

A. Specific Aims

The primary aim of this competitive renewal is to implement and evaluate the effects of a systems-based nutritional intervention program for the patients of primary care internists on dietary intake of saturated fatty acids (SFA) and on serum low density lipoprotein cholesterol levels (LDL-C). In this two-condition randomized clinical trial, the Intervention condition will be the systems-based intervention added to our previously developed and found-to-be-efficacious physician-delivered nutrition intervention training and office support program, which will be the Control condition in this study. The patient (pt) is the unit of randomization and analysis.

The study population will consist of primary care internists and 1200 of their pts with serum LDL-C levels in the highest quartile. The study will be conducted in the primary care practices of the University of Massachusetts Medical Center (UMMC). The Systems-Based Lipid Management Program (SBLMP) to be delivered to pts in the Intervention condition (Cond II) is implemented and coordinated by a Registered Dietitian Lipid Management Counselor (DLMC), who will utilize an innovative tracking system using a Lotus Notes “groupware” interface to track pt attainment of NCEP goals and to schedule indicated lipid tests and group nutrition intervention (GNI) program referrals, and to provide telephone-based behavioral counseling to support and extend the efforts of the physician. The GNI program will be similar to that used in our previous study, and will be made available to both study conditions. However, only condition II pts will be automatically referred and reinforced by the DLMC. Condition II pts also will be provided with other support materials (videotapes, audiotapes and monthly newsletters).

The underlying concept is the creation of a cost-effective program that builds on and reinforces the physician’s initial intervention, in a programmed manner, so that the care paradigm shifts to a situation where the physician must take a positive step to stop an action such as referral to the GNI, as opposed to the usual situation where the physician must take the step to initiate such an action.

The proposed study will extend the findings of the Worcester-Area Trial for Counseling in Hyperlipidemia (WATCH; RO1-HL44492), in which we found that a “patient-centered” physician-delivered counseling intervention, accompanied by an office support program, resulted at one year of follow-up in significant beneficial changes in pts’ diet, weight, and blood lipid levels, (1) and that an efficient dietitian-based GNI program, when utilized, adds substantially to this effect (see appendix C) (2). Unlike WATCH, however, because this study investigates the effect of a system that is transparent to the physician, it can be randomized at the level of the individual.

The primary outcomes which will be evaluated are the following:

1. changes in pts' consumption of SFA, and;
2. changes in pts' serum LDL-C levels

Products of the study will include the following:

- A tested model of a physician-delivered, systems-augmented intervention program that integrates physician intervention and multiple non-physician components to assist pts in the upper quartile of the LDL-C distribution to change their eating patterns and lower their LDL-C levels. This model will be packaged in an implementation manual for use in other large healthcare settings, and will include software and communications components to facilitate transportability to non-academic settings (see appendix N for an example of such a manual produced for the Physician-Delivered Smoking Intervention Project).
- An assessment of the cost and cost-effectiveness of this model and of the control intervention.

B. Background & Significance

Serum cholesterol and LDL-C are causally related to the development and progression of coronary heart disease (CHD), and alteration of lipoprotein levels can modify the clinical course of CHD. The evidence comes from epidemiologic investigations; (3-6) animal studies; (3, 7-9) studies of pts post-coronary artery bypass surgery; (10) and from a series of intervention studies in pts who are either at increased risk for or have had a coronary event, showing a diminution in myocardial infarction, CHD death, repeat hospitalization, and need for bypass surgery or coronary angioplasty with cholesterol reduction. (11-13) Studies have shown both slowing of progression and actual regression of CHD with both drug and diet therapy. (14-19) A recent review by Gaziano and colleagues of the benefits and risks of cholesterol lowering concluded that “nonpharmacologic interventions for about 30% of U.S. adults . . . seem both justified and warranted.” (20)

Based on the accumulated evidence, the National Cholesterol Education Program (NCEP) promulgated guidelines for lipid screening and treatment. (21) Initial lipid classification should be by total blood cholesterol and high-density cholesterol (HDL-C) measurement in all adults over 20 years of age. Levels of total cholesterol ≥ 240 mg/dl and above are classified as “high blood cholesterol”. The level of 240 mg/dl is approximately the 75th percentile value for the total adult U.S. population. A low level of HDL-C is recognized as an important risk factor. Further classification is based on lipoprotein analysis, with further therapy then based on

LDL-cholesterol levels. Dietary therapy is the cornerstone of intervention. A series of guidelines guide the clinician to further dietary intervention, retesting, and pharmacologic therapy if needed (appendix E).

The Healthy People 2000 guidelines discuss the relationship between nutrition and disease, and list “marked improvement in accessibility of nutrition information and education for the general public” as one of the “cornerstones” needed for the achievement of the year 2000 objectives. (22) They also note that “To increase the likelihood of behavior change, nutritional education programs should incorporate the principles and techniques of behavior modification”.

B.1. Importance of the Primary Care Setting, and physician interest in and use of the NCEP guidelines

Helping individuals to lower dietary fat intake is one of the greatest challenges facing medical and public healthcare providers today. This, coupled with the fact that 80% of all adults in the United States have at least one contact per year with a physician, (23) leads us to conclude that the physician and the medical system have great potential importance in education and counseling for elevated lipids. Four basic attributes of primary care: 1) first contact and easy access; 2) continuity; 3) comprehensiveness; and 4) integration and coordination; make the primary care setting the ideal location for screening and brief intervention. (24, 25)

Since the initiation of the NCEP in 1986 there has been a progressive increase both in physician interest in the therapy of hyperlipidemia and in adherence to the NCEP practice guidelines. Thus the physician-described median ranges of serum cholesterol for initiating dietary treatment fell from 240 to 259 mg/dl in 1986 to 200 to 219 mg/dl in 1990. (26, 27) In both years, however, only half of the physicians described themselves as “prepared” to provide diet counseling, and only 15% in both years thought of themselves as “successful” in helping pts achieve such dietary changes. In the 1986 survey, three-fourths of physicians noted the time required for counseling and two-thirds noted lack of staff with nutrition training as impediments to successful diet therapy in their practices. (26) By 1990 over 90% of physicians reported awareness and use of the NCEP guidelines. (27) Despite this, studies in which the primary intervention was the provision of information, even when accompanied by a program of physician reminders and prompts, have not demonstrated efficacy. (28, 29)

B.2. Physician-delivered nutrition intervention: Recent efficacy studies

Several recent studies have been designed specifically to evaluate differing nonacademic practice models for the detection, evaluation, and treatment of elevated blood cholesterol levels. (30) To date, these have reported only modest success. Caggiula and colleagues evaluated office-assisted (education of physicians about the NCEP guidelines and the provision of materials) and nutrition referral center interventions in a selected group of interested physician practices.(31) As compared to a historical control group, at a short follow-up time of 60 days the office-assisted model had a mean serum cholesterol reduction of 6.7 mg/dl in non-medication users. The nutrition referral center model in which patients were referred for individual and group counseling had a greater change (-15.6 mg/dl) but 42% of pts in this condition did not accept referral and were not included in the analysis. No dietary change data were reported. Beresford and colleagues evaluated dietary change in 28 primary care physician practices utilizing physician delivery of a 3-minute “motivational message” and a self-help booklet. At 12 months of follow-up there was a significant 1.2% decrease in reported intake of fat (% of energy). Saturated fat intake was not reported. There were no significant changes in either BMI or plasma cholesterol levels. (32) Our own WATCH study of physician-delivered pt-centered counseling plus an office support system is the only reported large, primary care-based study which thus far has demonstrated significant dietary, LDL-C and weight changes (see Section C.1.). (33)

B.3. Adjuncts to physician-delivered nutrition intervention

A team approach to lipid management and dietary intervention can make efficient use of physician time, and can enhance the physician’s effect on behavioral change. Such enhancement of effects has been demonstrated in smoking (34) and in diabetes control. (35) Both nutritionist-facilitated group dietary interventions and telephone counseling have demonstrated promise. In each, there is a need for close collaboration between physician and dietitian, and for a structured program that provides direction and allows evaluation of the results. (36)

Group intervention. Because they are less expensive to deliver than one-on-one interventions, group interventions have the potential to be very cost effective. Intervention groups are characterized by specific properties which facilitate change, including didactic instruction, instillation of hope, universality, altruism, interpersonal learning, group cohesiveness, and catharsis.(37) There is therefore a theoretical basis for believing that group interventions may be more effective than one-on-one counseling, especially when dealing with eating and food preparation behaviors, which are social activities. We are aware of no study in which such a comparison was investigated. There are no directly applicable studies available on the efficacy of group interventions to improve diet or reduce serum cholesterol levels in a primary care setting.

However, there are several studies, which, while they either were not conducted in a primary care setting (38-42) or were not primary prevention, (16) do provide support for the efficacy of group nutrition intervention.

A large randomized clinical trial, the Multiple Risk Factor Intervention Trial (MRFIT), employed both group (10 sessions) and individual counseling sessions in the special intervention (SI) condition as the format for teaching subjects (all males) and their spouses a low-fat, low-cholesterol eating pattern. At the end of the first year of intervention, about one-half of the study subjects were following the eating patterns at a good or excellent level (trained nutritionist assessment). (38) The MRFIT SI condition experienced an average cholesterol reduction of 7.5%, maintained for over 6 years. (39, 40) The MRFIT group intervention was complex, since it also dealt with smoking and hypertension. A worksite study also demonstrated a significant reduction of cholesterol in the Intervention condition provided an 8-week group intervention program compared to the Control condition. (41)

The Women's Health Trial (the feasibility study for the Women's Health Initiative (WHI)) - demonstrated that disease-free women attended group meetings and adhered to a low-fat diet for as long as two years. (42) In our own WHI program we have experienced excellent attendance at the groups (see C.2.5.). The landmark secondary intervention study of Ornish and colleagues demonstrated striking changes in dietary fat and LDL-C levels, but was a very intensive intervention and had a small sample size. (16)

Based on the available data and findings from our own studies summarized in section C, we conclude that the challenges of group interventions to effect reductions in serum cholesterol center around: 1. increasing the rate of referral to groups; 2. increasing the acceptance and attendance rates among those referred; and 3. improving the efficacy of the intervention with respect to lowering dietary SFA and serum LDL-C levels. Methods for achieving these aims are described in section D.

Telephone counseling (TC). TC has been used for recruitment, delivery of interventions, and enhancement of adherence to diagnostic tests and treatment interventions. TC can be an effective mechanism for simultaneously addressing the interplay of educational, psychosocial and practical barriers to adherence (43).

Little information is available on the use of TC as part of nutrition interventions. In a secondary prevention study carried out by DeBusk and colleagues, TC by nurses was effective in reducing SFA intake and serum LDL-C at 1-year follow-up, but the diet change was no greater than in the control condition, and the LDL reduction was primarily attributable to the far greater use of lipid-lowering medication in the intervention condition. (44).

