}_{kn}^2-\sigma^2(k)\right)^3,$$

for some $\hat{\tau}_{kn}$ between $\sigma(k)$ and $\hat{\sigma}_{kn}$. To derive an expression for $n_{kn}\hat{\sigma}_{kn}^2-n_{k,n-1}\hat{\sigma}_{k,n-1}^2$, we first introduce a new notation. Define $\tilde{\epsilon}_{kn}=\frac{\sum_{l=1}^{n}1\{X_l=k\}\bar{\epsilon}_l}{n_{kn}}$, where $\bar{\epsilon}_i=\frac{1}{m}\sum_{j=1}^{m}\epsilon_{ij}$. Then we can write

$$\begin{aligned}\hat{\sigma}_{kn}^2&=\frac{\sum_{l=1}^{n}\left[1\{X_l=k\}\sum_{j=1}^{m}(Y_{lj}-\tilde{Y}_{kn})^2\right]}{mn_{kn}}\\&=\sigma^2(k)\frac{\sum_{l=1}^{n}\left[1\{X_l=k\}\sum_{j=1}^{m}(\epsilon_{lj}-\tilde{\epsilon}_{kn})^2\right]}{mn_{kn}}\\&=\sigma^2(k)\frac{\sum_{l=1}^{n}1\{X_l=k\}\sum_{j=1}^{m}(\epsilon_{lj}-\bar{\epsilon}_l)^2+m\sum_{l=1}^{n}1\{X_l=k\}(\bar{\epsilon}_l-\tilde{\epsilon}_{kn})^2}{mn_{kn}}\\&=\frac{m-1}{m}\tilde{\sigma}_{kn}^2+\sigma^2(k)\frac{\sum_{l=1}^{n}1\{X_l=k\}\bar{\epsilon}_l^2}{n_{kn}}-\sigma^2(k)\tilde{\epsilon}_{kn}^2.\end{aligned}\tag{B.10}$$

The above expression can be used to produce a relationship between $\hat{\sigma}_{kn}^2$ and $\hat{\sigma}_{k,n-1}^2$:

$$\hat{\sigma}_{kn}^2=\frac{m-1}{m}\left(\frac{n_{k,n-1}}{n_{kn}}\tilde{\sigma}_{k,n-1}^2+\frac{1}{n_{kn}}S_n^2 1\{X_n=k\}\right)$$

$$
\begin{aligned}
&+\sigma^2(k)\left(\frac{n_{k,n-1}}{n_{kn}}\frac{\sum_{l=1}^{n-1}1\{X_l=k\}\bar{\epsilon}_l^2}{n_{k,n-1}}+\frac{1}{n_{kn}}\bar{\epsilon}_n^2 1\{X_n=k\}\right)\\
&-\sigma^2(k)\left(\frac{n_{k,n-1}}{n_{kn}}\tilde{\epsilon}_{k,n-1}+\frac{1}{n_{kn}}\bar{\epsilon}_n 1\{X_n=k\}\right)^2\\
&=\frac{n_{k,n-1}}{n_{kn}}\left(\frac{m-1}{m}\tilde{\sigma}^2_{k,n-1}+\sigma^2(k)\frac{\sum_{l=1}^{n-1}1\{X_l=k\}\bar{\epsilon}_l^2}{n_{k,n-1}}-\sigma^2(k)\tilde{\epsilon}^2_{k,n-1}\right)\\
&+\frac{1}{n_{kn}}\left[\frac{m-1}{m}S_n^2+\frac{n_{k,n-1}}{n_{kn}}\sigma^2(k)\left(\bar{\epsilon}_n-\tilde{\epsilon}_{k,n-1}\right)^2\right]1\{X_n=k\}\\
&=\frac{n_{k,n-1}}{n_{kn}}\hat{\sigma}^2_{k,n-1}+\frac{1}{n_{kn}}\left[\frac{m-1}{m}S_n^2+\frac{n_{k,n-1}}{n_{kn}}\sigma^2(k)\left(\bar{\epsilon}_n-\tilde{\epsilon}_{k,n-1}\right)^2\right]1\{X_n=k\}.
\end{aligned}
\tag{B.11}
$$

Representation (4.5) follows from (B.9) and (B.11) with

$$
e_n=\sigma(X_n)\left[\bar{\epsilon}_n+\frac{c_p}{2}\left(\frac{m-1}{m}\frac{S_n^2}{\sigma^2(X_n)}+\bar{\epsilon}_n^2-1\right)\right],
$$

and

$$
\begin{aligned}
\xi_n=&\frac{c_p}{nb}\sum_{k=1}^{K}\left(n_{kn}\hat{\eta}_{kn}-n_{k,n-1}\hat{\eta}_{k,n-1}\right)\\
&-\frac{c_p}{2nb}\sum_{k=1}^{K}\sigma(k)\left[-2\bar{\epsilon}_n\tilde{\epsilon}_{k,n-1}+\tilde{\epsilon}^2_{k,n-1}-n_{kn}^{-1}\left(\bar{\epsilon}_n-\tilde{\epsilon}_{k,n-1}\right)^2\right]1\{X_n=k\}.
\end{aligned}
$$

Again, it is easy to verify $E(e_n \mid \mathcal{F}_{n-1})=0$ a.s. The next step is to show $\sum_{n=1}^{\infty}E(|\xi_n| \mid \mathcal{F}_{n-1})<\infty$ a.s. First, for any $\delta>0$, applications of Colrollary 5 of [11] and Kronecker's lemma to the martingales $\left\{\sum_{i=1}^{n}n_{ki}^{-(1/2+\delta)}\left(\bar{\epsilon}_i^2-\frac{1}{m}\right)1\{X_i=k\},\mathcal{F}_n,n\geq 1\right\}$ and $\left\{\sum_{i=1}^{n}n_{ki}^{-(1/2+\delta)}\bar{\epsilon}_i\ \ 1\{X_i=k\},\mathcal{F}_n,n\geq 1\right\}$ give

$$
n_{kn}^{1/2-\delta}\left(\frac{\sum_{l=1}^{n}1\{X_l=k\}\bar{\epsilon}_l^2}{n_{kn}}-\frac{1}{m}\right)\to 0 \text{ on } \{n_{kn}\to\infty\},
\tag{B.12}
$$

$$
n_{kn}^{1/2-\delta}\tilde{\epsilon}_{kn}\to 0 \text{ on } \{n_{kn}\to\infty\}.
\tag{B.13}
$$

From (B.13)

$$
\sum_{n=1}^{\infty}n^{-1}E\left(\left|\sum_{k=1}^{K}\bar{\epsilon}_n\tilde{\epsilon}_{k,n-1}1\{X_n=k\}\right| \mid \mathcal{F}_{n-1}\right)\leq\sum_{n=1}^{\infty}\sum_{k=1}^{K}n^{-1}O\left(|\tilde{\epsilon}_{k,n-1}|\right)1\{X_n=k\}
$$

$$= \sum_{n=1}^{\infty} \sum_{k=1}^{K} O\left(n^{-1} n_{kn}^{-1/2+\delta}\right) 1\{X_n = k\} < \infty \text{ a.s.},$$

and it is easy to verify $\sum_{n=1}^{\infty} n^{-1} \sum_{k=1}^{K} E\left(|\tilde{\epsilon}_{k,n-1}^2 - n_{kn}^{-1} \left(\bar{\epsilon}_n - \tilde{\epsilon}_{k,n-1}\right)^2 | \mid \mathcal{F}_{n-1}\right) 1\{X_n = k\} < \infty$ a.s. Thus it remains to show $\sum_{n=1}^{\infty} n^{-1} \sum_{k=1}^{K} E\left(|n_{kn}\hat{\eta}_{kn} - n_{k,n-1}\hat{\eta}_{k,n-1}| \mid \mathcal{F}_{n-1}\right) < \infty$ a.s. To this end, let $\hat{D}_{kn} = \hat{\sigma}_{kn}^2 - \sigma^2(k)$, and $G_{kn} = \frac{m-1}{m} S_n^2 + \frac{n_{k,n-1}}{n_{kn}} \sigma^2(k) \left(\bar{\epsilon}_n - \tilde{\epsilon}_{k,n-1}\right)^2 - \sigma^2(k)$. Then

$$\hat{D}_{kn} = \frac{n_{k,n-1}}{n_{kn}} \hat{D}_{k,n-1} + \frac{1}{n_{kn}} G_{kn} 1\{X_n = k\}$$

and for any $\delta > 0$, as a consequence of (B.10), (B.7), (B.12) and (B.13),

$$\begin{aligned} n_{kn}^{1/2-\delta} \hat{D}_{kn} &= n_{kn}^{1/2-\delta} \left[\frac{m-1}{m} \tilde{D}_{kn} + \sigma^2(k) \left(\frac{\sum_{l=1}^{n} 1\{X_l = k\} \bar{\epsilon}_l^2}{n_{kn}} - \frac{1}{m}\right) - \sigma^2(k) \bar{\epsilon}_{kn}^2\right] \\ &\to 0 \text{ on } \{n_{kn} \to \infty\}. \end{aligned} \tag{B.14}$$

Now,

$$\begin{aligned} n_{kn}\hat{\eta}_{kn} - n_{k,n-1}\hat{\eta}_{k,n-1} = \Bigg\{ &\left[-\frac{n_{kn}}{16\hat{\tau}_{kn}^5} \left(\frac{n_{k,n-1}}{n_{kn}}\right)^3 + \frac{n_{k,n-1}}{16\hat{\tau}_{k,n-1}^5}\right] \hat{D}_{k,n-1}^3 \\ &- \frac{n_{k,n-1}}{n_{kn}} \left[\frac{1}{8\sigma^3(k)} + \frac{3}{16\hat{\tau}_{kn}^5} \left(\frac{n_{k,n-1}}{n_{kn}}\right) G_{kn}\right] \hat{D}_{k,n-1}^2 \\ &+ \frac{n_{k,n-1}}{n_{kn}} \left[\frac{G_{kn}}{4\sigma^3(k)} - \frac{3\, G_{kn}^2}{16\hat{\tau}_{kn}^5 n_{kn}}\right] \hat{D}_{k,n-1} \\ &+ \frac{1}{n_{kn}} \left[\frac{G_{kn}^2}{8\sigma^3(k)} - \frac{G_{kn}^3}{16\hat{\tau}_{kn}^5 n_{kn}}\right] \Bigg\} 1\{X_n = k\}. \end{aligned}$$

The desired result follows from applying the same arguments from the proof of LSRVO-B.

Finally, we turn to LSRVO-C. The recursion can be expressed as

$$\begin{aligned} X_{n+1}^* = X_n^* - \frac{1}{nb} \Bigg[&h(X_n^*) + \sigma(X_n)\bar{\epsilon}_n + \frac{c_p}{2} \sum_{k=1}^{K} \frac{1}{\sigma(k)} \left(n_{kn}\bar{\sigma}_{kn}^2 - n_{k,n-1}\bar{\sigma}_{k,n-1}^2\right) - \frac{c_p}{2}\sigma(X_n) - t_0 \Bigg] \\ &+ \frac{c_p}{nb} \sum_{k=1}^{K} \left(n_{kn}\bar{\eta}_{kn} - n_{k,n-1}\bar{\eta}_{k,n-1}\right). \end{aligned} \tag{B.15}$$

with

$$\bar{\eta}_{kn} = \frac{1}{8\sigma^3(k)} \left(\bar{\sigma}_{kn}^2 - \sigma^2(k)\right)^2 - \frac{1}{16\bar{\tau}_{kn}^5} \left(\bar{\sigma}_{kn}^2 - \sigma^2(k)\right)^3,$$

for some $\bar{\tau}_{kn}$ between $\sigma(k)$ and $\bar{\sigma}_{kn}$.

For an expression of $n_{kn}\bar{\eta}_{kn} - n_{k,n-1}\bar{\eta}_{k,n-1}$ we rely on the relationship between $\bar{\sigma}^2_{kn}$ and $\hat{\sigma}^2_{kn}$. From $\bar{\sigma}^2_{kn} = \frac{mn_{kn}}{mn_{kn}-1}\hat{\sigma}^2_{kn} = \hat{\sigma}^2_{kn} + \frac{1}{mn_{kn}}\bar{\sigma}^2_{kn}$ we have

$$\begin{aligned}(mn_{kn}-1)\left(\bar{\sigma}^2_{kn} - \bar{\sigma}^2_{k,n-1}\right) &= (mn_{kn}-1)\bar{\sigma}^2_{kn} - (mn_{k,n-1}-1)\bar{\sigma}^2_{k,n-1} - m1\{X_n = k\}\bar{\sigma}^2_{k,n-1} \\ &= m\left(n_{kn}\hat{\sigma}^2_{kn} - n_{k,n-1}\hat{\sigma}^2_{k,n-1}\right) - m1\{X_n = k\}\bar{\sigma}^2_{k,n-1},\end{aligned}$$

and

$$\begin{aligned}n_{kn}\bar{\sigma}^2_{kn} - n_{k,n-1}\bar{\sigma}^2_{k,n-1} &= n_{kn}\hat{\sigma}^2_{kn} - n_{k,n-1}\hat{\sigma}^2_{k,n-1} + \frac{\bar{\sigma}^2_{kn} - \bar{\sigma}^2_{k,n-1}}{m} \\ &= \left(n_{kn}\hat{\sigma}^2_{kn} - n_{k,n-1}\hat{\sigma}^2_{k,n-1}\right)\left(1 + \frac{1}{mn_{kn}-1}\right) - \frac{1\{X_n = k\}}{mn_{kn}-1}\bar{\sigma}^2_{k,n-1}.\end{aligned}$$

Substituting the above expression and (B.11) into (B.15) establishes (4.5) with

$$e_n = \sigma(X_n)\left[\bar{\epsilon}_n + \frac{c_p}{2}\left(\frac{m-1}{m}\frac{S^2_n}{\sigma^2(X_n)} + \bar{\epsilon}^2_n - 1\right)\right],$$

and

$$\begin{aligned}\xi_n =& \frac{c_p}{nb}\sum_{k=1}^{K}\left(n_{kn}\bar{\eta}_{kn} - n_{k,n-1}\bar{\eta}_{k,n-1}\right) \\ &- \frac{c_p}{2nb}\sum_{k=1}^{K}\sigma(k)\left\{-2\bar{\epsilon}_n\tilde{\epsilon}_{k,n-1} + \tilde{\epsilon}^2_{k,n-1} - n^{-1}_{kn}\left(\bar{\epsilon}_n - \tilde{\epsilon}_{k,n-1}\right)^2\right. \\ &\left. + \frac{1}{mn_{kn}-1}\left[\frac{m-1}{m}\frac{S^2_n}{\sigma^2(X_n)} + \frac{n_{k,n-1}}{n_{kn}}\left(\bar{\epsilon}_n - \tilde{\epsilon}_{k,n-1}\right)^2 - \frac{\bar{\sigma}^2_{k,n-1}}{\sigma^2(k)}\right]\right\}1\{X_n = k\}\end{aligned} \tag{B.16}$$

To show $\sum_{n=1}^{\infty} E(|\xi_n| \mid \mathcal{F}_{n-1}) < \infty$ a.s., it suffices to verify

$$\sum_{n=1}^{\infty} n^{-1}\sum_{k=1}^{K} E\left(|n_{kn}\bar{\eta}_{kn} - n_{k,n-1}\bar{\eta}_{k,n-1}| \mid \mathcal{F}_{n-1}\right) < \infty \text{ a.s.} \tag{B.17}$$

and

$$\sum_{n=1}^{\infty} n^{-1}\sum_{k=1}^{K} n^{-1}_{kn}\frac{\bar{\sigma}^2_{k,n-1}}{\sigma^2(k)}1\{X_n = k\} < \infty \text{ a.s.} \tag{B.18}$$

