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Decision Rules for Predicting Future Lipid Values in Screening for a Cholesterol Reduction Clinical Trial

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ABSTRACT: Recent large clinical trials have required screened patients to have serial measurements of an entry criteria variable, eliminating patients from further consideration if the average value is not in the eligibility range specified by the trial protocol. The increasing costs of large clinical trials required that they be executed efficiently. One way to improve efficiency would be to reduce the number of required screening measurements for a patient likely to be ineligible. A procedure is proposed that predicts the value of an average based on n measurements serially obtained on a patient during the screening phase when only $m < n$ measurements are available. The employment of this procedure in a large clinical trial that uses low-density lipoprotein (LDL) cholesterol, total cholesterol, and triglycerides as entry criteria during the screening process is described. As a second example, this procedure is applied to population screening for lipid levels above a treatment threshold. The National Cholesterol Education Program recommends that the average of two LDL cholesterol measurements be used to determine whether LDL cholesterol is above 130 mg/dl, the threshold for treating patients with coronary heart disease. However, data from a sample of patients from a postinfarction population suggest that, if a single LDL cholesterol is above 146 mg/dl, the probability is greater than 95% that the average of the two LDL cholesterol measurements will be above 130 mg/dl. © *Elsevier Science Inc. 1996 Controlled Clin Trials 1996; 17:536–546*

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INTRODUCTION

The screening process of large clinical trials represents a crucial first step on the experiment's path to success, a step that requires the trial's recruiters

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to seek potential participants vigorously. The increasing costs of clinical trials have forced these experiments to become more efficient. The drive to reach the recruitment goal quickly must be balanced against the costs incurred.

Several trials [1,2] used screening processes that required patients to have serial quantitative measures obtained over time. If, at the end of this process, the participant's average value of the measurement [e.g., low-density lipoprotein (LDL) cholesterol level] falls within the range prescribed by the trial's protocol, the participant is considered to have an eligible average. A consequence of this requirement is that the clinical center must follow the patient to the end of the screening process to determine if the participant will have an eligible average, thereby incurring the full screening cost. A decision rule for eligibility based only on a fraction of the full collection of values would be useful, since it would permit the early elimination of a patient likely to be ineligible if his or her average value is out of bounds. This article develops a rule that allows the clinical center to decide early in the screening process whether a patient will have an ineligible average measurement. An example is provided from both the screening experience of a long-term randomized placebo controlled clinical trial and from the population screening milieu.

METHODS

Our goal is to predict the value of the mean of measurements taken on an individual being screened. Assume that a patient who is being evaluated has a sequence of n measurements $x_1,x_2,x_3,,,,x_n$ obtained during the screening process. For the patient to be eligible for the experiment, the mean of these n measurements $\overline{X}_n$ must satisfy the inequality $[e_1 \leqslant \overline{X}_n \leqslant e_2]$, where e_1 and e_2 are constants specified by the trial's protocol. We seek the probability that the mean of n measurements is an eligible average given that only the first m $(0 < m < n)$ measurements have been obtained. If the probability of an eligible average is large for a particular patient, that patient can proceed through the screening process. Thus we require the value of $\overline{X}_m$ such that

$$P[e_1 \leqslant \overline{X}_n \leqslant e_2 \mid \overline{X}_m] = p_e$$

where p_e is specified by the trial's protocol.

We begin by assuming the observations on a single patient follow a multivariate normal distribution with unknown mean vector $\underline{\mu}$ and unknown variance covariance matrix Σ where

$$\underline{\mu} = \begin{bmatrix} \mu \\ \mu \\ \mu \\ \vdots \\ \mu \end{bmatrix}; \Sigma = \sigma^2 \begin{bmatrix} 1 & \rho & \rho & \rho & \ldots \\ \rho & 1 & \rho & \rho & \ldots \\ \rho & \rho & 1 & \rho & \ldots \\ & & \equiv & & \\ \rho & \rho & \rho & \ldots & 1 \end{bmatrix}.$$

Our plan is to identify the conditional probability distribution of $\overline{X}_n$ given the first m measurements have been obtained.