In a recent study seeking to improve the dietary self-care of diabetics, (35) pts received TC calls 1 and 3 weeks following their physician visit in combination with immediate computer-generated feedback, a 20-minute meeting with an intervention staff member, a copy of a mutually developed goal-setting/strategy worksheet, a self-help pamphlet with sections relevant to their goal highlighted, and videos aimed at enhancing self-efficacy. This brief intervention resulted in significant differences in cholesterol levels at 3 mo. follow-up.

There is substantial information on TC for smoking intervention. We demonstrated the efficacy of a TC protocol when used to counsel smokers with CHD in a randomized clinical trial. (45, 46) In a study of a physician-delivered smoking cessation intervention in a primary care setting, there was a trend towards a significant effect for TC. (47) Orleans and colleagues (48) found that TC intervention increased the use of self-help materials, and yielded significantly higher short- and long-term cessation rates. Likewise, in a study by Lando and colleagues (49) the use of 2 TC calls (averaging <15 min. each) led to significant differences in validated six-month cessation rates.

A recent meta-analysis of TC for smoking cessation also supports the effectiveness of counseling calls both at short- and long-term follow-up. (50) In one cited study there was a dose-response effect, with six calls significantly more effective than one call, which in turn was more effective than written materials. TC calls have been well-received in a number of studies (51, 52) including our own, where only 10% of cardiac patients who smoked refused TC. (45, 47).

Since TC calls have demonstrated efficacy in smoking with some support for their use in diet, we have elected to use TC as a major adjunct for physician-delivered nutrition intervention. TC will incorporate our pt-centered counseling model which enhances pts' adherence and motivation to change and the likelihood that the pt's goals are realistic (see Section 8.4.1.). (53) The primary objective of TC will be to enhance motivation, help the pt develop and adhere to realistic goals and a plan for change, (54) and facilitate the mobilization of a coping response when needed. Relapse prevention steps will be negotiated and practiced during the calls. Such relapse prevention strategies have shown effectiveness. (55)

C. Preliminary Studies

C.1. The Worcester-Area Trial for Counseling in Hyperlipidemia (WATCH) (RO1-HL44492) (1, 33)

The present proposal is a continuation of our successful WATCH project. The WATCH was designed to evaluate the effectiveness of a training program for physician-delivered nutrition counseling, alone and in combination with an office support program, on dietary fat intake and serum LDL-C levels in pts with hyperlipidemia. Forty-five primary care internists at the Fallon Clinic, a central Massachusetts health

maintenance organization (HMO), were randomized by site into 3 conditions: (I) Usual Care; (II) Physician nutrition counseling training; and (III) Physician nutrition counseling training plus an office support program. Twelve hundred and seventy-eight pts (85% of our design goal of 1500) with serum LDL-C levels in the highest 25th percentile, having previously-scheduled physician visits, were recruited into the study. The physician nutrition counseling training consisted of a 2½ hour group education/training program incorporating behavioral principles for brief, “patient-centered” counseling, and a 30-minute individual follow-up tutorial (see Section C.1.1.). The office support program consisted of a folder which was attached to the patient’s chart each time he/she saw the physician up through one year post-enrollment (see Section C.1.1.). Included in this folder were: 1) the patient’s most recent lipid levels, with a prompt indicating that the LDL-C level was in the highest quartile (if initial visit); 2) a self-administered brief Dietary Risk Assessment (DRA) form to be filled out in the waiting room by the pt before seeing the physician (see Section D.8.3.2. for description of DRA); 3) dietary goal sheets to be used with the pt; 4) a copy of our pt-centered counseling algorithm (see Appendix F); and 5) a copy of the NCEP initial and follow-up guidelines (Appendix E). As an adjunct to the physician-delivered counseling intervention, we designed a group nutrition intervention consisting of one 45-minute individual session, followed by two 2-hour group sessions, and then a second individual session (see Section C.1.1.). (2) Any WATCH pt given a dietitian referral, irrespective of physician condition, was provided this intervention.

C.1.1. Physician training: (56)

A training program was developed to teach general internists to perform a brief (7-10 minutes) “patient-centered” nutrition counseling intervention based on our efficacious pt-centered model for physician-delivered smoking intervention (47, 57-59), and to utilize the DRA tool adapted from Ammerman and colleagues. (60) Pt-centered counseling is grounded in social cognitive theory (61) and teaches the use of a sequence of 6 steps focused on eliciting information and feelings from pts to facilitate motivation and a positive self-efficacy and to help them develop dietary change goals (see Appendix F for Intervention algorithms and DRA and Appendix C for the training paper). The approach includes identification by the pt of personal benefits of change, past experience with dietary change, and skills and resources available to change diet.

Physicians were taught that the WATCH modification of the NCEP guidelines recommends that pts in the highest 10th percentile for LDL-C receive both physician counseling and immediate referral to a dietitian, whereas the remaining pts in the upper quartile first should be given a trial of physician-based nutrition counseling alone. The guidelines recommend reevaluations at 4-6 weeks and at three months, with referral to nutrition services if physician counseling alone does not help the pt meet the goal as defined by the NCEP criteria. (21) As part of the training, providers are taught to do a follow-up intervention at return visits, which includes assessing accomplishments and readiness to change. Physicians are taught that change is a dynamic process which often spans several contacts.

The training occurred in 2 sessions, the first a 2.5 hour small group session and the second a 30-minute individualized tutorial carried out in the physician’s office by a simulated pt. The small group sessions included: a) a didactic component teaching the relationship of elevated serum lipid levels to CHD morbidity and mortality and the importance of modest reductions in LDL-C when viewed in a public health framework; b) viewing and discussion of a videotape that demonstrates the pt-centered dietary intervention; c) filling out a DRA and learning how to use it with pts; d) role-playing in triads with fellow internists; and e) a question and answer period. Physicians were provided with the algorithms for the initial and follow-up counseling interventions, a sample script, and a DRA. They were taught to scan the DRA forms and review them with the pt in order to identify problem eating practices and to develop nutrition change goals.

Physicians were assessed, before and after training, using questionnaires and audiotapes to document changes in knowledge about diet, attitudes about intervention, reported nutrition intervention practices, and counseling and assessment skills. After training, the physicians' use of dietary counseling steps, as assessed by blinded evaluation of audiotaped physician-pt interactions, increased significantly (mean pre=5.4, mean post=9.2; $p<0.001$). They also had increases in self-perceived preparedness, confidence in having an effect, perception that materials were available to aid intervention, and perception that they have access to a nutritionist. Thus physicians are responsive to the teaching of skills important for promoting health behavior change in their pts.

C.1.2. The effect of the intervention on physician counseling behavior. (62)

After the initial physician/pt encounter a random quarter of the pts in the study ($n=325$) were given a ten-item patient exit interview (PEI) assessing whether the physician provided advice; assessed past changes, barriers and resources; negotiated specific plans and goals; provided pt materials; referred the pt to a dietitian; and developed plans for follow-up. The PEI is a valid and reliable measure of which intervention steps physicians perform. (63) As measured by the PEI, condition III physicians implemented significantly more of the nutrition counseling sequence than did physicians in either of the other two conditions (PEI by condition

(max. = 10): I = 4.09; II = 4.05; III = 6.28 (P<.0001). Referrals to nutrition services were markedly reduced in condition II, despite their PEI scores being no different than in condition I (see C.1.4.). Higher PEI scores for pts seen by physicians in condition III were stable for as long as three years beyond training. We concluded that primary care internists, when provided with both training in counseling and a supportive office environment, will carry out pt counseling appropriately, but that training alone is not sufficient and may be counterproductive.

C.1.3. Primary Endpoint Measures:

The primary outcome measures, as analyzed at one year of follow-up using a general linear model, included change in percentage of calories from fat and saturated fat; body mass index (BMI) and weight; and blood LDL-C levels (table C.1.3.). Significant improvement was seen in all primary outcome measures, but was limited to pts in condition III. As compared to condition I, condition III pts had average reductions of 2.40 percentage points (an 8% decline) for calories from fat (p=0.04), and 1.25 percentage points for calories from saturated fat (12% decline) (p=0.02); and a loss of 6.3 lb. (1.01 kg/m²) (p<0.0001 for both weight and BMI).

As with diet and weight, compared with the control condition, condition III participants demonstrated significant reductions in blood lipid levels not seen in condition II. There was a 6.9 mg/dl decrease in LDL-C (p=0.05) (9.3 mg/dl excluding pts placed on cholesterol-lowering medication (p=0.009)). Fewer pts in condition III than in condition I were placed on cholesterol-lowering medication (10.7% vs. 13.0%, respectively). The decrease in total cholesterol matched the decrease in LDL-C – there were no significant changes in either triglyceride (TG) or HDL-C levels, so that the cholesterol/HDL ratio improved in condition III, again approaching significance (p=0.09).

The time spent by physicians in delivering the intervention was estimated using the PEIs. Physicians in condition III spent an average of 9.2 minutes discussing diet, as compared to 4.3 and 6.2 minutes, respectively, for physicians in conditions I and II. This corresponds closely to the 8-10 minute time period planned for in the training sessions. As these data reflect pt perception, it is possible that pts perceived the time spent as longer than it was. This is suggested by their perception that the entire visit was some 40 minutes in length. If true, this time would have had to have been made up elsewhere, as these were regularly scheduled 30-minute visits. However, we have previously shown that patients see physician counseling very positively, even when they do not plan to adhere to the advice given, and they may perceive the visit as longer than it actually is. (47)

We concluded that brief patient-centered physician nutrition counseling training can produce beneficial changes in diet, weight and blood lipids, but only if combined with a supportive office environment.

Table C.1.3.: Change in serum lipoproteins and dietary variables (n = 929)

| Variable | Change score† | SE | 95% Confidence Interval | P |
|-------------------------------|---------------|------|-------------------------|---------------|
| <u>LDL-cholesterol</u> | | | | |
| I No training-no support | 0 | | | |
| II Training-no support | -2.9 | 4.4 | (-11.5, 5.8) | 0.52 |
| III Training with support | -6.9 | 3.4 | (-13.6, -0.2) | 0.05 |
| <u>Total cholesterol</u> | | | | |
| I No training-no support | 0 | | | |
| II Training-no support | -1.7 | 4.9 | (-11.3, 8.0) | 0.73 |
| III Training with support | -6.6 | 3.8 | (-14.0, 0.9) | 0.08 |
| <u>Weight</u> | | | | |
| I No training-no support | 0 | | | |
| II Training-no support | -1.16 | 1.96 | (-4.99, 2.68) | 0.55 |
| III Training with support | -6.28 | 1.55 | (-9.32, -3.23) | 0.0001 |
| <u>Fat (% kcal)</u> | | | | |
| I No training-no support | 0 | | | |
| II Training-no support | -0.24 | 1.35 | (-2.88, 2.41) | 0.86 |
| III Training with support | -2.40 | 1.16 | (-4.68, -0.13) | 0.04 |
| <u>Saturated Fat (% kcal)</u> | | | | |
| I No training-no support | 0 | | | |
| II Training-no support | -0.68 | 0.62 | (-1.89, 0.53) | 0.27 |
| III Training with support | -1.25 | 0.53 | (-2.29, -0.21) | 0.02 |

* controlling for age, gender, education, cholesterol medication use and participation in nutrition counseling classes

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† parameter estimates from the GLM model

We also found a strong and important inverse interaction between the successful condition III intervention and the patient's educational level. Patients with a college degree showed the least benefit from the intervention, whereas those with no more than a high school education showed a much greater effect. (table

C.1.4.)