Let $\bar{D}_{kn} = \bar{\sigma}^2_{kn} - \sigma^2(k)$, then

$$\bar{D}_{kn} = \frac{mn_{k,n-1} - 1}{mn_{kn} - 1}\bar{D}_{k,n-1} + \frac{m}{mn_{kn} - 1}G_{kn}1\{X_n = k\},$$

and due to (B.14), for any $\delta > 0$,

$$n_{kn}^{1/2-\delta}\bar{D}_{kn} = n_{kn}^{1/2-\delta}\left(\hat{D}_{kn} + \frac{\hat{\sigma}^2_{kn}}{mn_{kn} - 1}\right) \to 0 \text{ on } \{n_{kn} \to \infty\}. \tag{B.19}$$

The above result implies $\bar{\sigma}^2_{kn} \to \sigma^2(k)$ on $\{n_{kn} \to \infty\}$ which immediately establishes (B.17). Observing that

$$\begin{aligned}
n_{kn}\bar{\eta}_{kn} - n_{k,n-1}\bar{\eta}_{k,n-1} = \Bigg\{ & \left[-\frac{n_{kn}}{16\bar{\tau}^5_{kn}}\left(\frac{mn_{k,n-1} - 1}{mn_{kn} - 1}\right)^3 + \frac{n_{k,n-1}}{16\bar{\tau}^5_{k,n-1}}\right]\bar{D}^3_{k,n-1} \\
& + \left[\frac{n_{kn}}{8\sigma^3(k)}\left(\frac{mn_{k,n-1} - 1}{mn_{kn} - 1}\right)^2 - \frac{n_{k,n-1}}{8\sigma^3(k)}\right. \\
& \qquad \left. - \frac{3}{16\bar{\tau}^5_{kn}}\frac{mn_{kn}(mn_{k,n-1} - 1)^2}{(mn_{kn} - 1)^3}G_{kn}\right]\bar{D}^2_{k,n-1} \\
& + mn_{kn}\frac{mn_{k,n-1} - 1}{(mn_{kn} - 1)^2}\left[\frac{G_{kn}}{4\sigma^3(k)} - \frac{3G^2_{kn}}{16\bar{\tau}^5_{kn}}\frac{m}{mn_{kn} - 1}\right]\bar{D}_{k,n-1} \\
& + n_{kn}\left(\frac{m}{mn_{kn} - 1}\right)^2\left[\frac{G^2_{kn}}{8\sigma^3(k)} - \frac{G^3_{kn}}{16\bar{\tau}^5_{kn}}\frac{m}{mn_{kn} - 1}\right]\Bigg\} 1\{X_n = k\},
\end{aligned}$$

(B.18) can be verified by following the same approach as before. This completes the proof of Lemma 4.1 for LSR-based procedures.

□

Proof of Lemma 4.1 for SA-based procedures. We prove the results for SAVOR-B. Results for SAVOR-C and SAVOR-D can be obtained analogously. The design sequence $\{X^*_n\}$ generated by SAVOR-B can be written as

$$\begin{aligned}
X^*_{n+1} &= X^*_n - \frac{1}{nb}\left(\bar{Y}_n + c_p\sum_{k=1}^{K}\tilde{\sigma}_{kn}1\{X_n = k\} + \beta(X^*_n - X_n) - t_0\right) \\
&= X^*_n - \frac{1}{nb}\left(h(X^*_n) + \sigma(X_n)\bar{\epsilon}_n + c_p\sum_{k=1}^{K}\left(\tilde{\sigma}_{kn} - \sigma(k)\right)1\{X_n = k\} - t_0\right)
\end{aligned}$$

$$= X_n^* - \frac{1}{nb}\left(h(X_n^*) + \sigma(X_n)\bar{\epsilon}_n - t_0\right) + \frac{c_p}{nb}\sum_{k=1}^{K}\left(\tilde{\eta}_{kn} - \frac{\tilde{\sigma}_{kn}^2 - \sigma^2(k)}{2\sigma(k)}\right)1\{X_n = k\}$$

where $\tilde{\eta}_{kn}$ is defined in (B.3).

Now, from (B.6), $\tilde{\eta}_{kn} - \frac{\tilde{\sigma}_{kn}^2 - \sigma^2(k)}{2\sigma(k)}$

$$\begin{aligned}
&= -\frac{1}{16\tilde{\tau}_{kn}^5}\left(\frac{n_{k,n-1}}{n_{kn}}\right)^3 \tilde{D}_{k,n-1}^3 \\
&\quad + \left(\frac{n_{k,n-1}}{n_{kn}}\right)^2\left[\frac{1}{8\sigma^3(k)} - \frac{3}{16\tilde{\tau}_{kn}^5}\frac{S_n^2 - \sigma^2(k)}{n_{kn}}1\{X_n = k\}\right]\tilde{D}_{k,n-1}^2 \\
&\quad - \left[\frac{1}{2\sigma(k)} - \frac{n_{k,n-1}}{n_{kn}^2}\left(\frac{S_n^2 - \sigma^2(k)}{4\sigma^3(k)} - \frac{3\left(S_n^2 - \sigma^2(k)\right)^2}{16\tilde{\tau}_{kn}^5 n_{kn}}\right)1\{X_n = k\}\right]\tilde{D}_{k,n-1} \\
&\quad + \frac{1}{n_{kn}^2}\left[\frac{\left(S_n^2 - \sigma^2(k)\right)^2}{8\sigma^3(k)} - \frac{\left(S_n^2 - \sigma^2(k)\right)^3}{16\tilde{\tau}_{kn}^5 n_{kn}}\right]1\{X_n = k\}
\end{aligned}$$

Using arguments from the proof for LSRVO-B, we have

$$\sum_{n=1}^{\infty} n^{-1}\sum_{k=1}^{K} E\left(\left|\tilde{\eta}_{kn} - \frac{\tilde{\sigma}_{kn}^2 - \sigma^2(k)}{2\sigma(k)}\right|1\{X_n = k\} \mid \mathcal{F}_{n-1}\right) < \infty \text{ a.s.}$$

This shows that SAVOR-B can be represented by the general form (4.5).

Lastly, for SAVOR-A, the recursion can be written as

$$X_{n+1}^* = X_n^* - \frac{1}{nb}\left(\bar{Y}_n + c_p\sigma(X_n) + \beta(X_n^* - X_n) - t_0\right) - \frac{c_p}{nb}\sum_{k=1}^{K}\left(\check{\sigma}_{kn} - \sigma(k)\right)1\{X_n = k\}.$$

Since $\check{\sigma}_{kn} - \sigma(k) = \frac{n_{k,n-1}}{n_{kn}}\left(\check{\sigma}_{k,n-1} - \sigma(k)\right) + \frac{1}{n_{kn}}\left\{\left[E\left(S_n/\sigma(X_n)\right)\right]^{-1} S_n - \sigma(k)\right\}1\{X_n = k\}$, to get the desired result, it is enough to verify

$$\sum_{n=1}^{\infty} n^{-1}\sum_{k=1}^{K}\frac{n_{k,n-1}}{n_{kn}}|\check{\sigma}_{k,n-1} - \sigma(k)|1\{X_n = k\} < \infty \text{ a.s.}.$$

This can be established by applying Corollary 5 of [11] and Kronecker's lemma to the martingale $\left\{\sum_{i=1}^{n} n_{ki}^{-(1/2+\delta)}\left\{\left[E\left(S_i/\sigma(X_i)\right)\right]^{-1} S_i - \sigma(k)\right\}1\{X_i = k\}, \mathcal{F}_n, n \geq 1\right\}$ for some $0 < \delta < 1/2$. □

Proof of Theorem 4.1 (i). Under the conditions, $h(x) = t_0$ has a unique root at θ_β. Moreover, $C(\theta_\beta) = \nu_1$. Thus it remains to show that X_n^* will converge to θ_β with probability one.

Recall that the procedures can be represented by a general form:

$$X_{n+1}^* = X_n^* - \frac{1}{nb}\left(h(X_n^*) + e_n - t_0\right) + \xi_n,$$

where $E(e_n \mid \mathcal{F}_{n-1}) = 0$ and $\sum_{n=1}^{\infty} E(|\xi_n| \mid \mathcal{F}_{n-1}) < \infty$ almost surely. Repeatedly applying the inequalities $(a_1 + a_2)^2 \le 2a_1^2 + 2a_2^2$ and $2a_1a_2 \le a_1^2 + a_2^2$ gives,

$$\begin{aligned}
(X_{n+1}^* - \theta_\beta)^2 \le & (X_n^* - \theta_\beta)^2 - \frac{2}{nb}(X_n^* - \theta_\beta)\left(h(X_n^*) + e_n - t_0\right) + 2(X_n^* - \theta_\beta)\xi_n \\
& + \frac{2}{n^2b^2}(h(X_n^*) + e_n - t_0)^2 + 2\xi_n^2 \\
\le & (X_n^* - \theta_\beta)^2(1 + |\xi_n|) - \frac{2}{nb}(X_n^* - \theta_\beta)\left(h(X_n^*) + e_n - t_0\right) + |\xi_n| \\
& + \frac{2}{n^2b^2}(h(X_n^*) + e_n - t_0)^2 + 2\xi_n^2 \\
\le & (X_n^* - \theta_\beta)^2\left(1 + |\xi_n| + \frac{4\beta^2}{n^2b^2}\right) - \frac{2}{nb}(X_n^* - \theta_\beta)\left(h(X_n^*) + e_n - t_0\right) + |\xi_n| \\
& + \frac{8}{n^2b^2}e_n^2 + 2\xi_n^2 + O(n^{-2}),
\end{aligned}$$

where the last inequality follows since $|h(X_n^*)| = |f(X_n) + \beta(X_n^* - X_n)| = |f(X_n) + \beta(X_n^* - \theta_\beta) + \beta(\theta_\beta - X_n)| \le |\beta(X_n^* - \theta_\beta)| + O(1)$.

Taking conditional expectation with respect to $\mathcal{F}_{n-1}$ gives

$$\begin{aligned}
E\left((X_{n+1}^* - \theta_\beta)^2 \mid \mathcal{F}_{n-1}\right) \le & (X_n^* - \theta_\beta)^2\left(1 + E\left(|\xi_n| \mid \mathcal{F}_{n-1}\right) + O(n^{-2})\right) \\
& - \frac{2}{nb}(X_n^* - \theta_\beta)\left(h(X_n^*) - t_0\right) \\
& + E\left(|\xi_n| \mid \mathcal{F}_{n-1}\right) + E\left(\frac{8e_n^2}{n^2b^2} + 2\xi_n^2 \mid \mathcal{F}_{n-1}\right) + O(n^{-2}).
\end{aligned}$$

It can be verified that $\sum_{n=1}^{\infty} E\left(\frac{8}{n^2b^2}e_n^2 + 2\xi_n^2 \mid \mathcal{F}_{n-1}\right) < \infty$ a.s. Hence, Theorem 1 of Robbins and Siegmund (1971) [26] implies that $\lim_{n\to\infty}(X_{n+1}^* - \theta_\beta)^2$ exists and $\sum_{n=1}^{\infty} n^{-1}(X_n^* - \theta_\beta)\left(h(X_n^*) - t_0\right) < \infty$ a.s. Since $(X_n^* - \theta_\beta)\left(h(X_n^*) - t_0\right) > 0$ for $X_n^* \neq \theta_\beta$, we have $X_n^* \to \theta_\beta$ and $X_n = C(\theta_\beta) = \nu_1$ eventually almost surely.

□

Proof of Theorem 4.1 (ii). When $\pi(\nu_1) < p$, $h(\nu_1 + 0.5-) < t_0$ and $h(\nu_1 + 0.5) > t_0$. Replacing θ_β with $\nu_1 + 0.5$ in the proof of (i) gives $X_n^* \to \nu_1 + 0.5$ a.s. Similarly, we can show $X_n^* \to \nu_1 - 0.5$ a.s. when $\pi(\nu_1) > p$. □

Proof of Theorem 4.2 (i). For LSR-based procedures, we prove the result for LSRVO-C. Results for LSRVO-B and LSRVO-D can be established in similar but simpler arguments.

Following the approach of Sacks [27], let $\rho = \beta/b > 1/2$,

$$\gamma_{in} = \begin{cases} \prod_{j=i+1}^{n} \left(1 - \frac{\rho}{j}\right) & \text{if } 0 \le i < n \\ 1 & \text{if } i = n \end{cases} \quad \text{and } w_n = \left(\sum_{i=1}^{n} \rho^2 i^{-2} \gamma_{in}^2\right)^{-1/2}.$$

From equation 2.3, Lemmas 2, 5 and 3 of Sacks [27], we have the following properties

$$\text{(a) } (1-\delta_i)\, i^\rho n^{-\rho} \le \gamma_{in} \le (1+\delta_i)\, i^\rho n^{-\rho} \text{ where } \delta_i \to 0 \text{ as } i \to \infty \tag{B.20a}$$

$$\text{(b) } \lim_{n\to\infty} w_n \gamma_{in} = 0 \text{ for fixed } i \tag{B.20b}$$

$$\text{(c) } w_n \sim \rho^{-1}(2\rho-1)^{1/2} n^{1/2} = (b(2\beta - b))^{1/2}\, \beta^{-1} n^{1/2} \tag{B.20c}$$

(d) Let $\{W_j\}$ be a sequence of real numbers converging to W, then

$$\lim_{n\to\infty} w_n^2 \sum_{j=j_0}^{n} \rho^2 j^{-2} \gamma_{jn}^2 W_j = W, \text{ for fixed } j_0. \tag{B.20d}$$

Next, recall that under LSRVO-C,

$$X_{n+1}^* = X_n^* - \frac{1}{nb}\left(h(X_n^*) + e_n - t_0\right) + \xi_n$$

where $e_n = \sigma(X_n)\left[\bar{\epsilon}_n + \frac{c_p}{2}\left(\frac{m-1}{m} S_n^2/\sigma^2(X_n) + \bar{\epsilon}_n^2 - 1\right)\right]$ and ξ_n is defined in (B.16). Since $h(X_n^*) = f(X_n) + \beta(X_n^* - X_n)$ and $t_0 = h(\theta_\beta) = f(\nu_1) + \beta(\theta_\beta - \nu_1)$,

$$X_{n+1}^* - \theta_\beta = (X_n^* - \theta_\beta) - \frac{1}{nb}\left(h(X_n^*) + e_n - t_0\right) + \xi_n$$

$$= \left(1 - \frac{\rho}{n}\right)(X_n^* - \theta_\beta) - \frac{1}{nb}e_n - \frac{1}{nb}\left(f(X_n) - f(\nu_1) - \beta(X_n - \nu_1)\right) + \xi_n.$$

Iterating the above yields

$$\begin{aligned} X_{n+1}^* - \theta_\beta = \gamma_{0n}(X_1^* - \theta_\beta) &- b^{-1}\sum_{i=1}^{n} i^{-1}\gamma_{in}e_i \\ &- b^{-1}\sum_{i=1}^{n} i^{-1}\gamma_{in}\left(f(X_i) - f(\nu_1) - \beta(X_i - \nu_1)\right) + \sum_{i=1}^{n}\gamma_{in}\xi_i. \end{aligned}$$