We first determine the joint distribution of the two tuple vector $(\overline{X}_n,\overline{X}_m)$ by noting that if a random variable $\underline{x}$ has a multivariate normal distribution with mean $\underline{\mu}$ and variance covariance matrix Σ, the distribution of a new vector p-tuple $A\underline{x}$ has the following probability distribution

$$A\underline{x} \sim MVN_p\,(A\underline{\mu},\ A\Sigma A')$$

where A is a $p \times n$ matrix of known constants and $A\Sigma A'$ is full rank. For our purposes, consider the following transformation

$$\underline{Y} = A\underline{x} = \begin{bmatrix} \frac{1}{n} & \frac{1}{n} & \frac{1}{n} & \frac{1}{n} & \frac{1}{n} & \frac{1}{n} & \frac{1}{n} & \cdots & \frac{1}{n} \\ \frac{1}{m} & \frac{1}{m} & \frac{1}{m} & \frac{1}{m} & \cdots & \frac{1}{m} & 0 & \cdots & 0 \end{bmatrix} \begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \\ \vdots \\ x_m \\ \vdots \\ x_n \end{bmatrix} = \begin{bmatrix} \overline{x_n} \\ \overline{x_m} \end{bmatrix}$$

where A is a $2 \times n$ matrix premultiplying the n-tuple vector of observations for each patient. The evaluation of the expressions $A\underline{\mu}$ and $A\Sigma A'$ yield the mean and variance of the joint distribution of $\overline{X}_n$ and $\overline{X}_m$. Since each original measurement has the same mean, $A\underline{\mu}_n = \underline{\mu}_{2\times 1}$ where $\underline{\mu}_{2\times 1}$ is a two by one vector with each scalar element = μ. A direct computation shows that $A\Sigma A'$ is the 2 by 2 matrix

$$A\Sigma A' = \begin{bmatrix} \frac{(n-1)\rho + 1}{n} & \frac{(n-1)\rho + 1}{n} \\ \frac{(n-1)\rho + 1}{n} & \frac{(m-1)\rho + 1}{m} \end{bmatrix} \sigma^2.$$

To find the conditional distribution of $\overline{X}_n$ given $\overline{X}_m$, we invoke the result from Anderson [3, p. 26] to determine that the conditional distribution of $\overline{X}_n$ given $\overline{X}_m$ is normal with mean μ_p and variance v_p. Defining $\Sigma^* = A\Sigma A'$ we obtain

$$\mu_p = \underline{\mu}_1 + \Sigma^*_{12}\Sigma^{R\text{-}1}_{22}(\underline{y}_2 - \underline{\mu}_2)$$

$$v_p = \left[\Sigma^*_{11} - \Sigma^*_{12}\Sigma^{*-1}_{22}\Sigma^*_{21}\right] \tag{1}$$

where

$$\Sigma^*_{11} = \Sigma^*_{12} = \Sigma^*_{21} = \frac{1 + (n-1)\rho}{n};\quad \Sigma^*_{22} = \frac{1 + (m-1)\rho}{m}.$$

Thus we find

$$\mu_p = \mu_1 + \frac{m}{n}\left[\frac{1 + (n-1)\rho}{1 + (m-1)\rho}\right](\underline{y}_2 - \mu_2)$$

and

$$v_p = \frac{1 + (n-1)\rho}{n}\left[1 - \frac{m}{n}\left(\frac{1 + (n-1)\rho}{1 + (m-1)\rho}\right)\right]\sigma^2.$$

Here, μ_1 is the mean of the n measurements, μ_2 is the mean of the m measurements, and $\underline{y}_2$ is the $m \times 1$ vector containing the first m measurements. The probability that $\overline{X}_n$ will be an eligible average given $\overline{X}_m$ is therefore

$$P\left[e_1 \leq \overline{X}_n \leq e_2 \mid \overline{X}_m\right] = \Phi_z\left[\frac{e_2 - \mu_p}{\sqrt{v_p}}\right] - \Phi_z\left[\frac{e_1 - \mu_p}{\sqrt{v_p}}\right] \quad (2)$$

where μ_p and v_p are estimated from the available data and $\Phi_z(z)$ is the cumulative distribution function of the standard normal distribution. If the probability of an eligible average p_e is chosen by the investigators, then Eq. (2) is used to compute the values of μ_p and v_p and then the critical values of $\overline{X}_m$.