Table C.1.4.: Baseline values and change at one year by educational level; condition III patients

| Educational level | LDL-C (mg/dl) | | %calories from fat | | %calories saturated fat | |
|-----------------------------|---------------|--------|--------------------|--------|-------------------------|--------|
| | Baseline | Change | Baseline | Change | Baseline | Change |
| high school or less (n=293) | 172.1 | -21.1 | 31.2 | -2.6 | 10.8 | -1.4 |
| Some college (n=336) | 168.7 | -17.5 | 31.6 | 0.8 | 11.1 | 0.5 |
| college grad (n=224) | 162.9 | -10.1 | 30.5 | 1.8 | 10.5 | 0.8 |

The college graduates had lower baseline levels of fat and SFA intake, and lower LDL-C levels, despite being in the highest 25%. They also exercised more and were leaner. Given that they had elevated LDL-C levels, the more educated patients may have a greater genetic component to their cholesterol elevation. More educated patients also may have already had considerable exposure to lifestyle-improvement messages from peers and from the media, whereas this might not be so for the less-educated. The finding that a counseling intervention may have its greatest impact on those who are less educated is important because there is an inverse relationship between CHD incidence and education, and previous studies have demonstrated that pts with low levels of education are less likely to change. (40) However, the Community Intervention Trial for Heavy Smokers (COMMIT) also showed an inverse relationship between education level and smoking cessation. (64)

C.1.4. WATCH Group Nutrition Intervention (GNI) Outcomes

The GNI included one 45 minute individual session followed by two 2-hour group sessions, followed by another 45 minute individual session. Pts attending at least 3 of the 4 sessions had statistically significant improvements in diet, weight, and serum LDL-C levels that were larger than and additive to those of the condition III physician effect. There was no interaction between the physician and GNI components. For these analyses, we used dietary data from the Seven Day Diet Recall (7DDR) developed specifically for the WATCH, (2) (see C.1.7. and app. I) which allows for estimation of diet at the level of the individual (as opposed to the single 24HR which suffices only for group-level analyses). For pts who attended ≥ 3 sessions, there were reductions of 7.50% of kcal as fat ($p < 0.0001$), and 2.45% of kcal as SFA ($p < 0.0001$). These pts also lost an average of 7.4 lbs. ($p < 0.001$), with equivalent changes in BMI (-1.16 kg/m^2 , $p = 0.001$). There were large reductions in LDL-C (-15.43 mg/dl , $p < 0.0001$) and total cholesterol (-15.50 mg/dl , $p = 0.002$). 7DDR-derived estimates of change in consumption of fatty acids, when fit to the Keys and Hegsted equations (65), predicted the change in serum cholesterol within 15% and 10%, respectively, of the observed value.

The large effect of the WATCH GNI was evident only in individuals who attended at least 3 of the 4 sessions. It is not clear whether this relates to some characteristic of the group sessions, (e.g., factors inherent to group dynamics around making dietary change), is a function of total “dose” of intervention, or whether attendance at multiple classes is a marker for pt motivation. It is notable that only 155 participants overall (12%) were referred. Of these, 62% attended at least one session and 42% attended ≥ 3 sessions. The referral rates varied markedly by condition: I=19.5%; II=5.8%; III=12.1%. Attendance rates (≥ 3 sessions) were similar: I=43.5%; II=34.6%; III=43.1%. The especially low rate of referral of pts in condition II, the group comprised of trained but unsupported physicians, suggests that training without support may be counterproductive.

C.1.5. Discussion of the WATCH Results

The strength of the WATCH findings lies in their consistency: it is only physicians in condition III who carry out the counseling algorithm, and it is only the pts in condition III who demonstrate significant reductions in dietary intake of fat and SFA, weight, and LDL-C levels. These effects were seen with a minimal intervention effort. The initial intervention was fit into an already-scheduled visit in a busy HMO practice, and as measured by the PEIs, physicians spent an average of only 6 extra minutes discussing diet. The number of physician visits was only marginally higher in condition III (mean 3.4, 3.1, 3.6 for conditions I, II, and III respectively, $p = 0.08$), and the number of lipid measurements ordered by the physicians over the course of a year, although significantly higher in condition III, was suboptimal (mean 1.5, 1.6, 2.1 for conditions I, II, and III respectively, $p < 0.0001$)

The lipid outcomes, although significant, may seem modest, especially when compared with the results of recent studies involving pharmacologic intervention. (11-13) The findings, however, must be placed in context. WATCH was a primary care study involving a low-cost, minimal-effort counseling intervention. To achieve a 12% reduction in calories from saturated fat and a 5.5% reduction in LDL-cholesterol levels in pts not placed on pharmacologic therapy, maintained one year out from the intervention, is clearly worthwhile. Such an LDL change, if maintained, should lead to a 10% reduction in coronary event rates. (66)

It is especially important to understand that the present primary care proposal, building on and extending these results, is oriented toward the quarter of the population defined by the NCEP as warranting treatment of elevated lipid levels. These individuals do not have known CHD. No one has ever suggested that it would be

appropriate to treat such a large primary care population with pharmacologic therapy. Pedersen, the principal investigator of the landmark Scandinavian Simvastatin Survival Study, stated last year that "...this therapy is too expensive for use in a mass strategy to prevent coronary heart disease. Therefore, it should be limited to patients with a high risk". (67) A cost-effectiveness analysis carried out by Taylor et al (including our cost-effectiveness consultant, Dr. Shepard) also found that in a primary care setting nutritional counseling was likely to be cost-effective, whereas cholesterol lowering drugs, because of their high cost, were not cost-effective. Only the West of Scotland Study utilized pharmacologic therapy in a primary care setting, and this study was restricted to men over 45 years of age, with a mean plasma cholesterol level of 272 mg/dl, a level in the highest 10%. (11)

In reality, it is clear that at least half of the U.S. population is at risk for CHD, as the large majority of clinical CHD events occur in individuals with lipid levels within the "normal range." (13, 68) In the Framingham study the average levels of serum total cholesterol and LDL-C at which CHD events occurred in men were 225 mg/dl and 150 mg/dl, respectively, (69) numbers lower than the average levels among patients in our study. The corresponding numbers for women are 248 mg/dl and 164 mg/dl, respectively, higher than in men because of the older age at which clinical events occur in women, but still only modestly elevated. Even these numbers reflect lipid levels obtained in proximity to the event, as opposed to the lower levels present during the years of silent but progressive accumulation of atherosclerotic plaque. There is an important role, therefore, for nutritional intervention approaches, which by producing modest but important effects in large populations can be very cost effective. (70)

Physician participation in the training program was close to 100%, and we have shown that the use of the counseling skills demonstrated in condition III persisted for as long as 3 years following training. (62) It is clear, however, that when dealing with a low-acuity preventive intervention in a busy practice setting, a properly configured office support system is necessary to cue the physician and provide him or her with the materials needed to carry out the appropriate intervention. This has implications for continuing medical education programs and other forms of physician training, which rarely consider the entire intervention delivery system.

The program was low-cost. Other than 3 hours of physician time for training, the only operational cost involved was the time required to identify pts with elevated lipids (a function that can be computer-automated), place appropriate materials on their charts, and give the dietary risk assessment form to the pt. In a preliminary analysis of the WATCH data we have found that the effect of larger numbers of patients in the control condition being placed on lipid-lowering drugs (avg. Fallon Clinic cost \$2.00/pt/day) outweighed the operational costs of the intervention resulting in a net savings of \$11.08/pt, or -\$1.70 for each 1 mg/dl decrease in LDL-C/pt.

The American College of Physicians has raised concerns that increased screening in primary care will lead to increased and inappropriate use of cholesterol-lowering medication, and has recommended cholesterol screening guidelines that limit screening in young, elderly, and low-risk pts. (71, 72) We found no evidence of such an effect; rather, medication use was highest in the control condition.

The physicians did not follow the recommendations of the NCEP for follow-up, scheduling few extra visits and lipid profiles. Furthermore, although Condition III physicians were far superior at exploring behavioral issues such as problems encountered making dietary change (13.0%, 13.0%, 37.6% respectively for Conditions I, II, and III) even in this condition such discussion occurred in only slightly more than 1/3 of initial study encounters. **This suggests that further improvements in nutrition intervention need to come at a systems level, with improved patient tracking systems; automatically scheduled telephone counseling follow-up by health counselors; and interventions such as nutrition class referral and repeat lipid measurements scheduled or strongly suggested by the clinical system itself. It is such a system that we propose to test.**

C.1.6. WATCH manuscripts

The WATCH project has been quite productive. At this point there are 8 papers published or in press, (56, 62, 73-78) and the final endpoint paper and nutrition endpoint papers are currently undergoing revision. (1, 2) Copies of the endpoint manuscripts and other relevant papers are in appendix C.

C.1.7. Development of the Seven Day Diet Recall (7DDR) (79)

The 7DDR is an instrument designed specifically to measure short-term change in dietary fat in intervention trials. Historical methods such as the food frequency questionnaire (FFQ), although asking the respondent to report on habitual intake over a reference period long enough to establish long-term exposure to some sets of nutrients, are influenced by current diet, (80) and by limitations due to the cognitive inability of individuals to compose estimates of habitual memory and do the arithmetic necessary to provide long-term estimates of average dietary intake. (81-84) The 7DDR relies less on habitual intake (approximately equal contributions of habitual and episodic memory over a one-week time period) and it asks the respondent to provide data in counts rather than in terms of average intake. By focusing on nutrients which tend to vary relatively little over moderate (e.g., week-long) periods of time, it is possible to obtain more accurate estimates of intake. In a manner similar to various FFQ validation studies (85-87) the 7DDR was validated cross-

sectionally in comparison to multiple 24 hour diet recalls (24HR) in 3 separate studies in a total of 261 subjects. We found high levels of concordance for total energy ($r=0.67$), total fat ($r=0.67$), and SFA ($r=0.68$) (see appendix C). (73, 79, 88, 89) Despite its focus on a shorter time period than the FFQ, variance estimates are smaller (79). Although developed as a research tool, the 7DDR has proven to be very useful clinically. It is acceptable to pts, easily filled out (requiring about 20 minutes), and is optically scanned. The output program lists the top 3 foods contributing to fat, saturated fat, and calories. We propose to use the 7DDR as part of the SBLMP (see appendix I for the 7DDR form and examples of the report).

C.2. Other relevant investigator experience

C.2.1. The Physician Delivered Smoking Intervention Project (PDSIP) (R01-CA38360) (J. Ockene - P.I.)