Multiply w_n on both sides then the desired result will follow if we can show

$$w_n\gamma_{0n}(X_1^* - \theta_\beta) \xrightarrow{P} 0 \tag{B.21a}$$

$$w_n b^{-1}\sum_{i=1}^{n} i^{-1}\gamma_{in}e_i \xrightarrow{d} N\left(0, \frac{\sigma^2(\nu_1)}{m\beta^2}(1+\kappa)\right) \tag{B.21b}$$

$$w_n b^{-1}\sum_{i=1}^{n} i^{-1}\gamma_{in}\left(f(X_i) - f(\nu_1) - \beta(X_i - \nu_1)\right) \xrightarrow{P} 0 \tag{B.21c}$$

$$w_n\sum_{i=1}^{n}\gamma_{in}\xi_i \xrightarrow{P} 0. \tag{B.21d}$$

A direct application of (B.20b) gives (B.21a). As for (B.21c), we use (B.20a), (B.20c) and the fact that $X_n = \nu_1$ a.s. eventually to obtain

$$\begin{aligned} &w_n\sum_{i=1}^{n} i^{-1}\gamma_{in}\left(f(X_i) - f(\nu_1) - \beta(X_i - \nu_1)\right) \\ &\sim n^{1/2-\rho}\sum_{i=1}^{n} i^{\rho-1}\left(f(X_i) - f(\nu_1) - \beta(X_i - \nu_1)\right) \to 0 \text{ a.s.} \end{aligned}$$

Next, we verify (B.21b). Let $Q_{in} = w_n b^{-1} i^{-1}\gamma_{in}e_i$, then $Q_{in} \in \mathcal{F}_i$ and $E\left(Q_{in} \mid \mathcal{F}_{i-1}\right) = 0$ a.s. By evoking the martingale central limit theorem in [23] (p. 171), it suffices to verify the following conditions:

$$\text{(a)} \ \sum_{i=1}^{n} E\left(Q_{in}^2 \mid \mathcal{F}_{i-1}\right) \xrightarrow{P} \frac{\sigma^2(\nu_1)}{m\beta^2}(1+\kappa), \tag{B.22a}$$

$$\text{(b) For every } \delta > 0, \sum_{i=1}^{n} E\left(Q_{in}^2 1\{|Q_{in}| > \delta\} \mid \mathcal{F}_{i-1}\right) \xrightarrow{P} 0. \tag{B.22b}$$

Since

$$
\begin{aligned}
E\left(e_i^2 \mid \mathcal{F}_{i-1}\right) &= \sigma^2(X_i)\left[Var\bar{\epsilon}_i + \frac{c_p^2}{4}\left(\frac{m-1}{m}\right)^2 Var\left(\frac{S_i^2}{\sigma^2(X_i)}\right) + \frac{c_p^2}{4}Var\bar{\epsilon}_i^2\right. \\
&\quad \left. + c_p\frac{m-1}{m}E\left(\bar{\epsilon}_i\frac{S_i^2}{\sigma^2(X_i)}\right) + c_pE\bar{\epsilon}_i^3 + \frac{c_p^2}{2}\frac{m-1}{m}Cov\left(\bar{\epsilon}_i^2, \frac{S_i^2}{\sigma^2(X_i)}\right)\right] \\
&= \sigma^2(X_i)\left[\frac{1}{m} + \frac{c_p^2}{4}\left(\frac{m-1}{m}\right)^2 u_1 + \frac{c_p^2}{4}u_2 + c_p\frac{m-1}{m}u_3 + c_pu_4 + \frac{c_p^2}{2}\frac{m-1}{m}u_5\right] \\
&\overset{i\to\infty}{\longrightarrow} \frac{\sigma^2(\nu_1)}{m}(1+\kappa) \text{ a.s.},
\end{aligned}
$$

$$
\sum_{i=1}^{n} E\left(Q_{in}^2 \mid \mathcal{F}_{i-1}\right) = w_n^2 b^{-2}\rho^{-2}\sum_{i=1}^{n}\rho^2 i^{-2}\gamma_{in}^2 E\left(e_i^2 \mid \mathcal{F}_{i-1}\right) \overset{n\to\infty}{\longrightarrow} \frac{\sigma^2(\nu_1)}{m\beta^2}(1+\kappa) \text{ a.s.}
$$

by (B.20d).

We now verify (B.22b). Fix $\delta > 0$, then using (B.20a) and (B.20c),

$$
\begin{aligned}
|Q_{in}| > \delta &\Longrightarrow |e_i| > w_n^{-1} b\, i|\gamma_{in}^{-1}|\,\delta \\
&\Longrightarrow |e_i| > C\, n^{\rho-1/2} i^{1-\rho}\delta = C\left(\frac{n}{i}\right)^{\rho-1/2} i^{1/2}\delta \\
&\Longrightarrow |e_i| > \delta'\, i^{1/2},
\end{aligned}
$$

for some positive C and δ', and

$$
\begin{aligned}
0 &\le \sum_{i=1}^{n} E\left(Q_{in}^2 1\{|Q_{in}| > \delta\} \mid \mathcal{F}_{i-1}\right) \\
&\le \sum_{i=1}^{n} E\left(Q_{in}^2 1\left\{|e_i| > \delta' i^{1/2}\right\} \mid \mathcal{F}_{i-1}\right) \\
&= w_n^2\, b^{-2}\rho^{-2}\sum_{i=1}^{n}\rho^2 i^{-2}\gamma_{in}^2 E\left(e_i^2 1\left\{|e_i| > \delta' i^{1/2}\right\} \mid \mathcal{F}_{i-1}\right) \\
&\overset{n\to\infty}{\longrightarrow} 0 \text{ a.s.}
\end{aligned}
$$

Since δ is arbitrary this completes the proof of (B.21b).

Finally, we proceed to verify (B.21d). From (B.20a), (B.20c) and (B.16) we obtain

$$
w_n\sum_{i=1}^{n}\gamma_{in}\xi_i \sim n^{1/2-\rho}\sum_{i=1}^{n} i^{\rho-1}(i\xi_i)
$$

$$= c_p b^{-1} n^{1/2-\rho} \sum_{i=1}^{n} i^{\rho-1} \left\{ \sum_{k=1}^{K} \left(n_{ki} \bar{\eta}_{ki} - n_{k,i-1} \bar{\eta}_{k,i-1} \right) \right.$$
$$-2^{-1} \sum_{k=1}^{K} \sigma(k) \left[-2\bar{\epsilon}_i \tilde{\epsilon}_{k,i-1} + \tilde{\epsilon}_{k,i-1}^2 + n_{ki}^{-1} \left(\bar{\epsilon}_i - \tilde{\epsilon}_{k,i-1} \right)^2 \right.$$
$$\left. \left. + \frac{1}{m n_{ki} - 1} \left(\frac{m-1}{m} \frac{S_i^2}{\sigma^2(X_i)} + \frac{n_{k,i-1}}{n_{ki}} \left(\bar{\epsilon}_i - \tilde{\epsilon}_{k,i-1} \right)^2 - \frac{\bar{\sigma}_{k,i-1}^2}{\sigma^2(k)} \right) \right] 1\{X_i = k\} \right\}. \tag{B.23}$$

To show that the above will converge to 0 in probability, we tackle each term in turns. To handle the first term we follow the algebraic steps in the proof of Kronecker's lemma (e.g. Durrett 2005). Fix $0 < \delta < 1/2$. Let $c_i = \sum_{l=1}^{i} \sum_{k=1}^{K} \left(n_{kl} \bar{\eta}_{kl} - n_{k,l-1} \bar{\eta}_{k,l-1} \right)$ $= \sum_{k=1}^{K} n_{ki} \bar{\eta}_{ki} = O(n_{ki}^{\delta})$, then $n^{-1/2} c_n \to 0$ a.s. and,

$$n^{1/2-\rho} \sum_{i=1}^{n} i^{\rho-1} \sum_{k=1}^{K} \left(n_{ki} \bar{\eta}_{ki} - n_{k,i-1} \bar{\eta}_{k,i-1} \right)$$
$$= n^{1/2-\rho} \left(\sum_{i=1}^{n} i^{\rho-1} c_i - \sum_{i=1}^{n} i^{\rho-1} c_{i-1} \right)$$
$$= n^{1/2-\rho} \left(n^{\rho-1} c_n + \sum_{i=2}^{n} (i-1)^{\rho-1} c_{i-1} - \sum_{i=1}^{n} i^{\rho-1} c_{i-1} \right)$$
$$= n^{-1/2} c_n - n^{1/2-\rho} \sum_{i=1}^{n} \left(i^{\rho-1} - (i-1)^{\rho-1} \right) c_{i-1}$$

When $\rho > 1$, $n^{1/2-\rho} \sum_{i=1}^{n} \left(i^{\rho-1} - (i-1)^{\rho-1} \right) c_{i-1} = \sum_{i=1}^{n} \frac{i^{\rho-1} - (i-1)^{\rho-1}}{n^{\rho-1}} n^{-1/2} c_{i-1} \to 0$ a.s. When $1/2 < \rho \leq 1$,

$$n^{1/2-\rho} \sum_{i=1}^{n} \left| \left(i^{\rho-1} - (i-1)^{\rho-1} \right) c_{i-1} \right| \leq n^{1/2-\rho} \sum_{i=1}^{n} O\left((i-1)^{\rho-2} \right) O((i-1)^{\delta})$$
$$= n^{1/2-\rho} O\left((n-1)^{\rho-1+\delta} \right) \to 0 \text{ a.s.}$$

Next, fix $0 < \delta < \min\{1/4, \rho - 1/2\}$, then $\left\{ \sum_{i=1}^{n} i^{-1/2+\delta} \bar{\epsilon}_i \tilde{\epsilon}_{k,i-1} 1\{X_i = k\}, \mathcal{F}_n, n \geq 1 \right\}$ is a convergent martingale due to (B.13), Corollary 5 of Chow (1965) (with $p = 2$). Hence

$$n^{1/2-\rho} \sum_{i=1}^{n} i^{\rho-1} \sum_{k=1}^{K} \bar{\epsilon}_i \tilde{\epsilon}_{k,i-1} 1\{X_i = k\}$$

$$\leq n^{-\delta} \sum_{i=1}^{n} i^{-1/2+\delta} \sum_{k=1}^{K} \bar{\epsilon}_i \tilde{\epsilon}_{k,i-1} 1\{X_i = k\} \to 0 \text{ a.s.}$$

The rest of the terms in (B.23) can be shown to converge to 0 a.s. by similar arguments. This completes the proof of Theorem 4.2 (i).

□

Proof of Theorem 4.2 (ii). We prove the result for SAVOR-C. Results for SAVOR-A, SAVOR-B and SAVOR-D can be derived following the same approach. Under SAVOR-C,

$$X_{n+1}^* = X_n^* - \frac{1}{nb} \left\{ h(X_n^*) + \sum_{k=1}^{K} \left[\sigma(k)\bar{\epsilon}_n + c_p \left(\frac{\bar{\sigma}_{kn}^2 - \sigma^2(k)}{2\sigma(k)} - \bar{\eta}_{kn} \right) \right] 1\{X_n = k\} - t_0 \right\}.$$

Using the facts $h(X_n^*) - t_0 = \beta(X_n^* - \theta_\beta) + f(X_n) - f(\nu_1) + \beta(X_n - \nu_1)$, $\rho = \beta/b$ gives

$$\begin{aligned} X_{n+1}^* - \theta_\beta = & \left(1 - \frac{\rho}{n}\right)(X_n^* - \theta_\beta) - \frac{\sigma(\nu_1)}{nb} \left(\bar{\epsilon}_n + \frac{c_p}{2} \frac{\bar{\sigma}_{\nu_1 n}^2 - \sigma^2(\nu_1)}{\sigma^2(\nu_1)} \right) 1\{X_n = \nu_1\} \\ & + \frac{c_p}{nb} \sum_{k=1}^{K} \bar{\eta}_{kn} 1\{X_n = k\} - \frac{1}{nb} \left(f(X_n) - f(\nu_1) + \beta(X_n - \nu_1) \right) \\ & - \frac{1}{nb} \sum_{k \neq \nu_1} \sigma(k) \left(\bar{\epsilon}_n + \frac{c_p}{2} \frac{\bar{\sigma}_{kn}^2 - \sigma^2(k)}{\sigma^2(k)} \right) 1\{X_n = k\}. \end{aligned}$$

Let $T_{ki} = \left(\frac{m-1}{m} \frac{S_i^2}{\sigma^2(k)} + \bar{\epsilon}_i^2 - 1 \right) 1\{X_i = k\}$ and recall that $\bar{\sigma}_{kn}^2 = \hat{\sigma}_{kn}^2 + \frac{\bar{\sigma}_{kn}^2}{m n_{kn}} = \frac{m-1}{m} \tilde{\sigma}_{kn}^2 + \sigma^2(k) \frac{\sum_{j=1}^{n} 1\{X_j = k\} \tilde{\epsilon}_j^2}{n_{kn}} - \sigma^2(k) \tilde{\epsilon}_{kn}^2 + \frac{\bar{\sigma}_{kn}^2}{m n_{kn}}$ then the right-hand side of the last display

$$= \left(1 - \frac{\rho}{n}\right)(X_n^* - \theta_\beta) - \frac{\sigma(\nu_1)}{nb} \left(\bar{\epsilon}_n + \frac{c_p}{2} \frac{\sum_{j=1}^{n} T_{\nu_1 j}}{n_{\nu_1 n}} \right) 1\{X_n = \nu_1\} + R_n,$$

where

$$\begin{aligned} R_n = & \frac{c_p}{nb} \sum_{k=1}^{K} \bar{\eta}_{kn} 1\{X_n = k\} - \frac{1}{nb} \left(f(X_n) - f(\nu_1) + \beta(X_n - \nu_1) \right) \\ & - \frac{1}{nb} \sum_{k \neq \nu_1} \sigma(k) \left(\bar{\epsilon}_n + \frac{c_p}{2} \frac{\bar{\sigma}_{kn}^2 - \sigma^2(k)}{\sigma^2(k)} \right) 1\{X_n = k\} \\ & + \frac{c_p}{2nb} \left(\sigma(\nu_1) \tilde{\epsilon}_{\nu_1 n}^2 - \frac{\bar{\sigma}_{\nu_1 n}^2}{\sigma(\nu_1) m n_{\nu_1 n}} \right) 1\{X_n = \nu_1\}. \end{aligned}$$

Iteration yields

$$X_{n+1}^* - \theta_\beta = \gamma_{0n}\left(X_1^* - \theta_\beta\right) - \frac{\sigma(\nu_1)}{b}\sum_{i=1}^{n} i^{-1}\gamma_{in}\left(\bar{\epsilon}_i + \frac{c_p}{2}\frac{\sum_{j=1}^{i} T_{\nu_1 j}}{n_{\nu_1 i}}\right)1\{X_i = \nu_1\} + \sum_{i=1}^{n}\gamma_{in}R_i,$$

where $w_n\gamma_{0n}\left(X_1^* - \theta_\beta\right) \to 0$ a.s. and $w_n\sum_{i=1}^{n}\gamma_{in}R_i \to 0$ a.s. can be obtained by using arguments from previous proofs.

Thus, it remains to show

$$w_n\frac{\sigma(\nu_1)}{b}\sum_{i=1}^{n} i^{-1}\gamma_{in}\left(\bar{\epsilon}_i + \frac{c_p}{2}\frac{\sum_{j=1}^{i} T_{\nu_1 j}}{n_{\nu_1 i}}\right)1\{X_i = \nu_1\} \xrightarrow{d} N\left(0, \frac{\sigma^2(\nu_1)}{m\beta^2}\left(1 + \rho^{-1}\kappa\right)\right). \tag{B.24}$$

First we observe that the difference between

$$w_n\sum_{i=1}^{n} i^{-1}\gamma_{in}\frac{\sum_{j=1}^{i} T_{\nu_1 j}}{n_{\nu_1 i}}1\{X_i = \nu_1\}$$

and

$$w_n\sum_{i=1}^{n} i^{-2}\gamma_{in}\sum_{j=1}^{i} T_{\nu_1 j}$$

will converge to 0 a.s. and rearranging the above gives

$$w_n\sum_{j=1}^{n}\sum_{i=j}^{n} i^{-2}\gamma_{in}T_{\nu_1 j} = w_n\sum_{j=1}^{n} c_{jn}T_{\nu_1 j},$$

where $c_{jn} = \sum_{i=j}^{n} i^{-2}\gamma_{in}$.