RESULTS

The design of the CARE trial [2] has been described previously. The Cholesterol and Recurrent Events Trial (CARE) is a multicenter, randomized, double blind, placebo controlled clinical trial designed to assess the efficacy of the HmG CoA reductase inhibitor pravastatin in reducing fatal coronary heart disease and nonfatal myocardial infarction (MI). Patients who survived an MI (3–20 months prior to randomization), had a plasma total cholesterol < 240 mg/dl, low-density cholesterol of 115 to 174 mg/dl, and triglycerides < 350 mg/dl were eligible for the trial. From December 1989 through December 1991, 4159 men and women between 21 and 75 years of age were randomized to the study from 80 centers in North America. Patients were randomized to either active drug therapy or placebo. Active therapy consisted of pravastatin 40 mg/day, designed to achieve an average decrease in LDL cholesterol of approximately 30%, and an increase in high-density lipoprotein (HDL) cholesterol of 5%. At the trial's conclusion, the average duration of follow-up was 5 years.

Example 1. Eligibility Screening for a Clinical Trial

Each clinical center performed careful screening to assess subject eligibility for CARE. After a patient had been identified as having had an MI within the specified postinfarction time frame, hospital records were scrutinized for the inclusion and exclusion criteria stated in the protocol. Both the patient and the patient's private physician were contacted; the CARE protocol was explained and participation was invited. If the patient was willing and the private physician expressed support, an appointment was made for the patient to visit the clinic for further screening.

QUALIFYING VISITS

Baseline lipids were defined as the average of two measurements taken within a prescribed period of time. The first measurement was performed during a clinic visit occurring at least 8 weeks posthospitalization for the qualifying MI. At this first qualifying visit (QV1), the patient's index MI documentation was sent to a core MI confirmation center to verify its status as a qualifying MI, the patient was started and stabilized on a Phase I lipid reduction diet, and the first screening measurement of LDL cholesterol was obtained. At the second qualifying visit (QV2), which occurred between 7 and 31 days after QV1, a second blood sample was obtained.

Table 1 Descriptive Statistics for Lipid Values in CARE Screened Population (June 1990; 1610 Patients)

	Screening Visit 1		Screening Visit 2		
Variable	Mean (mg/dl)	SD	Mean (mg/dl)	SD	Correlation
LDL Cholesterol	137.3	29.4	135.8	29.3	0.79
Total Cholesterol	212.1	34.1	210.0	33.4	0.82
Triglycerides	180.6	122.6	178.9	122.7	0.81

During this screening process, the trial leadership noted the costs to both the patient and the clinical centers incurred by following patients through QV2 only to discover the patient had ineligible lipid values, Interest centered on removing patients early from the screening process if the QV1 measurement implied they were unlikely to have eligible lipid values. The decision rule for an individual patient with a QV1 LDL cholesterol measurement available is found by applying the above results of the Methods section for the case of $m = 1$ and $n = 2$ to find the estimate of the conditional mean from Equation (2). Equation (1) yields the conditional variance v_p:

$$v_p = \frac{\sigma^2}{4}(1 - \rho^2).$$

For the individual patient, the sample correlation coefficient estimated ρ, and the sample variance s^2 estimated σ^2. Thus, the probability that the mean of the two LDL's lies between 115 and 174 given the value of only the first LDL for the Ith patient follows from Equation (2)

$$p_e = P\left[115 \leq N(\mu_p(i), v_p(i)) \leq 175\right] = \Phi_z\left[\frac{175 - \mu_p(i)}{\sqrt{v_p(i)}}\right] - \Phi_z\left[\frac{115 - \mu_p(i)}{\sqrt{v_p(i)}}\right].$$