The pt-centered counseling methodology used in WATCH is based on a model developed by JK Ockene and colleagues at UMMC, and first utilized in PDSIP for smoking. (47, 57) PDSIP was a randomized clinical trial designed to assess the relative rates of long-term smoking cessation following 3 types of physician intervention: Advice, Counseling, and Counseling plus prescription of Nicorette gum; and as a secondary objective the development of a structured educational program for training residents to intervene effectively for smoking utilizing the pt-centered model (196/198 residents participated). Significant improvement in the residents' knowledge, attitudes and skills was demonstrated, and the counseling intervention also was shown to significantly improve smoking cessation rates. (47) The PDSIP counseling model has since been adapted for use with alcohol (90) as well as nutrition intervention, is taught to all our medical students and internal medicine and family practice residents, and has been widely adapted for use by other healthcare providers. (91) In PDSIP, TC was tested as an adjunct to physician intervention, using 3 TC calls implemented by health counselors. A favorable but not significant trend was demonstrated. Following PDSIP we improved on the TC protocol, as implemented in our CASIS study (see C.2.2.)

C.2.2. Coronary Artery Smoking Intervention Study (CASIS) (R01-HL35110) (J. Ockene - P.I.)

CASIS was a two-condition randomized clinical trial testing a special intervention (SI) (which was primarily pt-centered telephone counseling with an average of 4 calls; average cumulative duration 32.6 minutes) for smoking intervention with smokers with CHD. At 6 months there was a significant favorable effect on cessation rates ($p<.05$) in the SI group. (46) This study and PDSIP demonstrate our experience in developing TC protocols and training telephone counselors.

C.2.3. Project Health (NIAAA) (R01-AA09153) (J. Ockene - P.I.)

Project Health is a randomized clinical trial of intervention with high-risk or problem alcohol users seen in a primary care setting, with its primary outcome measured at 6 months. It tests whether an intervention package consisting of a brief (5-10 min), provider-delivered, pt-centered alcohol intervention in combination with an office support system is more efficacious in reducing alcohol use and number of episodes of high-risk drinking (binges), and in increasing the percentage of safe drinkers, than usual practice. Providers were randomized to Intervention or Usual Care. The development of a training program was successful (90) with significant improvement in post-training provider skill level, knowledge and attitudes. Trained and cued Project Health providers performed significantly more of the counseling steps (PEI score mean = 9.8) on the first visit than did Usual Care providers (PEI score mean = 1.7). As in WATCH, the PEI score did not diminish over 32 months post training. The self-reported 6-month usage of alcohol by the first 268 patients (data available to us as fully analyzable at the time of preparation of this proposal) in Project Health demonstrates a significant difference ($p=.04$) in the decrease from baseline to 6 months in average weekly alcohol usage and in the percentage of drinkers who were drinking at unsafe levels ($p<.01$) between the Intervention and Usual Care conditions.

C.2.4. BRIDGES (DAMD17-94-J-4475) (J. Hebert - P.I.)

In this study 178 women <65 years of age (99% of the goal of 180) with early-stage breast cancer (stage I or II) were randomized to usual supportive care (UC), to an intensive stress reduction course (SRC), or to a nutrition education program (NEP). Both the SRC and NEP consist of 15 (1 individual and 14 group) sessions. The model for the NEP stresses that a low-fat, whole-foods diet expands the world of choice and sensory experience rather than restricting it. Women report good adherence to the diet and enjoyment of the classes. Mean overall attendance was 11.1 (79%) of the 14 group sessions. Analyses of complete 4-month data from 107 of the women demonstrates a large reduction in dietary fat (7.25% of energy, $p<0.0001$) and body weight (1.59 kg, $p=0.02$) in the NEP, but no change in either the SRC or UC. In the proposed project we will incorporate elements of the NEP regarding group cooking and demonstration, adapted to a 4 session format.

C.2.5. Women's Health Initiative (WHI) (WH-93-30E) (J. Ockene - P.I.)

We are one of the sites of the WHI. This study has a large nutrition intervention component with 50 group nutrition sessions for disease-free, postmenopausal women in the dietary intervention (low-fat, high-fiber) trial arm, and contributes to our experience in counseling for nutrition change. Attendance at these classes is 90% through 4 sessions (comparable to the GNI in the present project), and remains over 75% through session 15.

C.2.6. Seasonal Variation of Blood Cholesterol Levels (“SEASONS”) (R01-HL52745) (I. Ockene - P.I.)

This presently-ongoing study is a direct outgrowth of WATCH, in which we observed significant variation of serum cholesterol levels by season (higher in Winter). We are investigating seasonal variation in dietary intake, physical activity, psychologic variables, and light exposure as well as blood lipids, antioxidant vitamins, and hemostatic factors. We also will explore the screening and therapeutic implications of our findings for physicians and for national guidelines. The study has reached 100% of its recruitment goal (600).

C.2.7. Energy Study (R01 DK52079-01) (J. Hebert, - P.I.)

This ongoing study examines response set biases in self-report of diet and physical activity in women. Using doubly labeled water as the criterion measure, it will employ a wide variety of dietary and physical activity measurements (including 24HR and the 7DDR used in this study) in 80 women aged 40-65 years.

D. Experimental Design and Methods

D.1. Overall Study Plan

We are proposing a 4½ year study in which 1200 pts of study physicians with LDL-C levels in the highest quartile will be randomized to one of two conditions, with 600 pts randomized per condition. All of the study physicians will receive identical training in pt-centered counseling for nutrition change; and will be provided with the office support program and referral access to the Group Nutrition Intervention program (GNI). Training and an office support program comprised the successful condition III intervention utilized in WATCH. In addition, pts in the Intervention condition will receive systems-based interventions interwoven with the physician intervention, to include a Systems-Based Lipid Management Program (SBLMP), and other support materials (videotapes, audiotapes, and monthly newsletters). A 3-month run-in phase, involving 200 pts (40, 60, and 100 in months 1-3, respectively), will allow testing and refinement of the program.

All pts will have baseline lipid profile measurements completed prior to their first physician visit. Physicians in both treatment conditions will be provided with the study-qualifying lipid profile results (see D.10.1.1.). The intervention components are illustrated in Table D.1. (see also Intervention Framework in appendix B). The evaluation will assess differences at one year in pt intake of SFA (% energy) and changes in serum LDL-C levels as the primary study endpoints, with change in total fat intake, body weight, and physician practices as secondary endpoints. We also will assess changes in physician knowledge and attitudes; and assess the cost and cost-effectiveness of the delivered intervention. Patient knowledge, attitudes and behaviors related to diet modification and other psychosocial and demographic variables also will be assessed.

Table D.1. - Components of Treatment Conditions

| Activity | Control (Cond I) | Intervention (Cond II) |
|---|------------------|------------------------|
| Physician counseling training | + | + |
| Office Support Program | + | + |
| Group nutrition intervention | MD initiated | MD or system initiated |
| Systems-Based Lipid Management Program | - | + |
| provision of: videotapes, audiotapes, newsletters | - | + |

D.2. Hypotheses

The primary goal of this study is to test the effect of a systems-based intervention for nutritional change, when added to a proven physician-delivered nutrition counseling intervention, on pt serum LDL-C levels and dietary SFA intake. Therefore our primary hypotheses are the following:

1. Mean serum LDL-C level will decrease significantly more from baseline levels to one-year follow-up in pts in condition II than for pts in condition I.
2. Mean intake of SFA (percent of total energy) will be significantly lower at one-year follow-up in condition II pts as compared to condition I pts.

Secondary hypotheses are the following:

1. Mean total fat intake (percent of total energy) will be significantly lower at one year of follow-up in condition II pts as compared to condition I pts.
2. Mean body weight will decline significantly more at one year in condition II pts than in condition I pts.
3. The number of intervention steps implemented by physicians during follow-up visits (as measured by PEIs) will be significantly greater for pts in condition II than for those in condition I.

D.3. Phases of the Investigation

There are six phases in the sequence of the investigation, as shown in table D.3.

Table D.3. – Study Timeline

| Phase | Months | Activity |
|-------|--------|---|
| I | 0-4 | hiring and training of staff, further development, refinement and pretesting of the protocols for RD & DLMP training, the SBLMP, and the intervention and evaluation materials |
| II | 5-7 | training of physicians in the patient-centered nutritional intervention, the RDs in the RD-implemented GNI, and the DLMPs in telephone counseling; development of the communication protocols, the databases, and the Lotus Notes interface |
| III | 8-10 | a three-month run-in phase designed to pretest the functioning of the entire trial design |
| IV | 11-34 | recruitment and follow-up for the study |
| V | 35-46 | follow-up only |
| VI | 47-54 | close-out, data analysis, manuscript preparation |

D.4. Study Site - The University of Massachusetts Medical Center (UMMC)

We will utilize the pts of 29 primary care internists at 2 practice sites of the UMMC. At these 2 sites, these practitioners follow some 27,000 adult pts, with 300 new pts being added each month. Other UMMC primary care sites also are available, but the volume of pts at the 2 sites chosen makes it unnecessary to use other locations. Volume is expected to continue to increase by 10-15% per year over the next several years. The two locations comprise the Benedict Building, the primary outpatient facility at the main UMMC campus, with 24 internists, and the Shrewsbury site, a satellite facility approximately 2.5 miles away, with 5 internists. Within the Benedict Center the physicians are divided into 4 “pods” that function as independent units, so that the size of physician work groups is equivalent at both sites. Follow-up appointments are made at the end of each visit, using a linked computerized appointment system. Laboratory facilities are available at each location.

We have changed from the original WATCH study location at the Fallon Clinic to UMMC. When WATCH began there was only a modest primary care presence at UMMC. Since then primary care at UMMC has grown remarkably, so that there are now 44 primary care internists in our network and adequate numbers of pts to carry out the proposed project successfully within our own institution. At the same time, growth at the Fallon Clinic has slowed with increased managed care competition. Recently the Fallon Clinic sold its hospital (St. Vincent’s) and an undisclosed share of the Clinic itself (it is a for-profit entity) to Orenda, a national for-profit managed care organization, and subsequent to this Orenda itself was purchased by Tenet, an even larger for-profit managed care organization. Given these factors, we elected to carry out the proposed project at UMMC.

D.4.1. Study physicians

There are no significant group differences between the physicians at the study sites. Of the 29 internists, 15 are male and 14 are female; 28 are board certified in internal medicine, one is board-eligible. The mean age of the internists is 39 years. Two are Asian minority. These physicians, although affiliated with an academic medical center, function little differently than the internists at the Fallon Clinic used in WATCH. Clinic time for a Fallon internist is 28 hours/week, for a UMass-Shrewsbury site internist 32 hours per week, and for internists at the UMass-Benedict Center 25 hours/week (allowing for 4 hours of teaching time and greater in-hospital responsibility). The UMass-Benedict MDs see approximately 60 patients/week; the corresponding figure for the Fallon internists in WATCH was 70/week. In fact, 65% of our pts are under managed care contracts, with some 20% of pts in capitated programs (half in a Fallon plan identical to that for the full-time Fallon physicians). Thus our physicians must meet the same time and efficiency demands as other primary care physicians, or we would not be competitive and experience the growth that is in fact occurring.