Next, let $Q_{in} = w_n\frac{\sigma(\nu_1)}{b}\left[i^{-1}\gamma_{in}\bar{\epsilon}_i + \frac{c_p}{2}c_{in}\left(\frac{m-1}{m}\frac{S_i^2}{\sigma^2(\nu_1)} + \bar{\epsilon}_i^2 - 1\right)\right]1\{X_i = \nu_1\}$, then $E\left(Q_{in} \mid \mathcal{F}_{i-1}\right) = 0$. To establish (B.24), it suffices to verify

$$\sum_{i=1}^{n} E\left(Q_{in}^2 \mid \mathcal{F}_{i-1}\right) \longrightarrow \frac{\sigma^2(\nu_1)}{m\beta^2}\left(1 + \rho^{-1}\kappa\right), \tag{B.25a}$$

and the Lindeberg's condition:

$$\sum_{i=1}^{n} E\left(Q_{in}^2 1\{|Q_{in}| > \delta\} \mid \mathcal{F}_{i-1}\right) \xrightarrow{P} 0 \text{ for every } \delta > 0. \tag{B.25b}$$

We now verify (B.25a):

$$
\begin{aligned}
&\sum_{i=1}^{n} E\left(Q_{in}^2 \mid \mathcal{F}_{i-1}\right) \\
&= w_n^2 \frac{\sigma^2(\nu_1)}{b^2} \sum_{i=1}^{n} \left[i^{-2}\gamma_{in}^2 Var\left(\bar{\epsilon}_i\right) + \frac{c_p^2}{4} c_{in}^2 \left(\tfrac{m-1}{m}\right)^2 Var\left(\frac{S_i^2}{\sigma^2(\nu_1)}\right) + \frac{c_p^2}{4} c_{in}^2 Var(\bar{\epsilon}_i^2) \right. \\
&\quad + c_p i^{-1}\gamma_{in} c_{in} \frac{m-1}{m} E\left(\bar{\epsilon}_i \frac{S_i^2}{\sigma^2(\nu_1)}\right) + c_p i^{-1}\gamma_{in} c_{in} E\left(\bar{\epsilon}_i^3\right) \\
&\quad \left. + \frac{c_p^2}{2} c_{in}^2 \frac{m-1}{m} Cov\left(\bar{\epsilon}_i^2, \frac{S_i^2}{\sigma^2(\nu_1)}\right) \right] 1\{X_i = \nu_1\} \\
&= \frac{\sigma^2(\nu_1)}{mb^2} \left\{ w_n^2 \sum_{i=1}^{n} i^{-2}\gamma_{in}^2 + \frac{c_p^2}{4} \left[\frac{(m-1)^2}{m} u_1 + m u_2 + 2(m-1)u_5 \right] w_n^2 \sum_{i=1}^{n} c_{in}^2 \right. \\
&\qquad \left. + c_p \left[(m-1)u_3 + m u_4 \right] w_n^2 \sum_{i=1}^{n} i^{-1}\gamma_{in} c_{in} \right\} 1\{X_i = \nu_1\}.
\end{aligned}
$$

Next, we evaluate the limit of $w_n^2 \sum_{i=1}^{n} c_{in}^2$:

$$
\begin{aligned}
w_n^2 \sum_{i=1}^{n} c_{in}^2 &= w_n^2 \sum_{i=1}^{n} \left(\sum_{j=i}^{n} j^{-4}\gamma_{jn}^2 + 2 \sum_{j=i}^{n} \sum_{k=i}^{j-1} j^{-2}k^{-2}\gamma_{jn}\gamma_{kn} \right) \\
&= w_n^2 \sum_{j=1}^{n} j^{-3}\gamma_{jn}^2 + 2 w_n^2 \sum_{j=1}^{n} \sum_{k=1}^{j-1} j^{-2}k^{-1}\gamma_{jn}\gamma_{kn} \\
&= w_n^2 \sum_{i=1}^{n} \left(i^{-2}\gamma_{in}^2 \right) i^{-1} + 2\rho^{-1} w_n^2 \sum_{i=1}^{n} i^{-2}\gamma_{in}^2 \left(1 - \rho i^{-1}\right) - 2\rho^{-1} w_n^2 \gamma_{0n} \sum_{i=1}^{n} i^{-2}\gamma_{in} \\
&\longrightarrow 0 + 2\rho^{-3} - 0
\end{aligned}
$$

The third equality follows from

$$
\sum_{j=1}^{i-1} j^{-1}\gamma_{jn} = \rho^{-1} \sum_{j=1}^{i-1} \left(\gamma_{jn} - \gamma_{j-1,n}\right) = \rho^{-1} \left(\gamma_{i-1,n} - \gamma_{0n}\right) = \rho^{-1} \left(\gamma_{in}\left(1 - \rho i^{-1}\right) - \gamma_{0n}\right).
$$

The limits of the first two terms follow from (B.20d) and the limit of last term can be obatined using (B.20a), (B.20b) and (B.20c):

$$
2\rho^{-1} w_n^2 \gamma_{0n} \sum_{i=1}^{n} i^{-2}\gamma_{in} \sim \left(w_n \gamma_{0n}\right) n^{1/2-\rho} \sum_{i=1}^{n} i^{\rho-2} \to 0.
$$

Using similar technique we have

$$\begin{aligned} w_n^2 \sum_{i=1}^{n} i^{-1}\gamma_{in}c_{in} &= w_n^2 \sum_{i=1}^{n}\sum_{j=i}^{n} i^{-1}\gamma_{in}j^{-2}\gamma_{jn} \\ &= w_n^2 \sum_{j=1}^{n} j^{-2}\gamma_{jn}\left(\sum_{i=1}^{j} i^{-1}\gamma_{in}\right) \\ &= \rho^{-1} w_n^2 \sum_{j=1}^{n} j^{-2}\gamma_{jn}\left(\gamma_{jn}-\gamma_{0n}\right) \longrightarrow \rho^{-3}-0. \end{aligned}$$

This completes the verification of (B.25a).

Finally, to verify the Lindeberg's condition (B.25b), it is sufficient to verify Liapounov's condition:

$$\sum_{i=1}^{n} E\left(|Q_{in}|^3 \mid \mathcal{F}_{i-1}\right) = o\left(\left(\sum_{i=1}^{n} E\left(Q_{in}^2 \mid \mathcal{F}_{i-1}\right)\right)^{3/2}\right).$$

The condition is indeed satisfied. Let $\delta' = \min\{1/2, \rho - 1/2\}$, then

$$\begin{aligned} \sum_{i=1}^{n} E\left(|Q_{in}|^3 \mid \mathcal{F}_{i-1}\right) &= O\left(w_n^3 \sum_{i=1}^{n} i^{-3}\gamma_{in}^3 + w_n^3 \sum_{i=1}^{n} i^{-2}\gamma_{in}^2 c_{in} + w_n^3 \sum_{i=1}^{n} i^{-1}\gamma_{in}c_{in}^2 + w_n^3 \sum_{i=1}^{n} c_{in}^3\right) \\ &= O\left(n^{1/2-\rho} w_n^2 \sum_{i=1}^{n} i^{\rho-1}\left(i^{-2}\gamma_{in}^2 + i^{-1}\gamma_{in}c_{in} + c_{in}^2\right) + n^{1/2-\rho} w_n^2 \sum_{i=1}^{n} i^{\rho-2}\sum_{j=1}^{n} c_{jn}^2\right) \\ &= O\left(n^{-\delta'} w_n^2 \sum_{i=1}^{n}\left(i^{-2}\gamma_{in}^2 + i^{-1}\gamma_{in}c_{in} + c_{in}^2\right) + n^{-\delta'} \sum_{i=1}^{n} i^{-3/2+\delta'}\left(w_n^2 \sum_{j=1}^{n} c_{jn}^2\right)\right) \\ &= o(1), \end{aligned}$$

where we use

$$\begin{aligned} w_n^3 \sum_{i=1}^{n} c_{in}^3 = w_n^3 \sum_{i=1}^{n} c_{in}^2 \sum_{j=i}^{n} j^{-2}\gamma_{jn} &= w_n^3 \sum_{j=1}^{n} j^{-2}\gamma_{jn} \sum_{i=1}^{j} c_{in}^2 \\ &\sim n^{1/2-\rho} w_n^2 \sum_{j=1}^{n} j^{\rho-2} \sum_{i=1}^{j} c_{in}^2 \le n^{1/2-\rho} w_n^2 \sum_{j=1}^{n} j^{\rho-2} \sum_{i=1}^{n} c_{in}^2. \end{aligned}$$

□

B.2 Chapter 5

Before giving the proof of Theorem 5.1, we first derive some preparatory results establishing strong consistency of $\hat{\phi}_n$ and $\hat{\tau}_n^2$.

Write

$$\hat{\phi}_n = \frac{\sum_{i=1}^n \bar{Y}_i}{\sum_{i=1}^n \bar{Z}_i} = \frac{\frac{1}{n}\sum_{i=1}^n \left[\bar{Y}_i - M(X_i)\right] + \frac{1}{n}\sum_{i=1}^n M(X_i)}{\frac{1}{n}\sum_{i=1}^n \left[\bar{Z}_i - \phi^{-1}M(X_i)\right] + \frac{1}{n}\sum_{i=1}^n \phi^{-1}M(X_i)}$$

and

$$\begin{aligned}
\hat{\tau}_n^2 &= \frac{\sum_{i=1}^n S_i^2}{\sum_{i=1}^n R_i^2} \\
&= \tau^2 \frac{\sum_{i=1}^n \sigma^2(X_i)\frac{1}{m-1}\sum_{j=1}^m (\epsilon_{ij} - \bar{\epsilon}_i)^2}{\sum_{i=1}^n \sigma^2(X_i)\frac{1}{m-1}\sum_{j=1}^m (e_{ij} - \bar{e}_i)^2} \\
&= \tau^2 \frac{\frac{1}{n}\sum_{i=1}^n \sigma^2(X_i)\left[\frac{1}{m-1}\sum_{j=1}^m (\epsilon_{ij} - \bar{\epsilon}_i)^2 - 1\right] + \frac{1}{n}\sum_{i=1}^n \sigma^2(X_i)}{\frac{1}{n}\sum_{i=1}^n \sigma^2(X_i)\left[\frac{1}{m-1}\sum_{j=1}^m (e_{ij} - \bar{e}_i)^2 - 1\right] + \frac{1}{n}\sum_{i=1}^n \sigma^2(X_i)}
\end{aligned}$$

It is easy to establish that $n^{-1}\sum_{i=1}^n \left[\bar{Y}_i - M(X_i)\right]$, $n^{-1}\sum_{i=1}^n \left[\bar{Z}_i - \phi^{-1}M(X_i)\right]$, $n^{-1}\sum_{i=1}^n \sigma^2(X_i)\left[(m-1)^{-1}\sum_{j=1}^m (\epsilon_{ij} - \bar{\epsilon}_i)^2 - 1\right]$ and $n^{-1}\sum_{i=1}^n \sigma^2(X_i)\left[(m-1)^{-1}\sum_{j=1}^m (e_{ij} - \bar{e}_i)^2 - 1\right]$ all converge to 0 a.s. Thus, $\hat{\phi}_n \to \phi$ a.s. and $\hat{\tau}_n^2 \to \tau^2$ a.s.

Proof of Theorem 5.1. It suffices to prove (i). Let $\mathcal{F}_{n-1}$ be the σ-field generated by $\{X_i^*, \epsilon_{i1}, \ldots, \epsilon_{im}, e_{i1}, \ldots, e_{im}\}$, $i = 1, \ldots, n-1$, and D_1, D_2, ... are positive constants appropriately chosen according to the context.

From (5.3), we have

$$nX_{n+1}^* = \sum_{i=1}^n X_i^* - \frac{1}{b}\sum_{i=1}^n (V_{in} - t_0),$$

and

$$(n-1)X_n^* = \sum_{i=1}^{n-1} X_i^* - \frac{1}{b}\sum_{i=1}^{n-1} (V_{i,n-1} - t_0).$$

Subtracting the two above equations gives

$$X_{n+1}^* = X_n^* - \frac{1}{nb}(V_{nn} - t_0) - \frac{1}{nb}\sum_{i=1}^{n-1} (V_{in} - V_{i,n-1}). \tag{B.26}$$

Under the accrual process 2, $V_{in} = V_{i,n-1}$ for $i \leq n-2$. Thus,

$$\begin{aligned} X^*_{n+1} &= X^*_n - \frac{1}{nb}\left(V_{nn} - t_0\right) - \frac{1}{nb}\left(V_{n-1,n} - V_{n-1,n-1}\right) \\ &= X^*_n - \frac{1}{nb}\left(W_{nn} + \beta(X^*_n - X_n) + U_{n-1} - W_{n-1,n-1} - t_0\right) \\ &= X^*_n - \frac{1}{nb}\left(V_n - t_0\right) + \frac{1}{nb}\left(\Delta_n - \Delta_{n-1}\right), \end{aligned}$$

where $\Delta_i = U_i - W_{ii}$.