Data from the CARE database (Table 1) allows calculation of the probability of an eligible average based on the QV1 LDL. As the QV1 IDL increases, the probability of an eligible average rises then declines rapidly (Fig. 1). Table 2 displays the extreme percentile values for an eligible average. Because only 1% of patients with QV1 LDL cholesterol less than 91 mg/dl and only 1% of patients with QV1 LDL cholesterol at least as large as 205 mg/dl are expected to have eligible averages from QV1 and QV2 measurements, these patients can be excluded immediately after QV1. A similar evaluation of the decision rule was determined for total cholesterol and for serum triglyceride. This evaluation led to the recommendation that CARE centers discontinue screening for a patient for any of the following QV1 lipid measures: LDL cholesterol < 91 mg/dl or ≥ 205 mg/dl, total cholesterol ≥ 270 mg/dl, or triglyceride ≥ 460 mg/dl.

Implementation of this decision rule led to modest savings in the number of patients requiring complete screening. At the end of the recruitment process, 146 patients had been found to have QV1 lipid values too extreme and were excluded from further screening. In addition, 104 patients with a QV1 LDL cholesterol < 91 mg/dl nevertheless proceeded to the QV2 measurement. Of these 104 patients, two were found to have an eligible average LDL cholesterol.

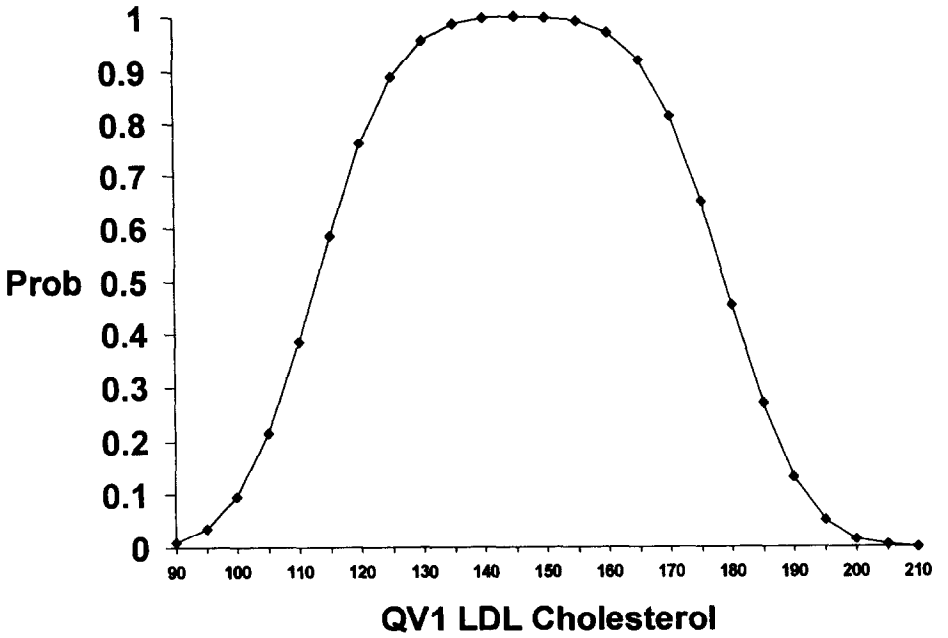

Figure 1 Probability of eligible LDL average based on QV1 LDL.

Of the original 1610 patients on whom the decision rule was modeled, 72 patients could have been eliminated from screening based on an extreme QV1 lipid value.