D.5. Rationale for Patient Population Chosen

We will study a primary care population. WATCH was a primary care study, and the present proposal builds directly on its results. Our major interest is in altering risk by delivering nutrition change brought about by a combination of practitioner counseling, office support, well-designed group nutritional interventions, and effective systems-based efforts that are synergistic with each other, and are designed to be cost-effective. For pts who already have clinical CHD the lipid-lowering goals are such as to require pharmacologic therapy for the majority. (44) In a primary-care population the opposite is true - pharmacologic therapy is not cost-effective, while nutrition-based interventions can affect very large numbers of pts at very low cost, and thus have the potential to reduce the population disease burden. (67, 92, 93)

D.5.1. Patient Eligibility and Exclusion Criteria

Included in this randomized controlled trial will be 1200 primary care pts, evenly randomized into the 2 conditions and blocked by gender, physician, and three 15-year age intervals (20-34, 35-54, 55-70).

A pt is eligible for this study if he/she meets the following criteria:

- 1) LDL-C in the highest 25th percentile
- 2) is between twenty and seventy years of age.

A pt will be excluded if he/she has any of the following characteristics:

1. an inability or unwillingness to give informed consent;
2. is presently or has within the prior two years been on specific pharmacologic therapy to lower lipid levels (e.g., resins, fibric acid derivatives, HMG-CoA reductase inhibitors, nicotinic acid);
3. has known coronary heart disease
4. has been referred to RDs within the prior two years for lipid-lowering intervention;
5. has a cholesterol level over 300 mg/dl, an LDL-C >200 mg/dl, or a triglyceride level >400 mg/dl;
6. has a secondary cause of hyperlipidemia (e.g., hypothyroidism, pregnancy);
7. plans to move out of the area within the study period;
8. has a psychiatric illness which limits ability to participate; or
9. has no telephone.

Pts with known CHD will be excluded to maintain the primary care paradigm of the study. Pts on drugs that can affect lipid levels (e.g., thiazide diuretics, hormone replacement agents) will not be excluded, provided that they have been on a stable dose of medication for at least 6 months. Such an exclusion would eliminate large numbers of older women from the study. Use of medications, however, will be tracked, and appropriately considered in the analysis phase.

D.5.2. Rationale for lipid exclusion criteria

We believe that pts with serum cholesterol levels >300 mg/dl or LDL-C >200 mg/dl are likely to require pharmacologic therapy, and that there will be considerable pressure on the physician to begin such therapy during the study period. We will now be using direct LDL-C measurement, and will be able to measure LDL-C in pts with TG>400 mg/dl (the upper limit for the usual clinical calculation of LDL-C). Nonetheless, we will still maintain the TG>400 exclusion, as patients with high TG levels have a disproportionate prevalence of metabolic disorders (e.g., poorly controlled diabetes, hypothyroidism) and the numbers of pts with high TGs will not be sufficient for subanalyses of this group. The direct LDL-C measurement will prevent the loss of pts in the analysis because of elevated TGs at the one-year measurement, as happened in WATCH (See D.10.1.1.).

D.6. Patient Recruitment

Pts who have appointments to be seen by the study physicians, have not been previously screened for the study, and are between the ages of 20 and 70, will be contacted by telephone. The medical center's computerized I.D.X. appointment system will identify age-eligible pts. Non-emergent pts are booked 4-8 weeks in advance, allowing ample time for recruitment prior to the physician visit. Initial eligibility will be assessed (no prior drug treatment or RD referral within the last 2 years), and the eligible pt will be invited to come in for an initial fingerstick cholesterol determination. (see D.10.1.1.) If this value is in the upper 30th percentile as determined from our own age, sex and seasonally adjusted data (62, 94) the pt will have an immediate repeat fingerstick which will be analyzed using the Cholestech lipid profile cassette. If the pt remains eligible (LDL-C in the upper 25th percentile; TG <400 mg/dl) full informed consent will be obtained by the research site coordinator and the pt will be randomized to one of the two study conditions. A venipuncture will be obtained for a baseline study lipid profile, and the pt will be given the baseline questionnaires to be filled out at home. One week later the pt will return for a second baseline study lipid profile. This design will allow us to recruit pts and obtain baseline bloods efficiently with only two visits, while keeping cost down (the lipid profile cassette is much more costly than the cholesterol-only cassette), minimizing regression to the mean, and maximizing recruitment (the 30% cut at the initial screen minimizes loss of pts with normal total cholesterol but low HDL-C and high LDL-C levels).

The internists see large numbers of pts, usually 60-70/week. A pool of some 1740 pts/wk (60x29) results in a potential population of 49 eligible pts/wk by the most conservative calculation (1740 x .25 (highest 25% LDL) x .8 (allowing for 20% refusals) x .85 (%pts age 20-70) ÷ 3.0 (avg. # visits/ yr/individual) x .5 (conservative estimate of those excluded for conditions listed in D.5.1.). Thus recruitment (12.5/wk) should not be limited by the number of available pts. However, the screening effort required to recruit the necessary number of pts is considerable. Based on our experience in WATCH (which was exactly in line with our projections) we estimate it will be necessary to do 7850 initial fingerstick cholesterol measurements to recruit 1200 subjects (15%). The projections are based on 25% of people being LDL-eligible, and additional losses related to regression towards

the mean and refusal to participate/no show on the 2nd visit). Some 10,000 telephone contacts (requiring 33,800 call attempts) will need to be made to result in 7850 initial cholesterol screens, allowing for loss from refusals, ineligible pts, and no-shows. We will utilize automatic dialing equipment to expedite this process. The study is screening-intensive, and we believe that a 24-month recruitment period is necessary to carry out such an effort.

D.7. Randomization

Because we are randomizing at the level of the individual, we will avoid some of the pt demographic imbalances that were seen in WATCH by blocking patients by age and gender within physician. Patients will be categorized by age (20-34, 35-54, 55-70) and gender into strata. Randomization will occur by order of entry into the age-gender-physician stratum, with the first patient randomly assigned to one of the conditions, and the subsequent patient in the stratum assigned the alternative condition. This pattern of condition assignment will continue as patients accrue. Assignment will be made using the random number generator in Lotus Notes.

D.8. Description of the Interventions and Methods of Patient Contact

D.8.1. Guiding Theories and Principles

Several theories and models of health behavior change and intervention, as well as what we have learned from WATCH, underlie the design and use of the pt-centered physician-delivered intervention, the telephone counseling model, and the GNI to be included. While a complete review of these theories and models is beyond the scope of this application, they are briefly mentioned here. The reader is referred to previous works by the investigators which discuss the theoretical underpinnings of the intervention strategies, with a particular focus on pt-centered counseling. (95-98) The pt-centered counseling model has its principles built mostly on Social Cognitive Theory (61, 99) with contributions from the Health Belief Model. (100) (see Section B). As with the Stages of Change Model, (101) it emphasizes the importance of understanding the pt's intentions and confidence relative to change in the target behavior in order to help move him/her forward in the change process. Stages of change theory reflects stages of dietary change – precontemplation, contemplation, ready for action, action, and maintenance. (101, 102) Providers are taught that because change occurs over several stages, they, by their persistent efforts, can be important resources in this process. Their assistance can move the precontemplator to contemplation and the contemplator to action. Physicians and pts need to be aware of and reminded of this process so that neither become discouraged or alienated from each other.

Important components of social cognitive theory reflected in pt-centered counseling include: the need for active participation by the pt in developing a plan for change, the importance of a positive self-efficacy (or confidence) to effect a specific change, and attention to the environment. (99, 103, 104) Pt-centered counseling emphasizes the use of past experiences of change to help the pt develop motivation and a positive self-efficacy.

The Relapse Prevention Model, (54, 105) in addition to social cognitive theory, figures prominently in the telephone counseling intervention. Relapse prevention training stresses the need to recognize cues and characteristics of high-risk situations (assessment skills) and to develop specific skills (e.g., communication, initiation of support, stress management) so as to mobilize a coping response to promote dietary change.

D.8.2. Treatment Conditions

Control (Condition I): This condition includes physician-delivered nutrition intervention training plus the office support program, in addition to the availability of the GNI program.

Intervention Condition (Condition II): includes the interventions in Condition I plus the Systems-Based Lipid Management Program (SBLMP) and other materials, as described below.

D.8.3. Interventions Common to Both Treatment Conditions (See Table D.1)

D.8.3.1. Physician-Delivered Pt-Centered Nutrition Counseling

Physician-delivered interventions need to be brief, occupying a small part of the outpatient encounter. (56, 57) The physician-delivered nutrition counseling intervention is designed to take the physician 7-10 minutes to implement, and uses the pt-centered counseling model emphasizing the use of questioning, provision of information, and eliciting of feelings related to six content areas: 1) desire and motivation to change dietary behavior; 2) experience with dietary change; 3) factors inhibiting dietary change (barriers); 4) resources for change (strengths); 5) plan for change; and 6) methods for dealing with factors that may interfere with the plan. The physician is also taught to provide information regarding the relationship of elevated lipids to CHD and of diet to elevated lipids; to paraphrase and feed back the information obtained from the pt to help him or her develop a plan for dietary change and for subsequent GNI visits if indicated; the importance of providing educational materials to pts; and the importance of follow-up for behavioral change. Thus, the intervention combines the use of questioning with the provision and feedback of relevant information and follow-up to assist the pt to make dietary changes necessary to reach the LDL-C goals. A pt-centered nutrition intervention counseling algorithm (and follow-up algorithm) was developed in WATCH (See Section C.1.1.) and is part of the packet affixed to each study pt's chart each time he/she is seen by the physician (see Section D.8.3.2.) (see

appendix F for algorithms).

D.8.3.1.1. Training of physicians to do patient-centered counseling.

All study physicians will be trained to perform pt-centered nutritional counseling and to use the DRA and dietary goal sheets with pts. Introducing the study and building adequate skills will take 3 hours, including a 2.5 hour group session (5-10 MDs), followed by a half-hour individual session conducted in their offices with a simulated pt (see Section C.1.1.) During the individual session physicians are provided with immediate feedback regarding their counseling skills, and have an opportunity to correct problems. The P.I., co-investigators, and project coordinator will conduct the training. These training sessions were well accepted in WATCH. The 2.5 hour group educational session will cover four subject areas:

1. Nutritional intervention for cholesterol lowering (including the NCEP guidelines).
2. Pt-centered counseling skills training.
3. Integrating RD (GNI) intervention into physician-delivered dietary intervention.
4. Use of pt nutrition education aids (i.e., DRA and dietary goal sheets) and other program materials.

The training package includes slides, videotape, role play exercises, handouts, and instruction for the use of the various materials (See appendix N for a single copy of a package of this type from the PDSIP project).