Rearranging the above and repeatedly applying the inequalities $(a_1+a_2)^2 \leq 2a_1^2+2a_2^2$ and $2a_1a_2 \leq a_1^2 + a_2^2$ give,

$$\begin{aligned} &\left(X^*_{n+1} - \frac{1}{nb}\Delta_n - \theta_\beta\right)^2 \\ &= \left(X^*_n - \frac{1}{(n-1)b}\Delta_{n-1} - \theta_\beta - \frac{1}{nb}\left(V_n - t_0\right) + \frac{1}{n(n-1)b}\Delta_{n-1}\right)^2 \\ &\leq \left(X^*_n - \frac{1}{(n-1)b}\Delta_{n-1} - \theta_\beta\right)^2 - \frac{2}{nb}\left(X^*_n - \theta_\beta\right)\left(V_n - t_0\right) \\ &\quad + \frac{2}{n(n-1)b^2}\Delta_{n-1}\left(V_n - t_0\right) + \frac{2}{n(n-1)b}\left(X^*_n - \frac{1}{(n-1)b}\Delta_{n-1} - \theta_\beta\right)\Delta_{n-1} \\ &\quad + \frac{2}{n^2b^2}\left(V_n - t_0\right)^2 + \frac{2}{n^2(n-1)^2b^2}\Delta^2_{n-1} \\ &\leq \left(X^*_n - \frac{1}{(n-1)b}\Delta_{n-1} - \theta_\beta\right)^2\left(1 + \frac{1}{n(n-1)b}\right) - \frac{2}{nb}\left(X^*_n - \theta_\beta\right)\left(V_n - t_0\right) \\ &\quad + \frac{D_1}{(n-1)^2}\left[\Delta^2_{n-1} + \left(V_n - t_0\right)^2\right] \\ &\leq \left(X^*_n - \frac{1}{(n-1)b}\Delta_{n-1} - \theta_\beta\right)^2\left(1 + \frac{D_2}{(n-1)^2}\right) - \frac{2}{nb}\left(X^*_n - \theta_\beta\right)\left(V_n - t_0\right) \\ &\quad + \frac{D_3}{(n-1)^2}\left(\Delta^2_{n-1} + U_n^2 + \left(X_n - \theta_\beta\right)^2 + t_0^2\right), \end{aligned}$$

The last equality uses

$$V_n = U_n + \beta(X^*_n - X_n) = U_n + \beta\left[\left(X^*_n - \frac{\Delta_{n-1}}{(n-1)b} - \theta_\beta\right) + \frac{\Delta_{n-1}}{(n-1)b} - \left(X_n - \theta_\beta\right)\right].$$

Taking conditional expectation yields

$$E\left[\left(X^*_{n+1} - \frac{1}{nb}\Delta_n - \theta_\beta\right)^2 \mid \mathcal{F}_{n-1}\right] \leq \left(X^*_n - \frac{1}{(n-1)b}\Delta_{n-1} - \theta_\beta\right)^2\left(1 + O((n-1)^{-2})\right)$$

$$- \frac{2}{nb} \left(X_n^* - \theta_\beta\right) \left(h(X_n^*) - t_0\right)$$
$$+ \frac{D_3}{(n-1)^2} \left(\Delta_{n-1}^2 + E\left(U_n^2 \mid \mathcal{F}_{n-1}\right)\right) + O((n-1)^{-2}).$$

Now, if we can show

$$\sum_{n=1}^{\infty} \frac{1}{(n-1)^2} \left(\Delta_{n-1}^2 + E\left(U_n^2 \mid \mathcal{F}_{n-1}\right)\right) < \infty \text{ a.s.}, \tag{B.27}$$

which in turns implies $\frac{1}{n-1}\Delta_{n-1} \to 0$ a.s. as $n \to \infty$, then by Theorem 1 of Robbins and Siegmund, $\lim_{n\to\infty} \left(X_n^* - \frac{1}{(n-1)b}\Delta_{n-1} - \theta_\beta\right)^2 = \lim_{n\to\infty} \left(X_n^* - \theta_\beta\right)$ exists and $\sum_{n=1}^{\infty} n^{-1} \left(X_n^* - \theta_\beta\right) \left(h(X_n^*) - t_0\right) < \infty$ a.s. Together with the fact that $\left(X_n^* - \theta_\beta\right) \left(h(X_n^*) - t_0\right) > 0$, we would have $X_n^* \to \theta_\beta$ a.s.

It remains to verify (B.27). First, since $\sup_n M(X_n) < \infty$ and $\sup_n \sigma(X_n) < \infty$,

$$\begin{aligned} U_{n-1}^2 &= \left(M(X_{n-1}) + \sigma(X_{n-1})\bar{\epsilon}_{n-1} + c_p \left[E\left(\frac{S_{n-1}}{\sigma(X_{n-1})}\right)\right]^{-1} S_{n-1}\right)^2 \\ &\leq D_4 \left(\bar{\epsilon}_{n-1}^2 + \frac{S_{n-1}^2}{\sigma^2(X_{n-1})}\right) + O(1). \end{aligned}$$

Recall $S_{n-1}^2/\sigma^2(X_{n-1}) = (m-1)^{-1} \sum_{j=1}^{m} \left(\epsilon_{n-1,j} - \bar{\epsilon}_{n-1}\right)^2$. It can be easily verified that $\sum_{n=1}^{\infty} (n-1)^{-2} \left(\bar{\epsilon}_{n-1}^2 + S_{n-1}^2/\sigma^2(X_{n-1})\right) < \infty$ a.s.

Similar arguments give

$$\sum_{n=1}^{\infty} \frac{W_{n-1,n-1}^2}{(n-1)^{-2}} \leq D_5 \sum_{n=1}^{\infty} (n-1)^{-2} \left[\hat{\phi}_{n-2}^2 (1 + \bar{e}_{n-1}^2) + \hat{\tau}_{n-2}^2 R_{n-1}^2/\sigma^2(X_{n-1})\right] < \infty \text{ a.s.}$$

and

$$\sum_{n=1}^{\infty} \frac{E\left(U_n^2 \mid \mathcal{F}_{n-1}\right)}{(n-1)^{-2}} \leq D_6 E\left(\bar{\epsilon}_n^2 + S_n^2/\sigma^2(X_n) \mid \mathcal{F}_{n-1}\right) + O(1) < \infty \text{ a.s.}$$

This finishes the proof.

□

Appendix C

Tables

Table C.1: Asymptotic variances of the virtual observation recursions under standard normal noises

Least Square Recursion	Stochastic Approximation
LSRVO $\frac{\sigma^2(\nu_1)}{mb(2\beta-b)}\left(1+mz_p^2(\lambda_m-1)\right)$	SAVOR $\frac{\sigma^2(\nu_1)}{mb(2\beta-b)}\left(1+mz_p^2(\lambda_m-1)\right)$
LSRVO-A $\frac{\sigma^2(\nu_1)}{mb(2\beta-b)}\left(1+mz_p^2(\lambda_m-1)\right)$	SAVOR-A $\frac{\sigma^2(\nu_1)}{mb(2\beta-b)}\left(1+\frac{b}{\beta}2mz_p^2(\lambda_m-1)\right)$
LSRVO-B $\frac{\sigma^2(\nu_1)}{mb(2\beta-b)}\left(1+\frac{z_p^2}{2}\frac{m}{m-1}\right)$	SAVOR-B $\frac{\sigma^2(\nu_1)}{mb(2\beta-b)}\left(1+\frac{b}{\beta}z_p^2\frac{m}{m-1}\right)$
LSRVO-C $\frac{\sigma^2(\nu_1)}{mb(2\beta-b)}\left(1+\frac{z_p^2}{2}\right)$	SAVOR-C $\frac{\sigma^2(\nu_1)}{mb(2\beta-b)}\left(1+\frac{b}{\beta}z_p^2\right)$
LSRVO-D $\frac{\sigma^2(\nu_1)}{mb(2\beta-b)}\left(1+\frac{z_p^2}{2}\right)$	SAVOR-D $\frac{\sigma^2(\nu_1)}{mb(2\beta-b)}\left(1+\frac{b}{\beta}z_p^2\right)$

Table C.2: Dose-limiting toxicity probability, mean function and standard deviation function of the continuous outcomes used in Section 4.4

		Dose level				
Scenario		1	2	3	4	5
1	P(DLT)	0.10	0.25	0.30	0.35	0.40
	$M(k)$	3.63	4.16	4.30	4.44	4.56
	$\sigma(k)$	0.92	0.96	0.97	0.98	0.99
2	P(DLT)	0.04	0.10	0.25	0.30	0.35
	$M(k)$	3.26	3.63	4.16	4.30	4.44
	$\sigma(k)$	0.89	0.92	0.96	0.97	0.98
3	P(DLT)	0.01	0.04	0.10	0.25	0.30
	$M(k)$	2.86	3.26	3.63	4.16	4.30
	$\sigma(k)$	0.84	0.89	0.92	0.96	0.97
4	P(DLT)	0.01	0.01	0.04	0.10	0.25
	$M(k)$	2.86	2.86	3.26	3.63	4.16
	$\sigma(k)$	0.84	0.84	0.89	0.92	0.96
5	P(DLT)	0.01	0.01	0.01	0.04	0.10
	$M(k)$	2.86	2.86	2.86	3.26	3.63
	$\sigma(k)$	0.84	0.84	0.84	0.89	0.92

Table C.3: Operating characteristics of virtual observation recursions and the CRM under a two stage design with $n = 11$, $m = 3$ and initial sequence $\{1, 2, 3, 4, 5, 5, 5, 5, 5, 5, 5\}$

	% Recommendation					# Treated						
	1	2	3	4	5	1	2	3	4	5	N_{ν_1+}	N_{DLT}
Scenario 1												
P(DLT)	0.10	0.25	0.30	0.35	0.40	0.10	0.25	0.30	0.35	0.40		
LSRVO	85.4	13.9	0.7	0.0	0.0	24.1	6.8	1.6	0.4	0.1	8.9	4.8
LSRVO-B	82.0	16.8	1.1	0.1	0.0	22.8	7.8	1.9	0.4	0.1	10.2	5.0
LSRVO-C	84.7	14.6	0.6	0.1	0.0	23.3	7.4	1.8	0.4	0.1	9.7	4.9
LSRVO-D	79.5	18.4	2.0	0.1	0.0	21.2	9.0	2.3	0.4	0.1	11.8	5.3
SAVOR	81.9	15.8	2.0	0.3	0.0	23.3	6.9	2.0	0.6	0.2	9.7	5.0
SAVOR-A	79.6	17.6	2.4	0.3	0.1	22.9	7.3	2.1	0.6	0.2	10.1	5.0
SAVOR-B	75.9	20.8	2.9	0.4	0.1	21.7	8.1	2.4	0.7	0.2	11.3	5.2
SAVOR-C	78.0	19.2	2.4	0.4	0.0	22.2	7.8	2.2	0.6	0.2	10.8	5.1
SAVOR-D	71.5	24.9	3.1	0.5	0.0	20.2	9.3	2.7	0.7	0.2	12.8	5.5
CRM	84.1	14.4	1.4	0.1	0.0	23.9	6.9	1.8	0.4	0.1	9.1	4.9
Scenario 2												
P(DLT)	0.04	0.10	0.25	0.30	0.35	0.04	0.10	0.25	0.30	0.35		
LSRVO	21.9	62.4	14.9	0.8	0.0	11.0	13.9	6.4	1.3	0.4	8.1	4.0
LSRVO-B	16.6	64.8	17.8	0.9	0.0	9.0	14.8	7.4	1.4	0.4	9.2	4.3
LSRVO-C	15.3	69.0	15.1	0.6	0.0	8.8	15.4	7.0	1.4	0.4	8.8	4.2
LSRVO-D	9.8	68.2	20.7	1.3	0.0	6.8	15.4	8.6	1.8	0.4	10.8	4.7
SAVOR	20.7	59.1	17.7	2.4	0.1	10.6	13.4	6.5	1.9	0.6	9.0	4.2
SAVOR-A	20.6	58.8	17.9	2.5	0.2	10.5	13.6	6.4	1.9	0.6	8.9	4.2
SAVOR-B	15.7	59.5	21.4	3.1	0.3	9.1	13.9	7.3	2.1	0.6	10.1	4.5
SAVOR-C	14.5	61.9	20.7	2.7	0.2	8.9	14.4	7.1	2.0	0.6	9.7	4.4
SAVOR-D	9.8	59.8	26.5	3.6	0.3	7.4	13.9	8.7	2.4	0.7	11.7	4.8
CRM	25.2	59.7	13.8	1.2	0.1	11.3	14.0	5.9	1.3	0.5	7.7	3.9
Scenario 3												
P(DLT)	0.01	0.04	0.10	0.25	0.30	0.01	0.04	0.10	0.25	0.30		
LSRVO	0.6	19.2	63.0	16.4	0.8	4.1	8.1	13.2	6.0	1.6	7.6	3.7
LSRVO-B	0.3	14.6	64.9	19.3	0.9	3.6	7.0	13.8	6.9	1.6	8.5	3.9
LSRVO-C	0.1	13.6	69.1	16.6	0.6	3.6	6.9	14.4	6.6	1.6	8.1	3.9
LSRVO-D	0.0	8.5	68.2	22.4	0.9	3.3	5.6	14.2	8.2	1.7	9.9	4.3
SAVOR	0.4	18.4	60.3	19.8	1.1	4.3	7.9	12.4	6.5	2.0	8.4	3.8
SAVOR-A	0.7	19.6	58.6	19.2	1.9	4.4	8.2	12.2	6.2	2.0	8.2	3.8
SAVOR-B	0.4	14.9	59.2	23.2	2.2	4.0	7.2	12.5	7.1	2.2	9.3	4.0
SAVOR-C	0.3	14.1	61.5	22.3	1.8	3.9	7.2	12.8	6.9	2.1	9.0	4.0
SAVOR-D	0.1	9.1	59.6	28.9	2.3	3.6	6.0	12.8	8.3	2.4	10.7	4.4
CRM	1.4	26.2	57.9	13.5	1.0	4.5	9.5	12.4	4.9	1.7	6.5	3.4
Scenario 4												
P(DLT)	0.01	0.01	0.04	0.10	0.25	0.01	0.01	0.04	0.10	0.25		
LSRVO	0.1	1.1	21.5	62.6	14.7	3.4	3.9	7.9	11.7	6.1	6.1	3.1
LSRVO-B	0.0	0.5	16.7	66.7	16.1	3.3	3.6	7.0	12.7	6.5	6.5	3.3
LSRVO-C	0.0	0.4	16.0	70.0	13.6	3.3	3.5	7.0	13.0	6.2	6.2	3.2
LSRVO-D	0.0	0.2	10.5	72.0	17.4	3.2	3.3	5.8	13.6	7.1	7.1	3.4
SAVOR	0.1	0.8	19.3	64.8	15.0	3.5	3.9	7.2	12.0	6.4	6.4	3.2
SAVOR-A	0.2	1.3	20.8	61.0	16.7	3.5	4.0	7.5	11.6	6.4	6.4	3.1
SAVOR-B	0.1	0.8	16.0	63.4	19.7	3.4	3.8	6.8	11.9	7.1	7.1	3.3
SAVOR-C	0.0	0.6	14.8	66.7	17.9	3.4	3.7	6.8	12.1	7.0	7.0	3.3
SAVOR-D	0.0	0.1	9.5	65.8	24.5	3.2	3.4	5.8	12.4	8.2	8.2	3.6
CRM	0.1	2.7	31.5	55.0	10.7	3.6	4.7	9.2	10.1	5.4	5.4	2.8
Scenario 5												
P(DLT)	0.01	0.01	0.01	0.04	0.10	0.01	0.01	0.01	0.04	0.10		
LSRVO	0.1	0.2	1.9	24.9	72.8	3.3	3.3	4.0	7.5	14.9		1.9
LSRVO-B	0.0	0.2	1.4	22.0	76.3	3.3	3.3	3.7	7.3	15.5		1.9
LSRVO-C	0.0	0.2	1.2	21.2	77.5	3.2	3.3	3.7	7.2	15.5		2.0
LSRVO-D	0.0	0.1	0.8	16.7	82.4	3.2	3.2	3.5	6.5	16.6		2.0
SAVOR	0.1	0.3	1.4	26.8	71.4	3.4	3.3	3.9	7.6	14.8		1.9
SAVOR-A	0.2	0.5	2.3	25.0	72.0	3.4	3.4	4.0	7.3	14.9		1.9
SAVOR-B	0.1	0.4	1.4	21.2	76.9	3.4	3.3	3.7	6.8	15.8		1.9
SAVOR-C	0.0	0.3	1.2	20.7	77.8	3.3	3.3	3.7	6.9	15.8		2.0
SAVOR-D	0.0	0.0	0.3	14.4	85.3	3.2	3.2	3.4	6.2	17.1		2.0
CRM	0.1	1.3	7.8	27.3	63.5	3.6	3.9	4.8	7.3	13.4		1.8

N_{ν_1+}: number treated above ν_1; N_{DLT}: total number of DLT

Table C.4: Operating characteristics of virtual observation recursions and the CRM under a one stage design with $X_1 = 1$, $n = 11$ and $m = 3$