Example 2. Population Screening

The National Cholesterol Education Program (NCEP) recommends that the average of two LDL cholesterol measurements be used to determine whether LDL cholesterol is above 130 mg/dl, the threshold of lipid treatment for patients with coronary heart disease. We used the data from the CARE trial (Table 1) to compute the probability that a post-MI patient will have an average LDL cholesterol less than 130 mg/dl based on the first measure (Table 3). When this probability of an LDL cholesterol below 130 mg/dl based on the first LDL cholesterol is small (for example, < 0.05), we say we have identified the minimum LDL cholesterol value requiring lipid lowering intervention according to the NCEP guidelines. Table 3 suggests that a postinfarction patient with an LDL cholesterol greater than 146 mg/dl should be treated at once without waiting for a second LDL cholesterol value, since it is unlikely that the average of the two LDL cholesterol determinations will fall below the NCEP initiation point (LDL cholesterol < 130 mg/dl) range.

DISCUSSION

Inefficient screening procedures retain large numbers of ineligible patients in the recruitment process for a long period of time, inconveniencing the patient

Table 2 Extreme Lipid Values (mg/dl) at First Screening Visit and the Probability of an Eligible Average*

	Probability of an Eligible Average†									
Lipid Value	Lower Lipid Bound (Lower percentile Values)					Upper Lipid Bound (Upper Percentile Values)				
	0.010	0.025	0.050	0.075	0.100	0.900	0.925	0.950	0.975	0.990
LDL Cholesterol	90	94	98	99	101	194	195	197	201	205
Total Cholesterol	—‡	—	—	—	—	258	260	262	266	270
Triglyceride	—	—	—	—	—	420	427	435	449	461

*The recommendations to the CARE centers were to discontinue screening for a patient if the QV1 lipid measures satisfy any of the following conditions.

LDL cholesterol < 91 mg/dl

LDL cholesterol ⩾ 205 mg/dl

Total cholesterol ⩾ 270 mg/dl

Triglyceride ⩾ 460 mg/dl

†Eligible average for LDL cholesterol (115–174 mg/dl) total cholesterol (0–240 mg/dl), and triglyceride (0–350 mg/dl).

‡Since the CARE protocol specified no lower bound for total cholesterol and triglycerides, patients were only excluded from screening for these values if the total cholesterol or triglyceride was too high.

who eventually will not gain entry to the trial, and increasing the financial and logistical burden of the centers as they continue to work with patients who ultimately will be ineligible. We used an elementary application of normal distribution probability theory to construct a decision rule providing clinical trials with the ability to remove from the screening process patients unlikely to be eligible for the trial. The parameterization of the rule provides trialists with the ability to set the sensitivity and specificity of the decision rule, according to the trial's needs.

One potential shortcoming of the described procedure is its requirement of estimates of means, variances, and intrasubject correlations. The timing of

Table 3 Probability of an Average LDL Cholesterol Less than the NCEP Initialization Threshold* of 130 mg/dl Based on One LDL Measurement (parameter estimates from Table 1)

LDL Cholesterol on 1st Measurement	P[average LDL cholesterol < 130 mg/dl]
130	0.500
132	0.420
134	0.344
136	0.274
138	0.211
140	0.158
142	0.115
144	0.081
146	0.055
148	0.036
150	0.023
152	0.014
154	0.008

*The NCEP goal for LDL cholesterol is ⩽ 100 mg/dl.

these estimates is crucial. The earlier in the screening process the procedure is implemented, the less precise the estimates of the required parameters obtained from the screened population. Waiting until the screening estimates are more accurate provides greater precision for estimating the critical boundary values, but the centers labor to screen essentially unrandomizable patients during this delay. Some balance must be reached between the precision of the estimator and the needs of the clinical centers. The percentile extreme values identified for LDL cholesterol, total cholesterol, and triglyceride are functions of the QV1 and QV2 average values, the standard deviations, the correlation coefficient, and the critical boundaries e_1 and e_2. These critical boundary values will change as estimates of these quantities change. Equation (2) allows direct assessment of the stability of the extreme QV1 LDL cholesterol value at the lower boundary $b_L(k)$ and the upper boundary $b_u(k)$.

$$b_L(k) = LDL_1(k) + \frac{2}{r(k) + 1}\left(e_1 - LDL_a(k) - \sqrt{.25(1 - r(k)^2)s^2(k)}\ \Phi^{-1}(1 - p)\right)$$

$$b_U(k) = LDL_1(k) + \frac{2}{r(k)}\left(e_2 - LDL_a(k) - \sqrt{.25(1 - r(k)^2)s^2(k)}\ \Phi^{-1}(1 - p)\right)$$