The half-hour individual training session will be completed in the physician's office within 2 weeks after the group session, with the physician delivering the nutrition counseling intervention to a simulated pt (a trained health educator/evaluator). The physician is given immediate feedback regarding his/her counseling skills. If the physician's level of skill is not adequate to do dietary counseling, the health educator/evaluator will request another individual session (This was available but did not occur in WATCH). In the unlikely event that a physician remains at an unsatisfactory level, we will nonetheless allow that physician to remain in the study.

D.8.3.1.2. NCEP Follow-up Guidelines.

During the training sessions the physicians will be introduced to the NCEP guidelines and their study-specific modifications. As in WATCH, we have chosen to have two intervention paths based on the pt's LDL-C level. For pts with LDL-C measurements in the upper decile, the guidelines will suggest initial physician intervention and immediate referral to the GNI. We believe that these pts have LDL-C levels that are unlikely to fall into the goal range (see NCEP guidelines, appendix E) with physician intervention only, and that a coordinated initial approach is appropriate. For pts in the 75th to 90th percentile, we will suggest initial physician intervention only as a cost-effective approach. The guidelines suggest that these pts be referred to the GNI at 3 months if they do not reach the goal LDL-C.

The NCEP guidelines may, in some pts, set a goal LDL-C that represents less than a 10% decrease (e.g., a pt with an LDL-C of 165 mg/dl and no other risk factors, for whom the goal is an LDL-C <160 mg/dl. As this study has a 5% difference in serum LDL-C between conditions I & II as one of its primary endpoints, the guidelines will suggest that a 10% reduction in LDL-C should be a minimum goal for all study pts.

D.8.3.2. Office Support Program.

All study physicians will have available the office support program utilized in WATCH, providing them with a packet each time they see a study pt through 12 months. It contains: 1) the pt's most recent lipid values (indicating the age/gender specific LDL-C percentiles and the NCEP LDL-C goal); 2) the DRA and Dietary Goal Sheets, (60); 3) counseling and follow-up algorithms; 4) the NCEP initial and follow-up guidelines; and 5) several useful pamphlets for the pt (e.g.: low-fat recipes, low-fat snacks, eating out advice). The DRA is essentially an abbreviated food frequency questionnaire divided into four areas: meats, snacks and side dishes, dairy and eggs, and spreads and oils. The physician reviews the DRA with the pt to identify problem eating practices and to develop nutrition-change goals, and provides the pt with suggested diet changes outlined in the matching goal sheets. The clinic personnel will be oriented to their role in the study, which is limited to inserting the packets into the pts' charts (as they do for other materials, e.g., lab reports, consult notes) and giving the DRA to the pt to be filled out in the waiting room. Site coordinators will prepare and deliver the pt packets to the clinic sites. The packets will be identified by participant's name, medical record number, and physician. The DRA will be flagged on the packet to be given to the pt on arrival at the clinic.

D.8.3.3. Group Nutrition Intervention Program (GNI)

The primary treatment approach for pts with elevated serum LDL-C who do not have CHD is dietary change. The NCEP recommends a two-phase dietary approach, incorporating reduction of fat intake to less than 30% of calories, restricted intake of SFA and dietary cholesterol, and reduced caloric intake to achieve desirable weight for overweight individuals. (21) The "Step One" diet resembles closely the dietary guidelines recommended by the American Heart Association for the general population. The "Step Two" diet is recommended for use when adherence to the Step One diet does not result in reduced serum lipid levels, and has been shown to be more effective. (106) It further limits intake of SFA (<7% vs.<10% of calories) and dietary cholesterol (<200mg/day vs. <300mg/day) and requires more intensive pt education and support.

The RD-implemented GNI will be similar to the 4-session program utilized in WATCH, and will include an initial individual session, followed by 3 group sessions. (see appendix G for outline of group sessions)

The primary nutritional and behavioral objectives of the GNI are to:

1. Increase the pt's awareness of the dietary risk factors associated with CHD;
2. Increase the pt's knowledge of nutrition in the context of a diet designed to lower serum cholesterol (Step One or Step Two with the addition of individual goals as indicated);
3. Negotiate and tailor realistic goals for each pt;
4. Enhance the pt's skills for adherence to a cholesterol lowering eating pattern; and
5. Increase the pt's confidence in his/her ability to make dietary changes

Spouses will be encouraged to attend the group sessions because support by family members, especially spouses, is important in achieving and maintaining behavioral change. (107) Groups will meet in the demonstration kitchen/classroom at the UMMC Prevention Center (see Facilities and Environment). This allows for the experience of working with foods (many may be new to study pts) and for the crucial element of group support. Pt and spouse attendance records will be kept and evaluated as possible outcome predictor variables.

The protocol for each pt is as follows:

Step 1. Referral to the GNI program by a physician or by the DLMC.

The GNI program will be available to pts in Conditions I and II. However, pts in Condition I must be referred by their physicians, while in Condition II they will be referred by their physician or by the Dietitian Lipid Management Counselor (DLMC) who coordinates the Systems-Based Lipid Management Program for pts in condition II (See Section D.8.4.1.) Study pts in both conditions will be tracked by the site coordinators, and when referred by their physicians to dietitian services for assistance with cholesterol lowering all study pts (conditions I & II) will be placed in the GNI program.

Step 2. Individual Counseling Session with the RD

On referral to the GNI, the pt will be scheduled for an individual counseling session within two weeks. The purpose of the individual session is to provide a thorough assessment of nutritional status; including measurements of height, weight, and basal energy expenditure (based on the Harris-Benedict Equation), and an evaluation of any medical history with nutritional implications. The RD will review the pt's typical eating pattern, targeting specific areas of concern. An assessment of pt barriers to dietary change will be made, and customized goals according to pt needs and abilities will be developed. The pt will be given a 7DDR (see section C.1.7.) to complete. The 7DDR will be used both to educate the pt about diet and as a basis for setting individual dietary goals. The referring physician will be sent a note indicating that the pt has started the GNI program and giving information about the pt's dietary behavior and goals. This note will also be placed in the Lotus Notes data base, for use by the DLMC. Because the RD is blinded to pt assignment, such electronic notes for condition I pts will be sent but not utilized (but they are identical to the written note sent to the physician).

Step 3. Participation in Group Sessions

The pt will attend the first group session within 2 weeks of the individual session, and can choose a day or evening class. Three GNI sessions will be held 2 weeks apart over a period of 6 weeks (appendix G). Each RD-led group session will last 2 hours and will be activity-oriented. The decision to run three 2-hour sessions is based on the need for approximately 6 hours for adequate teaching, learning, and skill development (e.g. food preparation and cooking demonstrations and practice) and the desire to not reduce adherence by requiring the pts to return to the clinical center too many times. The number of sessions also represents a compromise between the very potent effect seen with expensive, intensive multisession programs (16) and what is realistic in a real-world primary care setting. We have found this number of sessions to be efficacious (see section C.1.4.) If a pt misses a GNI session he/she will have the option of attending an equivalent session of another group. Pts will be given simple assignments to complete at home. After the last group session a summary note will be sent to the referring physician, describing the pt's progress and suggesting areas for physician support.

D.8.3.3.1. Training of Registered Dietitians

At the beginning of Phase II of the project, the 2 participating RDs will be trained to implement the GNI. The training program will consist of two four-hour joint sessions and one half-hour individual session.

Joint Training Sessions

The objectives of the first training session will be to:

1. Acquaint RDs with the scope and aim of the project, including the rationale underlying the interventions.
2. Review the NCEP guidelines for identifying and treating high-risk pts, including discussion of the major risk factors for CHD and how the approach adopted by this project complements the guidelines.
3. Acquaint the RDs with the components of the GNI program.

4. Provide an overview of group process theory and adult learning theory.
5. Present the theoretical and practical basis for whole-food dietary change, and the transition to a more healthful and interesting way of eating.

The objectives of the second session will be to:

1. Provide detailed instruction on the components of the intervention: objectives of the 1 individual and 3 group sessions; use of the pt instruction materials: use of the diet assessment and pt evaluation forms; procedures to be followed for monitoring pts' progress through the program.
2. Provide training to improve the RDs' counseling skills in a manner similar to that given the physicians.
3. Provide an overview of cognitive and behavioral techniques.
4. Identify pt and RD barriers to implementing the intervention and ways to overcome them.

Individual Training Session

This half-hour training session will be held with each nutritionist within 2 weeks after the joint training sessions. The purpose is to provide the RDs with individual feedback regarding their counseling (and teaching) skills and to correct any problems. The format is similar to the physician's individual sessions (section D.8.3.1.1.) One of the project nutritionists will be our lead nutritionist, Barbara Olendzki, and skills development will not be an issue. However, we will train another nutritionist as a backup. If after these sessions the backup nutritionist's level of counseling and teaching skills are not adequate, further practice will be requested. If the individual's skills remain inadequate, she or he will be replaced. This is very unlikely to occur, as our nutritionists are chosen to have strong nutritional and behavioral skills.

D.8.4. Components Unique to Condition II.

D.8.4.1. The Systems-Based Lipid Management Program (SBLMP)

The SBLMP is implemented and coordinated by the Dietitian Lipid Management Counselor (DLMC), who has two critical intervention roles: the use of the Lotus Notes tracking system to track condition II pt attainment of NCEP goals and to schedule indicated lipid tests and GNI referrals (both of which are subject to physician veto), and provision of telephone-based behavioral counseling to support and extend the efforts of the physician and the GNI and provide more individualized support. A more detailed description of these activities is provided below. Contact with pts will be primarily by telephone, although mail also will be used as appropriate.

Lotus Notes-Based Tracking System

The tracking system used for monitoring lipid-related activities and providing necessary prompts has been upgraded from the D-BASE system used in WATCH to a software and communication system using Lotus Notes from IBM as described in D.11.1. Because of its responsiveness to changes in study participants' data, the Lotus Notes tracking system functions as a watchdog for the SBLMP, automatically flagging any pt who is nearing a deadline for a measurement or intervention (see appendix O). The software also incorporates electronic mail for staff communication. The Lotus Notes system will be linked to the PCHIS system used by Primary Care Medicine, as described in D.9.

Although we will be using sophisticated tracking systems to satisfy the research needs of the study, the clinical part of the tracking system will be easy to use. Therefore, it can be easily disseminated to non-academic settings. The customized software developed for the proposed project will be one of the products of this study, and will be made available to others at no charge. The only requirement for another site to operate the database system is a Lotus Notes client software package (less than \$100 expense) and a low-cost personal computer, and the availability of an individual to maintain the system.

The NCEP guidelines recommend a repeat serum lipid measurement by 3 months. (21) Using the Lotus Notes tracking system linked to laboratory data via PCHIS, pts in condition II who have not had their lipids remeasured by 3 months following the initial physician visit will be contacted directly by the DLMC, a lipid profile scheduled, and the physician notified. Similar monitoring and scheduling also can occur at the 6 and 9 month points. Likewise, SBLMP monitoring and follow-up of these measurements can lead to a referral to the GNI. The physician is notified of scheduled lipid-related activities and can veto any such recommendations.