	% Recommendation					# Treated						
	1	2	3	4	5	1	2	3	4	5	N_{ν_1+}	N_{DLT}
Scenario 1												
P(DLT)	0.10	0.25	0.30	0.35	0.40	0.10	0.25	0.30	0.35	0.40		
LSRVO	85.9	13.5	0.6	0.0	0.0	25.3	6.5	1.0	0.1	0.0	7.7	4.5
LSRVO-B	83.4	15.9	0.7	0.0	0.0	24.2	7.4	1.3	0.1	0.0	8.8	4.7
LSRVO-C	86.2	13.3	0.5	0.0	0.0	24.7	7.1	1.2	0.1	0.0	8.3	4.6
LSRVO-D	82.8	16.2	0.9	0.0	0.0	22.7	8.7	1.6	0.1	0.0	10.3	5.0
SAVOR	87.0	12.6	0.4	0.0	0.0	26.0	6.1	0.8	0.1	0.0	7.0	4.4
SAVOR-A	84.0	15.3	0.6	0.1	0.0	25.4	6.6	0.9	0.1	0.0	7.6	4.5
SAVOR-B	80.5	18.5	0.9	0.0	0.0	23.9	7.8	1.2	0.1	0.0	9.1	4.8
SAVOR-C	82.5	16.6	0.9	0.0	0.0	24.3	7.6	1.0	0.1	0.0	8.7	4.7
SAVOR-D	74.0	24.1	1.8	0.1	0.0	21.3	9.9	1.7	0.1	0.0	11.7	5.2
CRM	84.1	14.4	1.4	0.1	0.0	23.9	6.9	1.8	0.4	0.1	9.1	4.9
Scenario 2												
P(DLT)	0.04	0.10	0.25	0.30	0.35	0.04	0.10	0.25	0.30	0.35		
LSRVO	21.3	63.2	14.8	0.6	0.0	11.6	14.5	6.0	0.8	0.0	6.9	3.7
LSRVO-B	16.9	65.8	16.6	0.7	0.0	9.8	15.4	6.9	0.9	0.0	7.9	4.0
LSRVO-C	15.4	69.8	14.2	0.6	0.0	9.5	16.0	6.6	0.8	0.0	7.5	3.9
LSRVO-D	10.5	71.7	17.2	0.6	0.0	7.5	16.6	7.9	0.9	0.0	8.9	4.3
SAVOR	24.7	61.5	13.5	0.3	0.0	12.9	14.4	5.2	0.5	0.0	5.7	3.4
SAVOR-A	23.6	61.9	13.9	0.5	0.0	12.8	14.5	5.1	0.5	0.0	5.7	3.4
SAVOR-B	17.8	64.0	17.5	0.7	0.0	10.6	15.5	6.3	0.7	0.0	7.0	3.8
SAVOR-C	15.7	67.9	16.0	0.4	0.0	10.1	16.3	6.1	0.5	0.0	6.6	3.7
SAVOR-D	9.0	66.2	23.8	1.0	0.0	7.3	16.3	8.4	0.9	0.0	9.4	4.3
CRM	25.2	59.7	13.8	1.2	0.1	11.3	14.0	5.9	1.3	0.5	7.7	3.9
Scenario 3												
P(DLT)	0.01	0.04	0.10	0.25	0.30	0.01	0.04	0.10	0.25	0.30		
LSRVO	0.5	18.4	64.0	16.2	0.8	4.5	8.2	13.8	5.9	0.7	6.5	3.4
LSRVO-B	0.3	14.5	65.8	18.6	0.8	4.0	7.3	14.4	6.6	0.7	7.3	3.7
LSRVO-C	0.1	13.2	70.2	15.9	0.6	3.9	7.1	15.0	6.3	0.6	7.0	3.6
LSRVO-D	0.0	9.4	71.8	18.2	0.5	3.5	6.2	15.6	7.2	0.5	7.8	3.8
SAVOR	0.9	22.9	63.1	12.9	0.2	5.2	9.8	13.6	4.2	0.2	4.4	2.9
SAVOR-A	1.1	24.8	59.7	14.0	0.4	5.4	10.2	13.0	4.1	0.3	4.4	2.9
SAVOR-B	0.5	19.2	62.4	17.3	0.6	4.5	9.0	14.1	5.0	0.3	5.3	3.2
SAVOR-C	0.3	17.6	67.1	14.7	0.3	4.3	8.9	14.8	4.7	0.3	5.0	3.2
SAVOR-D	0.1	10.1	67.0	22.3	0.5	3.6	6.9	15.4	6.7	0.4	7.1	3.7
CRM	1.4	26.2	57.9	13.5	1.0	4.5	9.5	12.4	4.9	1.7	6.5	3.4
Scenario 4												
P(DLT)	0.01	0.01	0.04	0.10	0.25	0.01	0.01	0.04	0.10	0.25		
LSRVO	0.1	1.0	20.5	63.2	15.2	4.0	4.0	8.0	12.2	4.8	4.8	2.8
LSRVO-B	0.0	0.7	17.1	65.9	16.4	3.7	3.7	7.4	13.0	5.2	5.2	3.0
LSRVO-C	0.0	0.4	15.7	69.5	14.4	3.6	3.7	7.3	13.5	4.9	4.9	3.0
LSRVO-D	0.0	0.3	13.3	72.7	13.7	3.4	3.5	6.8	14.5	4.7	4.7	3.0
SAVOR	0.1	1.4	25.6	61.3	11.6	4.1	4.6	9.7	11.8	2.8	2.8	2.4
SAVOR-A	0.2	2.1	28.4	57.5	11.8	4.3	5.0	9.9	10.9	2.9	2.9	2.3
SAVOR-B	0.1	1.1	22.3	61.7	14.8	3.8	4.3	9.1	12.2	3.6	3.6	2.6
SAVOR-C	0.0	0.7	21.1	65.7	12.5	3.8	4.2	9.1	12.7	3.1	3.1	2.5
SAVOR-D	0.0	0.3	12.8	67.9	19.0	3.3	3.6	7.3	14.0	4.7	4.7	3.0
CRM	0.1	2.7	31.5	55.0	10.7	3.6	4.7	9.2	10.1	5.4	5.4	2.8
Scenario 5												
P(DLT)	0.01	0.01	0.01	0.04	0.10	0.01	0.01	0.01	0.04	0.10		
LSRVO	0.1	0.4	2.5	25.4	71.6	4.0	3.7	4.3	8.2	12.8		1.7
LSRVO-B	0.0	0.3	2.0	23.5	74.1	3.7	3.5	4.1	8.1	13.6		1.8
LSRVO-C	0.0	0.2	1.7	22.6	75.6	3.6	3.5	4.1	8.1	13.7		1.8
LSRVO-D	0.0	0.2	1.6	22.4	75.8	3.4	3.4	3.9	8.4	13.8		1.8
SAVOR	0.1	0.3	2.5	31.2	65.9	4.1	3.9	4.9	9.5	10.6		1.6
SAVOR-A	0.2	1.0	4.2	31.9	62.6	4.2	4.3	5.1	9.2	10.2		1.5
SAVOR-B	0.1	0.5	2.9	26.9	69.5	3.8	3.9	4.6	8.9	11.8		1.7
SAVOR-C	0.0	0.4	2.3	27.5	69.8	3.7	3.9	4.6	9.2	11.6		1.6
SAVOR-D	0.0	0.1	0.9	18.1	80.9	3.3	3.5	3.9	8.1	14.2		1.9
CRM	0.1	1.3	7.8	27.3	63.5	3.6	3.9	4.8	7.3	13.4		1.8

N_{ν_1+}: number treated above ν_1; N_{DLT}: total number of DLT

Table C.5: Operating characteristics of virtual observation recursions and the CRM under a one stage design with $X_1 = 3$, $n = 11$ and $m = 3$

	% Recommendation					# Treated						
	1	2	3	4	5	1	2	3	4	5	N_{ν_1+}	N_{DLT}
Scenario 1												
P(DLT)	0.10	0.25	0.30	0.35	0.40	0.10	0.25	0.30	0.35	0.40		
LSRVO	81.4	17.1	1.4	0.1	0.0	20.6	6.5	5.1	0.8	0.1	12.4	5.5
LSRVO-B	76.5	21.0	2.3	0.2	0.0	18.2	8.0	5.7	1.0	0.1	14.8	5.9
LSRVO-C	80.7	17.8	1.4	0.1	0.0	19.2	7.4	5.4	0.9	0.1	13.8	5.8
LSRVO-D	72.8	24.2	2.7	0.2	0.0	15.7	9.3	6.4	1.4	0.2	17.3	6.4
SAVOR	81.7	17.0	1.2	0.1	0.0	20.7	6.5	5.0	0.7	0.0	12.3	5.5
SAVOR-A	80.3	17.8	1.7	0.2	0.0	20.6	6.5	4.9	0.9	0.1	12.4	5.5
SAVOR-B	74.6	22.5	2.5	0.4	0.0	18.4	7.7	5.6	1.1	0.1	14.6	5.9
SAVOR-C	76.0	21.1	2.7	0.2	0.0	18.4	7.8	5.6	1.0	0.1	14.6	5.9
SAVOR-D	61.1	32.9	5.3	0.7	0.0	13.9	10.2	7.1	1.6	0.2	19.1	6.7
CRM	77.6	19.7	2.6	0.2	0.0	18.4	7.7	5.1	1.4	0.4	14.6	6.0
Scenario 2												
P(DLT)	0.04	0.10	0.25	0.30	0.35	0.04	0.10	0.25	0.30	0.35		
LSRVO	21.5	64.8	13.2	0.6	0.0	9.3	13.8	8.4	1.4	0.1	9.9	4.4
LSRVO-B	15.6	67.9	15.8	0.7	0.0	6.8	14.7	9.6	1.8	0.2	11.5	4.8
LSRVO-C	15.4	71.1	12.9	0.6	0.0	7.1	14.8	9.2	1.7	0.2	11.1	4.7
LSRVO-D	10.0	70.9	18.0	1.0	0.1	4.4	14.9	10.8	2.5	0.4	13.7	5.3
SAVOR	21.5	65.3	12.7	0.5	0.0	9.3	13.9	8.4	1.4	0.1	9.8	4.3
SAVOR-A	23.0	60.3	15.7	1.0	0.0	9.7	12.5	8.8	1.8	0.2	10.8	4.5
SAVOR-B	16.1	62.3	20.0	1.5	0.0	7.3	13.0	10.2	2.3	0.3	12.7	4.9
SAVOR-C	13.7	66.8	18.2	1.2	0.1	6.8	13.8	10.1	2.0	0.2	12.4	4.9
SAVOR-D	6.8	63.3	27.2	2.5	0.2	3.7	13.2	12.5	3.0	0.4	16.0	5.7
CRM	20.3	63.3	15.2	1.2	0.0	7.4	14.7	8.0	2.2	0.6	10.8	4.7
Scenario 3												
P(DLT)	0.01	0.04	0.10	0.25	0.30	0.01	0.04	0.10	0.25	0.30		
LSRVO	0.6	20.0	66.1	12.8	0.5	1.7	6.9	17.2	6.4	0.8	7.2	3.9
LSRVO-B	0.3	15.2	68.5	15.5	0.6	0.9	5.5	18.0	7.5	1.1	8.5	4.2
LSRVO-C	0.1	14.0	72.9	12.5	0.4	1.0	5.3	18.5	7.2	1.1	8.3	4.2
LSRVO-D	0.0	9.7	72.6	16.9	0.9	0.4	3.6	18.2	8.9	1.8	10.7	4.8
SAVOR	0.6	20.4	67.0	11.7	0.4	1.7	7.1	17.6	6.1	0.6	6.7	3.8
SAVOR-A	1.2	21.3	62.4	14.4	0.7	2.5	6.8	16.3	6.6	0.9	7.5	3.8
SAVOR-B	0.5	15.2	65.4	18.0	0.9	1.5	5.3	17.0	8.0	1.3	9.2	4.3
SAVOR-C	0.2	13.1	69.9	15.9	0.8	1.2	5.0	18.0	7.7	1.0	8.7	4.3
SAVOR-D	0.1	6.6	67.2	24.5	1.6	0.5	3.0	17.5	10.3	1.8	12.0	5.0
CRM	0.8	23.2	63.3	12.2	0.5	1.1	8.1	16.2	6.1	1.7	7.7	4.0
Scenario 4												
P(DLT)	0.01	0.01	0.04	0.10	0.25	0.01	0.01	0.04	0.10	0.25		
LSRVO	0.1	1.0	20.3	66.6	12.0	0.5	1.4	9.9	15.5	5.6	5.6	3.4
LSRVO-B	0.0	0.5	16.1	69.3	14.1	0.3	0.9	8.7	16.3	6.8	6.8	3.7
LSRVO-C	0.0	0.2	14.9	72.5	12.4	0.3	0.9	8.3	16.8	6.7	6.7	3.7
LSRVO-D	0.0	0.0	10.3	72.6	17.0	0.1	0.4	6.7	16.6	9.2	9.2	4.3
SAVOR	0.1	1.1	21.5	67.1	10.2	0.5	1.5	10.5	15.9	4.5	4.5	3.2
SAVOR-A	0.2	1.5	22.7	62.3	13.2	0.9	1.7	10.3	14.7	5.4	5.4	3.2
SAVOR-B	0.0	0.6	17.3	65.2	16.9	0.5	1.1	8.9	15.6	6.9	6.9	3.7
SAVOR-C	0.0	0.4	15.7	69.1	14.9	0.4	1.0	8.7	16.5	6.4	6.4	3.6
SAVOR-D	0.0	0.1	8.8	68.4	22.8	0.1	0.4	6.7	16.7	9.1	9.1	4.2
CRM	0.1	1.5	28.4	61.5	8.5	0.1	1.9	11.0	14.4	5.5	5.5	3.3
Scenario 5												
P(DLT)	0.01	0.01	0.01	0.04	0.10	0.01	0.01	0.01	0.04	0.10		
LSRVO	0.0	0.1	1.1	19.7	79.1	0.1	0.4	4.4	8.8	19.2		2.3
LSRVO-B	0.0	0.0	0.6	15.8	83.6	0.1	0.2	3.9	7.9	20.9		2.4
LSRVO-C	0.0	0.0	0.3	13.6	86.0	0.1	0.2	3.8	7.4	21.5		2.5
LSRVO-D	0.0	0.0	0.1	9.0	90.9	0.0	0.1	3.4	5.9	23.7		2.6
SAVOR	0.0	0.2	1.2	24.2	74.5	0.1	0.4	4.7	10.6	17.1		2.2
SAVOR-A	0.1	0.2	1.9	25.4	72.4	0.3	0.6	4.9	10.1	17.0		2.2
SAVOR-B	0.0	0.0	0.9	19.6	79.4	0.1	0.3	4.3	9.0	19.3		2.3
SAVOR-C	0.0	0.1	0.6	18.2	81.1	0.1	0.3	4.1	9.0	19.5		2.3
SAVOR-D	0.0	0.0	0.2	10.6	89.2	0.0	0.1	3.5	7.0	22.4		2.6
CRM	0.0	0.1	2.6	32.1	65.2	0.0	0.4	4.9	10.5	17.1		2.2

N_{ν_1+}: number treated above ν_1; N_{DLT}: total number of DLT

Table C.6: Probability of response and mean function of the continuous outcomes used in Section 5.3

		Dose level				
Scenario		1	2	3	4	5
1	P(Rsp)	0.50	0.66	0.75	0.80	0.85
	$M(k)$	10.00	23.20	31.58	36.93	43.17
2	P(Rsp)	0.40	0.50	0.66	0.75	0.80
	$M(k)$	1.89	10.00	23.20	31.58	36.93
3	P(Rsp)	0.35	0.40	0.50	0.66	0.75
	$M(k)$	-2.33	1.89	10.00	23.20	31.58
4	P(Rsp)	0.25	0.35	0.40	0.50	0.66
	$M(k)$	-11.58	-2.33	1.89	10.00	23.20