Here, $LDL_1(k)$ is the LDL cholesterol based on the QV1 visit and $LDL_a(k)$ is the average of the QV1 and QV2 LDL cholesterols, $s^2(k)$ is the estimate of the variance of the screening visit measurements, $r(k)$ is the estimate of the correlation coefficient based on a sample of k patients. In this formula p is the percentile value of interest (the 1% percentile value in this case). Examination of this relationship revealed important variability in the 1% LDL percentile value, from 77 mg/dl to 100 mg/dl as the correlation was allowed to move from 0.70 to 0.90, the mean from 130 mg/dl to 140 mg/dl, and the standard deviation from 20 mg/dl to 40 mg/dl.

Acknowledging this sensitivity of the percentile values to sample estimates, we must assess the variability in these estimates that took place during CARE screening, since remarkable variability in these sample estimates would diminish the utility of this aid to screening in the early portion of the screening period. Table 4 shows the estimates of these parameters through the time course of screening. The actual variability over time resulted in little change in the 1% extreme LDL value (92 mg/dl to 94 mg/dl) when the lower bound of eligibility is 115. Thus, although the extreme percentile values are sensitive to changes in the parameter estimates, these parameter estimates can stabilize early in a clinical experiment. This may not be the case in every experiment, e.g., in the case where there are important changes in the characteristics of the screened patients as time progresses.

The exigencies of the trial led us to choose a screening sample of 1610. Postponing the implementation of a decision rule would have increased the difficulties of the clinical centers who were already in need of immediate relief from their screening labors. The application of rules such as ours potentially loses eligible patients by excluding patients whose lipid level at the first screening visit is < 91 mg/dl. The choices of the 1% percentile value will exclude an expected 1% of patients who would have had an eligible LDL cholesterol average. The decision made in CARE was to choose a value that would provide relief to the centers but minimize the impact on recruitment efforts. When the

Table 4 Variability in Sample Estimates over Time in CARE Screening and Its Effect on the 1% Percentile Extreme LDL Cholesterol Value mg/dl

Visit	Parameter	Sample Size and Parameter Estimates			
		$k = 500$	$k = 1000$	$k = 1500$	$k = 5000$
QV1 LDL	Mean	138.4	139.3	138.9	138.5
	SD	25.7	27.8	27.8	26.3
QV2 LDL	Mean	136.8	137.8	137.6	136.9
	SD	26.1	28.2	27.9	26.9
	Correlation	0.77	0.81	0.80	0.80
1% Extreme LDL Value		92	93	93	94

* The lower LDL cholesterol value at QV1 for which the probability of an eligible average is 0.01.

** The high LDL cholesterol value at QV1 for which the probability of an eligible average is 0.01.

decision rule based on QV1 lipids was implemented, 42 patients out of 1727 patients (2.4%) with QV1 LDL cholesterol values had LDL cholesterol less than 91 mg/dl. Using the 1% decision rule we would expect 0.024% of the sample of QV1 visits to be excluded incorrectly (i.e., have a QV1 LDL < 91 mg/dl and have an eligible average). Anticipating a total QV1 sample of approximately 6500 patients, we would expect two patients to be incorrectly excluded. The 5% extreme LDL value rule would lead to the exclusion of an estimated twenty patients with an eligible average.

Certainly the critical value of $\overline{X}_m$ depends on the desired probability of an eligible average p_e. Thus, choice of p_e must consider the trial's requirements, balancing recruitment needs with trial costs. Choosing a low value of p_e (e.g., $p_e = 0.25$) would remove from screening patients who have a 25% chance of achieving an eligible average. Although such a strategy would reduce the centers' workloads since these patients would be removed early in the screening process, it would adversely affect he recruitment effort. Thus, the clinical trial workers must balance the need to minimize the unnecessary work and cost of the center (low value of p_e) with the need to speed recruitment (requiring a high value of p_e). The needs of CARE required adjusting the work of the centers while leaving the recruitment effort unencumbered. Thus, CARE selected a value of 0.99 for p_e.