Note: we have elected to recommend the use of lipid profiles at UMMC, not surrogate total cholesterol measurements as discussed in the NCEP guidelines. (21) At UMMC a full lipid profile is only slightly more costly than a cholesterol alone and provides TG, HDL-C, and LDL-C.

The telephone counseling (TC) intervention

The TC intervention calls also will use the pt-centered counseling model (See Section D.8.1. and D.8.3.). The first TC call will be scheduled by the site coordinator immediately after pt randomization. Subsequent TC calls will be scheduled by the DLMC. Calls optimally will be made at 3 and 6 weeks, and 3, 6 and 9 months following the initial scheduled physician visit. If the initial physician visit is delayed, the initial call, in addition to covering the material described below, will be oriented towards facilitating the physician appointment. If the pt is in the top decile of LDL-C, the DLMC also will make a referral to the GNI if the pt has not seen his/her

physician, and is not able/willing to schedule an appointment. The physician will be notified of the referral and can veto it. If by the 3 month call the physician appointment has still not occurred (in WATCH 162 pts (12.7%), despite having been scheduled, never saw their physician during the study period), the DLMC will refer the pt to the GNI if the 3-month lipid profile indicates the need based on NCEP guidelines, and will notify the physician of the referral.

Primary objectives of the TC calls are to:

- Facilitate at least an initial visit with the pt's physician
- Encourage and facilitate attendance at the GNI when appropriate (i.e., top 10% LDL-C right after MD visit; next 15% LDL-C after 3 months if pt did not reach LDL-C goal) by facilitating motivation to change dietary intake.
- Reinforce and review plan to facilitate the pt's meeting dietary change goals set.
- If the pt has not seen the physician, or has not gone to the GNI, or has not set dietary goals, the DLMC will help the pt set dietary goals
- Address potential barriers to adherence to dietary change goals and set plan for dealing with problems
- Develop and practice relapse prevention strategies (once change has occurred)

Optimally the TC call schedule will be coordinated with the GNI. Since the pt's attendance at the GNI can occur at various times during the study year, depending on baseline LDL-C or MD contact, or not at all, there are 3 likely scenarios:

1. Pts in the top decile of LDL-C (i.e. 40% of pts in study) are recommended for immediate referral to the GNI. In WATCH only 8% of condition III pts were referred to the GNI at the initial visit. For the small proportion of pts referred early the first two TC calls will be oriented towards reinforcing the physician and GNI goals and intervention. Later calls will be oriented towards maintenance of change and relapse prevention. For the remaining pts in the top decile of LDL-C who are not referred by their physician, the DLMC will refer the pt to the GNI and inform the physician, who can veto the referral.
2. Some 35% of pts will be at their NCEP goal by the 3 month point (our experience in WATCH) and will not need the GNI. For these pts the TC calls will be utilized to help reinforce the goals set with the physician or to set goals if this has not been done. The later calls will be oriented towards maintenance of change and relapse prevention.
3. The remaining 25% of pts who will not have reached their NCEP goal will be referred to the GNI by the physician or the DLMC after the 3-month point. For these pts the first two TC calls will be oriented towards reinforcing the physician intervention and goals set with the physician for nutrition change, or helping the pt set dietary goals, with later calls oriented towards reinforcement of the GNI counseling.

In both 1 and 3 there will be pts who choose not to attend the GNI, or attend only some sessions. For these pts the DLMC will use the TC calls to encourage GNI attendance. Non-attending pts will fall into 2 categories: those interested in dietary change who are either unable to attend for situational reasons (e.g., lack of child-care) or believe they do not need the GNI; and those who are pre-contemplators not yet willing to commit to dietary behavior change. For the former the DLMC will work with the pt to set dietary change goals and will follow the counseling sequence; for the latter the DLMC will help the pt to address barriers and motivation for change and move along the sequence of stages-of-change.

TC calls will follow a structured format with extensive flexibility to allow tailoring to individual needs. As noted above, if a pt does not plan to attend the GNI sessions, or, as with the majority of pts, does not yet need to be referred to the GNI because he/she is not in the highest LDL-C decile and/or has not reached the 3 month decision point for GNI referral, the DLMC will assist the pt to set realistic dietary goals to lower cholesterol. For these pts, subsequent to the first TC call, a 7DDR will be mailed for discussion at the time of the next call.

Training of Dietitian Lipid Management Counselors (DLMCs) to do TC

The DLMC will be trained in the behavioral and support components included in the TC protocol. The training will be conducted in three two-hour sessions consisting of: (1) a session to teach the core nutrition interventions, pt-centered counseling, theories of change, strategies to help the pt develop a self-efficacy, and problem-solving and relapse prevention strategies; (2) a follow-up session for evaluation and feedback to refine counseling skills, to include role-playing exercises; and (3) use of the tracking procedures being put into place to facilitate the delivery of interventions. As part of session 2 Dr. J. Ockene will listen to a practice TC call conducted by the DLMCs with a trained "participant simulator". For quality control she also will listen to TC calls monthly for the first two months and then bimonthly through year 2. The DLMC will be told of the "spot checks" on the day that they will occur and informed consent will be obtained from the pt.

D.8.4.2. Other Support Materials

Videotapes: All pts in condition II will receive a copy of “A guide to controlling your cholesterol - A lifetime of good eating (AMA Health Heart Series - AMA/Milner-Fenwick), personalized with an introduction by project staff. We have used this 17 minute video, and find it superior to others available. It includes information on the relationship of cholesterol to atherosclerosis, explains the significance of LDL-C and HDL-C, discusses reducing fat, SFA, and cholesterol in the diet; weight loss, and exercise. It includes practical advice on dietary modification. These videotapes would be sent to the pt within 1 week following the appointment with the physician, or at the time of the initial SBLMP phone call if the physician appointment is delayed. Pts in the GNI also will have available a library of videotapes produced by the GNI program.

Newsletters: Bimonthly newsletters will be sent to condition II pts. These newsletters will be similar to those we have been publishing for a number of projects, including WATCH (see appendix K for examples), but will be oriented towards the pts and will reinforce other aspects of the intervention.

D.9. Patient Follow-up, Potential Patient Losses, and Measures To Ensure Complete Data Collection

Patient Contact: The study tracking and project management systems will interface with PCHIS, the Primary Care Health Information System. This clinical database has been in use in the Adult Primary Care Clinic at UMMC since 1985. Clinical information is obtained at the time of a pt’s first clinic visit. Updates as well as test orders and referrals are then obtained via standard worksheets at each subsequent visit. The clinical data are entered into the system by dedicated data entry clerks within 2 days of an encounter.

PCHIS obtains additional data via electronic links with other UMMC systems. Demographic updates are obtained from the Meditech registration module. Future appointments are obtained from the IDX scheduling system. Lab results are obtained through Meditech’s Patient Care Inquiry module. We will utilize PCHIS as the front end into appointment, registration, and nutrition referral information to be used both by study recruitment personnel and by the SBLMP. PCHIS can also validate and cross-check pt information, ensuring data quality.

Patient Losses: Loss of pts can occur via illness or death, or refusal to participate further. As this is a primary care population without CHD, the recruitment is from routine, non-emergent visits, and pts over age 70 are excluded, loss to death or serious illness should be minimal (in WATCH 7 pts (.05%) died during the study). Refusal to finish the study also should be modest, as the two initial visits required to become a participant should uncover most pts who will not follow-up appropriately (in WATCH 91 pts dropped out during the study). Placement of pts on lipid-lowering medication requires special consideration. Few pts are likely to be placed on such therapy. Pts with serum total cholesterol >300 mg/dl or LDL-C>200mg/dl are excluded, and the guidelines taught and provided to physicians suggests consideration of drug therapy during the study year only for pts with LDL-C over the 90th percentile, and then only after the 6-month mark if dietary treatment has failed. Despite marketing pressure to increase utilization of lipid-lowering agents, there is considerable resistance to their use. (71, 108) In WATCH only 10.7% of pts in condition III (the control state in the present proposal) were placed on lipid-lowering medications during the study year, despite multiple reminders of the pt’s lipid levels. Pt placement on such medication will be considered as a control variable in analyses.

Measures To Ensure Completeness Of Data Collection: At UMMC, as compared to the Fallon clinic, we will have increased control over all aspects of data collection. The tracking system will assure that pts are contacted to obtain study endpoint data, and to ensure that such data collection is within the correct time window. For diet studies conducted within the past year we have obtained a completion rate for 24HRs of 98%. In addition, the WATCH exclusion of 99 pts (8%) with TG>400 will not occur in the present study, as LDL-C will be directly measured (see D.10.1.). These improvements should increase overall endpoint data availability to approximately 92%. We will also provide a \$25.00 incentive to pts for completion of the one-year data collection.

D.10. Measurements

Measurements fall into several categories, as follows:

D.10.1. Primary Endpoints

D.10.1.1. Lipid measurements

Serum lipids function both as the primary study endpoint and the means by which we assess study eligibility. Pt eligibility is determined by sequential measures (see D.5.1.). Such duplicate determination for eligibility recognizes the considerable natural variation in individual cholesterol levels. (109) If the pt is eligible and consents to participation, duplicate fasting lipid profile samples drawn one week apart will be sent to the CDC-standardized reference laboratory of Dr. Robert Nicolosi at UMass-Lowell. The mean of the results of these two venous LDL-C determinations will be used as the study baseline levels.

All physicians will have the screening fingerstick lipid profile results available at the time of the scheduled initial visit. They will not receive the results of the study baseline venous samples sent to UMass-Lowell. At 12

months all pts will have a final endpoint venous lipid profile sent to the reference laboratory. The protocols for cholesterol screening will follow the “Recommendations for improving cholesterol measurement: A report from the laboratory standardization panel of the National Cholesterol Education Program.” (110)

Screening Instrument: The Cholestech[®] analyzer will be used for fingerstick cholesterol and lipid profile screening. It is both accurate and convenient. We used and validated this instrument in WATCH. (76) Each analyzer has been documented to achieve $\pm 3\%$ for accuracy and precision as compared to the CDC-standardized laboratory setting.

Instrument Operators: Licensed laboratory personnel experienced in the use of the Cholestech[®] analyzer.

Quality Control-UMMC: Control sera at 2 levels which bracket the 200 and 240 mg/dl decision values are run on the Cholestech[®] analyzers at the beginning of each screening day. If bias is more than 5% from either control serum value, the pools are run again, and if the bias is still greater than 5%, the instrument is taken out of service until the problem is corrected.