Table C.7: Operating characteristics of (5.3) with (5.5) ($b = \beta = 13$, $\phi = \tau = 2$, $\rho = 0.8$)

	% Recommendation					# Treated						
	1	2	3	4	5	1	2	3	4	5	N_{MED-}	N_{Rsp}
Scenario 1												
P(Rsp)	0.50	0.66	0.75	0.80	0.85	0.50	0.66	0.75	0.80	0.85		
Fixed, $\xi = 1$	6.6	66.6	25.1	1.8	0.0	5.7	23.1	15.5	3.4	0.3	5.7	32.6
Fixed, $\xi = 2$	6.5	65.8	26.1	1.7	0.0	6.0	22.6	15.5	3.4	0.5	6.0	32.6
Fixed, $\xi = 3$	6.6	67.5	24.5	1.4	0.0	6.0	23.7	15.5	2.5	0.2	6.0	32.5
Fixed, $\xi = 4$	6.8	68.3	23.5	1.4	0.0	6.1	24.6	14.7	2.4	0.2	6.1	32.4
Fixed, $\xi = 5$	6.2	66.8	25.3	1.6	0.0	6.8	22.5	14.8	3.6	0.4	6.8	32.4
Fixed, $\xi = 6$	6.3	67.5	24.8	1.4	0.0	6.9	22.9	14.6	3.3	0.3	6.9	32.3
Fixed, $\xi = 7$	6.2	67.4	25.3	1.0	0.0	5.0	22.5	18.4	2.0	0.1	5.0	32.7
Fixed, $\xi = 8$	6.2	68.4	24.6	0.8	0.0	6.2	22.2	17.6	1.8	0.2	6.2	32.4
Fixed, $\xi = 9$	6.4	69.8	23.1	0.8	0.0	7.0	23.1	16.1	1.7	0.1	7.0	32.2
Fixed, $\xi = 10$	6.4	70.5	22.4	0.6	0.0	7.4	23.3	15.8	1.4	0.1	7.4	32.0
Fixed, $\xi = 11$	6.0	68.7	24.9	0.4	0.0	7.6	21.8	16.0	2.4	0.2	7.6	32.2
Fixed, $\xi = 12$	6.0	69.0	24.5	0.4	0.0	8.0	21.8	15.8	2.2	0.2	8.0	32.1
Poisson, $\xi = 1$	6.6	66.0	25.9	1.5	0.0	5.8	22.8	15.8	3.2	0.3	5.8	32.6
Poisson, $\xi = 2$	6.4	66.8	25.2	1.5	0.0	6.0	23.0	15.7	3.1	0.3	6.0	32.6
Poisson, $\xi = 3$	6.6	66.5	25.4	1.4	0.0	6.0	22.9	15.8	3.0	0.3	6.0	32.6
Poisson, $\xi = 4$	6.4	67.1	25.1	1.4	0.0	6.1	22.6	16.2	2.9	0.3	6.1	32.5
Poisson, $\xi = 5$	6.3	67.0	25.6	1.1	0.0	6.0	22.6	16.5	2.6	0.3	6.0	32.5
Poisson, $\xi = 6$	6.5	67.6	24.9	0.9	0.0	6.2	22.5	16.6	2.5	0.3	6.2	32.5
Poisson, $\xi = 7$	6.4	68.0	24.6	0.8	0.0	6.3	22.3	16.9	2.3	0.2	6.3	32.4
Poisson, $\xi = 8$	6.2	68.4	24.6	0.8	0.0	6.4	22.2	17.0	2.2	0.2	6.4	32.4
Poisson, $\xi = 9$	5.9	68.7	24.6	0.7	0.0	6.6	22.2	17.1	2.0	0.2	6.6	32.4
Poisson, $\xi = 10$	6.2	68.8	24.4	0.6	0.0	6.8	22.0	17.2	1.8	0.2	6.8	32.3
Poisson, $\xi = 11$	6.1	69.0	24.3	0.5	0.0	7.0	21.9	17.3	1.7	0.1	7.0	32.3
Poisson, $\xi = 12$	6.2	69.0	24.6	0.3	0.0	7.2	21.5	17.5	1.6	0.1	7.2	32.2
Scenario 2												
P(Rsp)	0.40	0.50	0.66	0.75	0.80	0.40	0.50	0.66	0.75	0.80		
Fixed, $\xi = 1$	0.0	8.5	69.2	21.5	0.8	0.7	7.5	26.5	11.6	1.7	8.2	31.5
Fixed, $\xi = 2$	0.0	8.4	68.7	22.2	0.7	0.8	8.0	25.6	11.6	2.0	8.8	31.5
Fixed, $\xi = 3$	0.0	8.4	71.2	19.7	0.6	0.9	9.4	26.1	10.4	1.2	10.3	31.0
Fixed, $\xi = 4$	0.0	8.4	71.3	19.7	0.6	0.9	9.8	25.5	10.5	1.3	10.7	31.0
Fixed, $\xi = 5$	0.0	8.5	69.9	21.1	0.5	1.6	9.4	23.9	11.4	1.7	11.0	31.0
Fixed, $\xi = 6$	0.0	8.6	70.4	20.4	0.5	1.6	9.7	24.2	11.1	1.4	11.3	30.9
Fixed, $\xi = 7$	0.0	8.5	72.1	19.1	0.4	0.6	8.5	28.5	9.4	1.0	9.1	31.1
Fixed, $\xi = 8$	0.0	8.7	72.2	18.8	0.3	1.5	9.3	27.6	8.7	1.0	10.8	30.7
Fixed, $\xi = 9$	0.0	9.4	73.0	17.4	0.2	2.2	11.0	26.2	8.0	0.6	13.2	30.1
Fixed, $\xi = 10$	0.0	9.5	73.8	16.5	0.2	2.5	11.2	26.3	7.4	0.6	13.7	29.9
Fixed, $\xi = 11$	0.0	9.3	73.0	17.5	0.1	2.7	10.8	25.1	8.6	0.9	13.5	30.1
Fixed, $\xi = 12$	0.0	9.4	73.1	17.3	0.1	3.0	10.9	25.1	8.1	0.9	13.9	29.9
Poisson, $\xi = 1$	0.0	8.3	70.0	21.0	0.6	0.9	8.1	26.1	11.4	1.6	9.0	31.4
Poisson, $\xi = 2$	0.0	8.3	70.3	20.8	0.5	1.0	8.5	25.9	11.1	1.5	9.5	31.2
Poisson, $\xi = 3$	0.0	8.5	71.1	20.1	0.4	1.1	8.8	25.9	10.8	1.4	9.9	31.1
Poisson, $\xi = 4$	0.0	8.5	71.1	20.0	0.4	1.2	9.0	25.8	10.7	1.3	10.2	31.0
Poisson, $\xi = 5$	0.0	8.7	71.2	19.7	0.4	1.3	9.3	25.9	10.3	1.2	10.6	30.9
Poisson, $\xi = 6$	0.0	8.8	71.9	18.9	0.4	1.4	9.6	26.0	9.9	1.1	11.0	30.8
Poisson, $\xi = 7$	0.0	9.1	72.2	18.2	0.4	1.6	9.7	26.5	9.3	1.0	11.2	30.6
Poisson, $\xi = 8$	0.0	9.2	72.5	17.9	0.3	1.8	10.0	26.5	8.8	0.9	11.7	30.5
Poisson, $\xi = 9$	0.0	9.0	73.2	17.4	0.4	2.0	10.3	26.7	8.2	0.9	12.2	30.3
Poisson, $\xi = 10$	0.0	9.1	73.6	17.1	0.2	2.3	10.4	26.7	7.9	0.8	12.6	30.1
Poisson, $\xi = 11$	0.0	9.1	73.9	16.9	0.2	2.5	10.6	26.6	7.6	0.8	13.0	30.1
Poisson, $\xi = 12$	0.0	9.5	73.6	16.8	0.1	2.7	10.8	26.6	7.2	0.7	13.5	29.9

Continued on next page

	% Recommendation					# Treated						
	1	2	3	4	5	1	2	3	4	5	N_{MED-}	N_{Rsp}
Scenario 3												
P(Rsp)	0.35	0.40	0.50	0.66	0.75	0.35	0.40	0.50	0.66	0.75		
Fixed, $\xi = 1$	0.0	0.1	9.0	71.8	19.1	0.1	1.2	10.3	25.5	10.8	11.7	30.6
Fixed, $\xi = 2$	0.0	0.1	9.0	71.6	19.2	0.2	1.8	10.5	24.4	11.1	12.5	30.4
Fixed, $\xi = 3$	0.0	0.1	9.9	72.6	17.4	0.2	3.0	11.7	23.7	9.5	14.9	29.8
Fixed, $\xi = 4$	0.0	0.1	9.8	73.1	17.1	0.2	3.3	11.4	23.8	9.3	14.9	29.7
Fixed, $\xi = 5$	0.0	0.1	10.1	72.2	17.6	0.5	3.0	11.2	23.5	9.8	14.7	29.8
Fixed, $\xi = 6$	0.0	0.1	10.4	72.5	17.0	0.5	3.3	11.6	23.5	9.2	15.4	29.6
Fixed, $\xi = 7$	0.0	0.0	9.0	73.3	17.6	0.1	1.9	14.5	22.6	8.9	16.5	29.6
Fixed, $\xi = 8$	0.0	0.0	9.9	73.0	17.1	0.4	2.6	15.4	20.8	8.8	18.4	29.2
Fixed, $\xi = 9$	0.0	0.2	11.3	73.4	15.2	0.8	4.1	15.4	20.9	6.9	20.3	28.5
Fixed, $\xi = 10$	0.0	0.2	11.6	73.6	14.6	0.9	4.4	15.9	20.2	6.6	21.2	28.2
Fixed, $\xi = 11$	0.0	0.0	11.3	73.3	15.3	0.9	4.0	15.5	20.0	7.5	20.5	28.5
Fixed, $\xi = 12$	0.0	0.0	11.5	73.0	15.6	1.1	4.2	15.8	19.5	7.4	21.1	28.3
Poisson, $\xi = 1$	0.0	0.1	9.2	71.8	19.0	0.2	1.9	10.9	24.6	10.5	12.9	30.3
Poisson, $\xi = 2$	0.0	0.1	9.3	72.2	18.2	0.2	2.2	11.2	24.2	10.1	13.7	30.1
Poisson, $\xi = 3$	0.0	0.1	9.6	73.0	17.3	0.2	2.5	11.8	23.7	9.7	14.5	29.9
Poisson, $\xi = 4$	0.0	0.0	10.0	72.5	17.4	0.3	2.7	12.4	23.2	9.4	15.4	29.7
Poisson, $\xi = 5$	0.0	0.1	10.2	72.5	17.3	0.4	2.9	12.9	22.8	9.1	16.1	29.5
Poisson, $\xi = 6$	0.0	0.1	10.6	72.4	16.9	0.4	3.1	13.7	22.1	8.8	17.2	29.3
Poisson, $\xi = 7$	0.0	0.1	10.7	72.7	16.5	0.5	3.3	14.1	21.7	8.3	17.9	29.1
Poisson, $\xi = 8$	0.0	0.0	11.0	72.6	16.4	0.5	3.5	14.8	21.2	8.0	18.8	28.9
Poisson, $\xi = 9$	0.0	0.0	10.8	73.4	15.8	0.6	3.6	15.6	20.7	7.5	19.8	28.7
Poisson, $\xi = 10$	0.0	0.0	11.1	73.5	15.4	0.7	3.9	16.2	20.0	7.2	20.8	28.4
Poisson, $\xi = 11$	0.0	0.0	11.2	73.2	15.5	0.8	4.1	16.7	19.6	6.8	21.6	28.2
Poisson, $\xi = 12$	0.0	0.1	11.4	73.6	14.9	0.9	4.3	17.6	18.6	6.6	22.7	28.0
Scenario 4												
P(Rsp)	0.25	0.35	0.40	0.50	0.66	0.25	0.35	0.40	0.50	0.66		
Fixed, $\xi = 1$	0.0	0.0	0.3	10.8	88.9	0.0	0.4	4.5	10.3	32.7	15.3	28.6
Fixed, $\xi = 2$	0.0	0.0	0.2	11.6	88.1	0.0	0.8	4.7	10.7	31.8	16.2	28.4
Fixed, $\xi = 3$	0.0	0.0	0.4	14.1	85.5	0.1	1.8	6.0	11.8	28.4	19.6	27.6
Fixed, $\xi = 4$	0.0	0.0	0.3	14.3	85.4	0.1	2.1	5.6	12.0	28.4	19.6	27.6
Fixed, $\xi = 5$	0.0	0.0	0.4	13.6	86.1	0.2	1.7	5.3	12.5	28.3	19.7	27.6
Fixed, $\xi = 6$	0.0	0.0	0.3	14.1	85.6	0.2	1.9	5.6	12.7	27.6	20.4	27.5
Fixed, $\xi = 7$	0.0	0.0	0.2	13.6	86.2	0.0	0.8	8.9	11.5	26.8	21.2	27.2
Fixed, $\xi = 8$	0.0	0.0	0.3	14.7	85.0	0.1	1.3	9.9	11.7	25.1	22.9	26.7
Fixed, $\xi = 9$	0.0	0.0	0.3	17.1	82.7	0.4	2.6	9.3	13.6	22.1	25.9	26.0
Fixed, $\xi = 10$	0.0	0.0	0.4	17.5	82.2	0.4	2.8	10.0	13.3	21.5	26.5	25.8
Fixed, $\xi = 11$	0.0	0.0	0.4	17.1	82.5	0.4	2.3	9.9	13.1	22.3	25.7	26.0
Fixed, $\xi = 12$	0.0	0.0	0.4	17.3	82.2	0.5	2.5	10.0	13.1	22.0	26.0	25.9
Poisson, $\xi = 1$	0.0	0.0	0.3	12.0	87.6	0.1	0.9	5.1	10.9	31.0	17.0	28.2
Poisson, $\xi = 2$	0.0	0.0	0.3	12.6	87.1	0.1	1.2	5.5	11.3	29.9	18.1	28.0
Poisson, $\xi = 3$	0.0	0.0	0.2	13.0	86.8	0.1	1.4	6.0	11.8	28.7	19.3	27.7
Poisson, $\xi = 4$	0.0	0.0	0.4	13.8	85.8	0.1	1.5	6.6	12.0	27.9	20.1	27.5
Poisson, $\xi = 5$	0.0	0.0	0.4	14.0	85.7	0.1	1.6	7.2	12.1	26.9	21.1	27.3
Poisson, $\xi = 6$	0.0	0.0	0.3	14.8	85.0	0.2	1.7	7.9	12.4	25.8	22.2	26.9
Poisson, $\xi = 7$	0.0	0.0	0.4	14.9	84.7	0.2	1.8	8.6	12.6	24.7	23.3	26.7
Poisson, $\xi = 8$	0.0	0.0	0.3	15.5	84.2	0.3	1.9	9.4	12.8	23.7	24.3	26.4
Poisson, $\xi = 9$	0.0	0.0	0.3	16.2	83.5	0.3	2.1	9.9	13.1	22.6	25.4	26.1
Poisson, $\xi = 10$	0.0	0.0	0.2	17.2	82.6	0.3	2.2	10.7	13.1	21.6	26.4	25.8
Poisson, $\xi = 11$	0.0	0.0	0.2	17.8	82.0	0.3	2.4	11.4	13.3	20.6	27.4	25.6
Poisson, $\xi = 12$	0.0	0.0	0.4	18.2	81.5	0.4	2.5	12.1	13.2	19.7	28.3	25.3