An alternative approach would be to compute the relative frequency of he QV1 LDL cholesterol of patients who were randomized and of those who were excluded because of extreme LDL cholesterol average after all screening visits were completed. The difficulty with this approach is the paucity of data in the tails of these frequency distributions; this lack of data makes it difficult to generate a robust decision rule. The approach outlined here incorporates all of the data to aid in constructing a formal decision rule.

Example 2 suggests an implementation of this rule that would be very useful in population screening for elevated LDL cholesterols. The data on which the decision rule is constructed must be chosen with care and with great attention provided for the population to which the decision rule is applied. In this example, the data from a postinfarction clinical trial were used to predict thresholds for treatment of LDL cholesterol in the postinfarction population at large based on the NCEP guidelines. This same approach could conceivably be applied to blood pressure and other serial measurements whose values, if

extreme, require treatment, but where more than one measure is taken per patient in an attempt to consider the intrapatient variability.

The literature has recognized the issue of increasing screening efficiency in clinical trials. The criteria for determining the presence of a condition or disease after the results of a screening test in the literature have focused on predictive value probabilities. The probability that a person with a positive test for a disease or condition truly has that condition is the predictive value positive, and the probability that a person with a negative test truly is free of that condition is he predictive value negative. Decision rules based on these predictive value approaches have been studied in the setting of diagnostic tests for conditions such as pulmonary tuberculosis [4], urinary tract infections [5], and acute myocardial infarction [6]. Rosner and Polk [7] have developed a process termed "predictive value screening rule" to allow patients being screened for hypertension to be removed early in the screening process if the blood pressure indicates either hypertension or normotension, with continued screening of patients for whom the determination is uncertain. Rosner and Polk recognized the importance of both intrasubject and intersubject variability in the computation of these probabilities, identifying them through analysis of variance procedures for blood pressure measurements in each age, race, and sex stratum of interest. However, the events whose probabilities Rosner and Polk compute differ from those analyzed here. Each begins with consideration of a sequence of screening visits. The predictive value approach computes the probability that the average of the m measurements obtained on the patient thus far fall in the interval of interest. The work described in the present article computes the probability that the future average (i.e., the average obtained not just from the m measurements obtained thus far, but from the entire set of n measurements) lies in an interval based on the m measurements available. In addition, the method of Rosner and Polk uses the prevalence in the underlying population to compute this conditional predictive probability, while the work developed here relies only on the data obtained in the screening sample considered for entry to the clinical trial.

Recent work on the variability of lipid measures [8,9] has emphasized the necessity of including this component in any model attempting to predict lipid measurements. Some investigations have combined prior or population information with conditional information (information for the particular patients) to construct a posterior distribution of cholesterol levels [10]. The results presented in this work could generalize further by incorporating information from each of the variables measured during the screening process to estimate the likelihood of an eligible average for one of the variables. For example, one could compute the probability that a patient will have an eligible average for LDL given not just the patient's QV1 LDL but also the QV1 total cholesterol and QV1 triglyceride values as well. Although this was not attempted during the screening period of CARE, it may led to a rule with improved performance if the correlations between LDL cholesterol, total cholesterol, and triglycerides are not small.

The assumption of equality of the correlation between measurements over time warrants close examination. This compound symmetry is most reasonable when the time between the first and last measurements is short. The greater the intermeasurement time, the less correlated we might expect them to be. In

clinical trials characterized with short screening periods for each patient, the assumption is reasonable. If the screening process is such that the compound symmetry assumption is untenable, the derivation of the decision rule requires only the the correlation matrix for $x_1, x_2, x_3, , , x_n$ have the correct form for the modeled screening process.

Screening processes in clinical trials are sometimes complex, and in their complexity lose efficiency. The multivariate analysis procedures presented in this article demonstrate a monitoring procedure for the early identification of ineligible patients.

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