P(Rsp): probability or response; N_{MED-}: number treated below MED; N_{Rsp}: total number of responses

Table C.8: Operating characteristics of TITE-CRM

	% Recommendation					# Treated						
	1	2	3	4	5	1	2	3	4	5	N_{MED-}	N_{Rsp}
Scenario 1												
P(Rsp)	0.50	0.66	0.75	0.80	0.85	0.50	0.66	0.75	0.80	0.85		
Fixed, $\xi = 1$	11.7	59.5	25.8	2.9	0.1	7.9	20.4	16.0	3.4	0.3	7.9	32.3
Fixed, $\xi = 2$	11.4	60.8	24.9	2.9	0.0	8.6	21.1	14.8	3.2	0.3	8.6	32.0
Fixed, $\xi = 3$	12.2	59.1	25.9	2.6	0.0	8.9	22.0	14.1	2.7	0.3	8.9	31.9
Fixed, $\xi = 4$	11.6	61.1	24.9	2.2	0.0	9.7	22.5	13.3	2.4	0.2	9.7	31.6
Fixed, $\xi = 5$	11.8	60.1	25.9	2.1	0.0	10.1	21.0	13.4	3.2	0.2	10.1	31.7
Fixed, $\xi = 6$	11.5	61.4	25.5	1.6	0.0	10.8	21.4	12.7	2.9	0.2	10.8	31.4
Fixed, $\xi = 7$	11.2	63.3	23.8	1.7	0.0	9.9	20.3	16.2	1.6	0.1	9.9	31.6
Fixed, $\xi = 8$	10.9	63.7	23.9	1.4	0.0	10.7	20.3	15.6	1.3	0.1	10.7	31.4
Fixed, $\xi = 9$	11.9	62.7	23.8	1.6	0.0	11.9	20.2	14.2	1.7	0.1	11.9	31.2
Fixed, $\xi = 10$	11.6	62.7	24.1	1.6	0.0	13.0	20.0	13.6	1.3	0.1	13.0	30.9
Fixed, $\xi = 11$	10.9	63.2	24.4	1.4	0.0	12.5	19.3	14.0	2.1	0.1	12.5	31.1
Fixed, $\xi = 12$	11.0	63.6	24.1	1.3	0.0	13.4	19.3	13.2	2.0	0.1	13.4	30.9
Poisson, $\xi = 1$	11.6	59.9	25.7	2.7	0.0	8.4	21.2	15.2	2.9	0.3	8.4	32.1
Poisson, $\xi = 2$	11.5	61.0	25.4	2.1	0.0	9.0	21.3	14.7	2.8	0.3	9.0	31.9
Poisson, $\xi = 3$	11.8	60.4	25.6	2.2	0.0	9.3	21.2	14.6	2.7	0.2	9.3	31.8
Poisson, $\xi = 4$	12.1	60.8	24.8	2.3	0.0	9.7	21.1	14.5	2.4	0.2	9.7	31.7
Poisson, $\xi = 5$	11.2	61.2	25.5	2.1	0.0	10.1	20.9	14.5	2.2	0.2	10.1	31.6
Poisson, $\xi = 6$	11.8	61.2	25.4	1.6	0.0	10.5	20.6	14.6	2.1	0.2	10.5	31.5
Poisson, $\xi = 7$	11.2	62.4	25.1	1.2	0.0	10.8	20.3	14.9	2.0	0.1	10.8	31.5
Poisson, $\xi = 8$	11.5	62.7	24.6	1.2	0.0	11.5	19.9	14.7	1.8	0.1	11.5	31.3
Poisson, $\xi = 9$	11.5	63.8	23.2	1.5	0.0	11.9	19.6	14.8	1.7	0.1	11.9	31.3
Poisson, $\xi = 10$	10.8	63.6	24.2	1.3	0.0	12.3	19.1	15.0	1.5	0.1	12.3	31.2
Poisson, $\xi = 11$	11.2	62.5	25.1	1.2	0.0	12.7	18.7	15.1	1.4	0.1	12.7	31.1
Poisson, $\xi = 12$	11.3	63.2	24.1	1.4	0.0	13.0	18.5	15.1	1.4	0.1	13.0	31.1
Scenario 2												
P(Rsp)	0.40	0.50	0.66	0.75	0.80	0.40	0.50	0.66	0.75	0.80		
Fixed, $\xi = 1$	0.2	13.4	62.6	22.3	1.5	1.6	9.2	24.9	10.6	1.8	10.8	31.0
Fixed, $\xi = 2$	0.2	12.6	63.6	22.1	1.4	1.7	10.0	24.8	10.0	1.5	11.6	30.7
Fixed, $\xi = 3$	0.2	13.3	63.4	21.6	1.5	1.9	11.1	23.8	9.7	1.5	13.0	30.5
Fixed, $\xi = 4$	0.1	12.8	64.6	21.0	1.4	2.5	11.6	23.6	9.1	1.3	14.0	30.2
Fixed, $\xi = 5$	0.1	14.1	63.3	21.2	1.1	2.8	11.4	22.7	9.8	1.3	14.2	30.2
Fixed, $\xi = 6$	0.1	13.9	65.0	19.9	1.1	3.1	12.1	22.5	9.2	1.1	15.2	29.9
Fixed, $\xi = 7$	0.1	13.2	64.8	21.1	0.8	2.6	11.2	25.7	7.7	0.8	13.8	29.9
Fixed, $\xi = 8$	0.0	13.3	65.4	20.4	0.8	3.0	11.7	25.4	7.2	0.6	14.8	29.7
Fixed, $\xi = 9$	0.1	13.2	65.7	20.5	0.5	4.0	12.6	23.4	7.3	0.7	16.6	29.3
Fixed, $\xi = 10$	0.0	13.8	66.1	19.5	0.6	4.7	13.1	23.1	6.4	0.7	17.8	29.0
Fixed, $\xi = 11$	0.1	13.6	65.6	20.0	0.8	4.4	12.7	22.7	7.4	0.7	17.1	29.2
Fixed, $\xi = 12$	0.1	14.2	65.0	20.1	0.7	5.0	13.1	22.5	6.8	0.7	18.1	28.9
Poisson, $\xi = 1$	0.2	13.4	63.6	21.3	1.4	1.8	10.0	24.6	10.1	1.6	11.7	30.8
Poisson, $\xi = 2$	0.1	13.4	63.5	21.6	1.4	2.0	10.5	24.1	9.9	1.5	12.6	30.5
Poisson, $\xi = 3$	0.1	13.9	63.7	20.8	1.5	2.3	10.9	23.9	9.5	1.4	13.2	30.4
Poisson, $\xi = 4$	0.1	13.8	63.3	21.6	1.1	2.6	11.3	23.7	9.1	1.3	13.9	30.1
Poisson, $\xi = 5$	0.1	13.0	64.4	21.5	1.0	2.8	11.7	23.7	8.6	1.2	14.5	30.0
Poisson, $\xi = 6$	0.2	13.8	64.5	20.5	1.0	3.0	12.0	23.7	8.3	1.0	15.0	29.8
Poisson, $\xi = 7$	0.1	13.8	65.5	19.9	0.8	3.3	12.1	23.8	7.9	0.8	15.4	29.7
Poisson, $\xi = 8$	0.1	13.8	64.7	20.5	0.9	3.6	12.2	23.7	7.7	0.8	15.8	29.5
Poisson, $\xi = 9$	0.1	14.1	64.1	21.0	0.7	3.8	12.6	23.6	7.3	0.7	16.4	29.3
Poisson, $\xi = 10$	0.1	13.6	65.2	20.4	0.6	4.2	12.7	23.6	6.8	0.6	16.9	29.2
Poisson, $\xi = 11$	0.0	13.6	65.8	20.1	0.6	4.6	12.7	23.4	6.7	0.6	17.3	29.0
Poisson, $\xi = 12$	0.1	14.2	64.8	20.3	0.5	4.9	12.8	23.6	6.1	0.5	17.7	28.9

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	% Recommendation					# Treated						
	1	2	3	4	5	1	2	3	4	5	N_{MED-}	N_{Rsp}
Scenario 3												
P(Rsp)	0.35	0.40	0.50	0.66	0.75	0.35	0.40	0.50	0.66	0.75		
Fixed, $\xi = 1$	0.0	0.4	13.6	64.7	21.2	0.3	1.7	13.4	22.8	9.8	15.4	29.8
Fixed, $\xi = 2$	0.0	0.4	14.1	65.2	20.3	0.4	2.6	13.0	23.0	9.0	16.0	29.6
Fixed, $\xi = 3$	0.0	0.4	15.8	63.5	20.2	0.5	3.8	13.2	21.6	8.9	17.5	29.2
Fixed, $\xi = 4$	0.0	0.4	15.7	64.4	19.5	0.7	4.2	13.7	21.4	8.0	18.6	28.9
Fixed, $\xi = 5$	0.0	0.5	15.6	64.1	19.9	0.8	3.9	13.7	21.6	8.0	18.3	28.9
Fixed, $\xi = 6$	0.0	0.4	15.8	65.0	18.7	0.9	4.5	14.1	21.4	7.0	19.5	28.6
Fixed, $\xi = 7$	0.0	0.4	13.2	66.8	19.7	0.5	3.2	17.4	19.8	7.1	21.2	28.5
Fixed, $\xi = 8$	0.0	0.4	14.1	66.3	19.3	0.7	3.6	17.7	19.3	6.7	22.0	28.2
Fixed, $\xi = 9$	0.0	0.4	15.5	65.9	18.2	1.2	5.0	16.7	18.9	6.2	22.9	27.8
Fixed, $\xi = 10$	0.0	0.6	15.3	66.5	17.5	1.6	5.5	17.4	18.0	5.6	24.4	27.4
Fixed, $\xi = 11$	0.0	0.4	15.4	66.5	17.7	1.2	5.1	17.5	18.3	5.9	23.8	27.6
Fixed, $\xi = 12$	0.0	0.4	15.8	66.6	17.1	1.5	5.4	17.9	17.7	5.5	24.8	27.4
Poisson, $\xi = 1$	0.0	0.4	14.2	65.6	19.8	0.4	2.6	13.3	22.7	9.0	16.2	29.5
Poisson, $\xi = 2$	0.0	0.5	14.1	65.5	19.9	0.5	3.1	13.7	22.1	8.6	17.3	29.3
Poisson, $\xi = 3$	0.0	0.5	14.8	64.5	20.2	0.6	3.5	14.1	21.6	8.3	18.2	29.0
Poisson, $\xi = 4$	0.0	0.5	15.2	65.0	19.4	0.7	3.7	14.6	21.3	7.7	18.9	28.8
Poisson, $\xi = 5$	0.0	0.2	14.7	65.1	19.9	0.7	3.9	15.2	20.8	7.4	19.8	28.6
Poisson, $\xi = 6$	0.0	0.4	14.5	66.1	19.0	0.8	4.1	15.9	20.2	7.1	20.8	28.4
Poisson, $\xi = 7$	0.0	0.5	14.2	66.1	19.1	0.9	4.3	16.4	19.6	6.8	21.6	28.2
Poisson, $\xi = 8$	0.0	0.4	14.5	66.5	18.6	1.0	4.6	17.2	18.8	6.4	22.8	27.9
Poisson, $\xi = 9$	0.0	0.4	15.1	66.4	18.1	1.1	4.8	17.7	18.3	6.1	23.6	27.7
Poisson, $\xi = 10$	0.0	0.5	14.7	66.8	18.0	1.2	5.1	18.3	17.6	5.9	24.6	27.5
Poisson, $\xi = 11$	0.0	0.4	14.9	67.6	17.1	1.3	5.3	18.7	17.3	5.5	25.3	27.3
Poisson, $\xi = 12$	0.0	0.5	15.8	66.7	17.0	1.4	5.5	19.4	16.5	5.3	26.2	27.1
Scenario 4												
P(Rsp)	0.25	0.35	0.40	0.50	0.66	0.25	0.35	0.40	0.50	0.66		
Fixed, $\xi = 1$	0.0	0.0	0.4	16.9	82.7	0.1	0.6	5.9	12.8	28.5	19.5	27.8
Fixed, $\xi = 2$	0.0	0.0	0.5	17.6	81.8	0.1	1.0	5.9	13.4	27.6	20.4	27.6
Fixed, $\xi = 3$	0.0	0.0	0.8	19.9	79.4	0.2	2.1	6.4	13.7	25.7	22.3	27.0
Fixed, $\xi = 4$	0.0	0.0	0.5	19.8	79.7	0.3	2.3	6.7	14.1	24.7	23.3	26.8
Fixed, $\xi = 5$	0.0	0.0	0.6	20.0	79.5	0.3	2.0	6.5	14.7	24.5	23.5	26.8
Fixed, $\xi = 6$	0.0	0.0	0.8	19.4	79.9	0.3	2.3	7.0	15.1	23.2	24.8	26.5
Fixed, $\xi = 7$	0.0	0.0	0.6	18.9	80.5	0.2	1.3	10.8	13.5	22.2	25.8	26.1
Fixed, $\xi = 8$	0.0	0.0	0.8	19.1	80.1	0.2	1.6	11.2	13.9	21.1	26.9	25.9
Fixed, $\xi = 9$	0.0	0.0	0.8	21.9	77.3	0.5	2.9	10.1	14.9	19.7	28.3	25.5
Fixed, $\xi = 10$	0.0	0.0	0.9	22.9	76.2	0.6	3.3	11.0	14.8	18.3	29.7	25.1
Fixed, $\xi = 11$	0.0	0.0	0.8	22.4	76.8	0.5	2.6	11.2	14.8	18.9	29.1	25.3
Fixed, $\xi = 12$	0.0	0.0	0.9	23.5	75.5	0.6	2.9	11.6	14.9	18.1	29.9	25.1
Poisson, $\xi = 1$	0.0	0.0	0.6	17.8	81.5	0.1	1.1	6.3	13.1	27.4	20.6	27.5
Poisson, $\xi = 2$	0.0	0.0	0.6	18.6	80.8	0.2	1.5	6.7	13.7	26.0	22.0	27.2
Poisson, $\xi = 3$	0.0	0.0	0.6	18.8	80.6	0.2	1.7	7.1	13.9	25.1	22.9	26.9
Poisson, $\xi = 4$	0.0	0.0	0.8	19.1	80.2	0.3	1.8	7.8	14.2	24.0	24.0	26.6
Poisson, $\xi = 5$	0.0	0.0	0.8	19.7	79.5	0.2	2.0	8.4	14.2	23.0	25.0	26.4
Poisson, $\xi = 6$	0.0	0.0	0.8	20.0	79.2	0.3	2.1	9.1	14.5	22.0	26.0	26.1
Poisson, $\xi = 7$	0.0	0.0	0.9	20.5	78.6	0.3	2.3	9.8	14.5	21.1	26.9	25.9
Poisson, $\xi = 8$	0.0	0.0	0.8	20.5	78.8	0.4	2.3	10.6	14.7	20.1	27.9	25.6
Poisson, $\xi = 9$	0.0	0.0	0.8	22.0	77.2	0.4	2.5	11.3	14.5	19.2	28.8	25.4
Poisson, $\xi = 10$	0.0	0.0	0.7	21.9	77.3	0.4	2.6	12.0	14.6	18.3	29.7	25.1
Poisson, $\xi = 11$	0.0	0.0	0.9	22.7	76.4	0.5	2.8	12.6	14.8	17.4	30.6	24.9
Poisson, $\xi = 12$	0.0	0.0	0.9	22.6	76.5	0.5	2.9	13.3	14.6	16.7	31.3	24.7

P(Rsp): probability or response; N_{MED-}: number treated below MED; N_{Rsp}: total number of responses