Lipoprotein Measurements: Prior to obtaining blood the pt will sit for 5 minutes, since postural changes can alter serum cholesterol concentrations. Venous blood samples from an antecubital vein will be collected into 7 ml vacutainer tubes without anticoagulant, and will be centrifuged to harvest serum after separation from the clot within 2 hours. The sera will be stored at -80°C . until transported to Dr. Nicolosi’s laboratory on a weekly basis, where they will be analyzed within 1 week. Total and HDL cholesterol and TG will be analyzed using the Abbott VP Autoanalyzer and Sigma reagents. HDL-C will be measured in the supernatant after magnesium-phosphotungstate precipitation of apo B-containing lipoproteins. All assays have met the standardization criteria of the CDC-NHLBI Lipid Standardization Program. (111) A copy of a recent review of the laboratory’s performance is included as appendix L. LDL-C will be determined indirectly as follows: $\text{LDL-C} = \text{TC} - \text{HDL-C} - \text{TG}/5$. (112) LDL-C will also be measured directly utilizing the RDI LipiDirect[®] Magnetic LDL Reagent kit (Reference Diagnostics Inc., Bedford, MA) (see appendix L). Briefly, this FDA-approved methodology precipitates LDL-C while leaving HDL-C and VLDL in the supernatant solution. LDL-C is obtained directly by subtracting the cholesterol concentration of the supernatant from the total cholesterol. Therefore, in our assay of total serum LDL, 400 μl of Magnetic LDL Precipitating Reagent is added to a test tube. Then 250 μl of serum or appropriate reference control are added. Samples are vortexed immediately and allowed to stand at $18 - 30^{\circ}\text{C}$ for 10 minutes. Each tube is then placed on a magnetic surface for 5 minutes to allow for complete sedimentation of LDL-C. An aliquot of the supernatant is then assayed for cholesterol using the assay described above. Direct LDL-C measurement will be the primary study lipid endpoint. Total cholesterol, HDL-C, and TG will be recorded and analyzed as additional endpoints.

D.10.1.2. Dietary measurements

The premise of this study is that an intervention which leads to a reduced consumption of dietary fat, in particular SFA, will result in decreased LDL-C levels. Therefore, assessment of diet, in particular dietary fat consumption, is of primary importance. Because of the reduced probability of bias and concomitant ability to accurately characterize group mean nutrient intake (113-115) in relation to other assessment methods we will use computer-assisted telephone interview (CATI) 24 hour recalls (24HRs) as the assessment method for the primary dietary endpoints. A single 24HR will be conducted on a randomly selected day at the 12-month point. The 24HR will be administered within the 3-week period prior to the pt’s 12-month endpoint serum lipid measurement. The 24HRs will be administered by non-intervention RDs (currently working in our group) blinded to pt condition and trained to collect dietary data using our interview system. The 24HR-derived data is analyzed using the Nutrition Data System (NDS 2.9) (see below). Though a single 24HR is not suitable for assessing individual intake, it is appropriate for determining group means. (65) Because of the large contribution of intra-person variability in a single 24HR, analysis of change scores based on pairs of nutrient scores derived from single 24HRs results in large total variance and limited ability to detect an effect (see 11.2). (65) Analyses based on comparison of one-year data by condition are more powerful than analyses of change scores.

We also will use the 7DDR developed in WATCH, for assessment of individual change. As noted (see C.1.7. and appendix C), the 7DDR-derived nutrients agree closely with those derived from multiple 24HR. (73, 79, 88, 89) Such use allows us to examine the relation between individuals’ reported dietary change and covariates that could modify the effect of the intervention, produce an independent effect, or act as a biaser. Such variables include education level, self-efficacy, motivation, social desirability, and stage of change.

The 7DDR also will be used by the RDs in the GNI, and by the DLMCs for telephone counseling.

The 7DDR will be given at baseline and at the 12-month point for endpoint study measures, and variably for clinical use during the year as determined by the GNI, the DLMC, and the pts’ physicians. The endpoint study 7DDRs will not be available clinically, and the clinical 7DDRs will not be used in endpoint analyses.

The Nutrition Data System/Nutrient Database

As in WATCH, for analysis of 24HRs and 7DDRr we will use the University of Minnesota Nutrition Coordinating Center's Nutrition Data System (UMNCC-NDS) software. (116) For 24 HR interviewing, this easy-to-use software accomplishes a number of data management tasks, checking for errors in range and logic and prompting interviewers for information and corrections. The system is well suited to open-ended assessment techniques such as 24HRs that demand matches for a wide array of specific food items. At the end of the interview it produces an analytic data file.

The UMNCC-NDS consists of data entry and analysis software and comprehensive food nutrient databases. It was developed in 1974 to support nutrient analyses for randomized intervention trials, and has become the leading U.S. resource for nutrient database and analysis systems for research. The database contains over 16,000 foods and 5,000 brand name products and values for 93 nutrients, allowing over 150,000 food variants, differing in preparation methods and ingredients. The database includes culturally unique foods. It is updated at least annually. We have contributed data on an assortment of foods to the NDS from our on-going studies.

D.10.2. Secondary Endpoints

Secondary study endpoints (see section D.2.) include dietary total fat intake and body weight, and implementation of the counseling sequence by the physicians. As for SFA, total fat intake is measured utilizing the techniques described above in D.10.1.2. Body weight is measured using standard methodology, with the pt wearing only light clothing and no shoes. Physician implementation of the counseling sequence is measured using PEIs, as follows:

D.10.2.1. Survey of Patients: Interventions Delivered:

As in WATCH, during the clinical trial phase of this project a random 25% of study pts will be asked to complete a brief PEI (appendix J) assessing the type and extent of nutrition intervention provided by their physicians. All physicians receive the same training and office support program whose value we have previously demonstrated (see C.1.2), (62) and the primary purpose of the PEI here is to evaluate the effect of systems-based feedback on physician behavior. Therefore PEIs will not be conducted on the initial physician-pt encounter, but only on follow-up visits. The PEI questionnaire will be administered by telephone within 2 days following the clinic visit. In WATCH we used both in-person and telephone PEIs and obtained comparable scores. Standardizing on telephone PEIs in this study will minimize logistic difficulty and cost.

The PEI includes the critical intervention steps important for effective dietary intervention: 1. discussed cholesterol level; 2. discussed diet-cholesterol connection; 3. advised dietary change to lower cholesterol; 4. discussed past efforts to lower cholesterol; 5. discussed problems making dietary change (barriers); 6. discussed solutions to problems (resources); 7. Pt agreed to make changes or MD discussed goals; 8. gave nutrition materials; 9. referred pt for nutrition counseling; 10. set a follow-up contact. A score is determined for each pt encounter by adding up the scores for each step reported, and normalizing to a maximum score of ten. (62)

Although physicians will not be notified specifically of the status of their pts, they are likely to be aware that pts are in the Intervention Condition because of reports from the DLMC and potential comments by the pts re phone contacts and mailings. We are especially interested in seeing if the practices of the physicians are influenced, as judged by PEIs, by such prompts, and we hypothesize that there will be a favorable effect on PEI scores for condition II pt/physician encounters. There are 3 possible outcomes:

1. The physicians may be unaffected by condition II feedback. In this case, PEI scores will be identical in both conditions, and the rate of GNI referral in condition I will be low.
2. The physicians may be favorably affected by condition II feedback, but only as it applies to their interaction with the condition II pts. In this case there will be a differential effect, with PEI scores higher in physician encounters with condition II pts. We hypothesize that this will be the likely outcome.
3. The physicians may be favorably affected by condition II feedback, and this effect may spill over into their interactions with condition I pts. In this case PEI scores in condition I pt encounters should progressively increase over the course of the study, as should the rates of referral of condition I pts to the GNI. Although this would be a desirable outcome (although probably analytically difficult), akin to safeguarding an entire population by immunizing half, we believe this is unlikely to occur. It is in part the complexity of the potential effects of the intervention on physician behavior that has led us to consider PEI outcomes only as a secondary endpoint.

D.10.3. Other Variables that are potential modifiers of the intervention effect

These include variables that may change as a consequence of the intervention (i.e., intervening variables). They are noted below with an asterisk (*) (also see Intervention Framework figure in Appendix B).

D.10.3.1. Physician Nutrition Knowledge and Attitudes

Nutrition knowledge and attitudes will be measured in all physicians following training to evaluate baseline characteristics. These data will be used as covariates in secondary analyses designed to evaluate the manner in

which provider characteristics modify the effect of the intervention. We will use the WATCH questionnaire which assesses knowledge related to dietary behavior and its effects on lipids; barriers to change; elements of counseling; and proper use of a structured nutrition intervention. (appendix J). To evaluate cholesterol-lowering attitudes among physicians, the questionnaire uses a scale developed by Ammerman et al. at the University of North Carolina. (117) There is a nutrition intervention self-efficacy subscale in this assessment. Reliability has been established for this instrument and is in the range of .60 to .80 for each subscale. As we have already documented the development and persistence of the training effect in a similar group of providers in WATCH, it is not necessary to obtain either pre-training or one-year measures. (56, 62)

D.10.3.2 Patient variables

D.10.3.2.1. Data Collected at Baseline only

D.10.3.2.1.1. Patient Demographic information: age, gender, education, occupation, ethnicity, household data.

D.10.3.2.1.2. Social Desirability and Social Approval

Social desirability (SD) is the defensive tendency of individuals to portray themselves in a manner adhering to social norms. (118, 119) Persons scoring high on the Marlowe-Crowne Personal Reaction Inventory (MCSD) tend to have acquiescent personality types that may, in turn, modify their susceptibility to interventions. (119) We have shown that increased SD scores are associated with a downward bias in the estimation of nutrient intake. (73) Because SD can function either as a biaser of nutrient intake estimates, or as a proxy for acquiescent personality type, or both, we will measure SD using the well-established MCSD. The MCSD is a 33-item true/false subscale of the Minnesota Multiphasic Personality Inventory. The internal consistency coefficient (from the Kuder-Richardson Formula) is 0.88 and test-retest reliability is 0.89. (120) Social approval (SA), the tendency to seek a positive response in a testing situation, is less focused on defensiveness. It is assessed by the 20 Likert-scale questions of the Martin-Larsen Approval Motivation Scale. (121) In the WATCH we found that responses to the 7DDR were biased by social approval. (77) Time to complete: 8 minutes.

D.10.3.2.2. Data Measured at Baseline and One Year

The following variables are included in the baseline and one-year questionnaires:

D.10.3.2.2.1. Nutrition Stage of Change*

While we are listing this as a potential predictor or modifier, Nutrition Stage of change could also be a secondary outcome with a greater change in condition II as compared to condition I pts. Nutrition Stage of change is categorized by 2 questions concerning the individual's intention to change his nutrition behavior, and his recent history of attempted change. (101) The responses place the pt in one of 4 stages:

Precontemplation: The subject is not considering changing nutritional behavior within the next 6 months.

Contemplation: The subject is seriously considering changing nutritional behavior within the next 6 months.

Ready for Action: The subject is seriously considering changing nutritional behavior in the next month.

Action: The subject reports having changed nutritional behavior within the past 3 months.

D.10.3.2.2.2. Nutrition Change History

Each of the items to be used to assess nutrition change history have previously been shown to be related to behavior change in our prior studies on smoking. (107)The scale includes items which assess prior change attempts, and the difficulty encountered during those attempts.

D.10.3.2.2.3. Social Support*

These items measure the degree and type of support a pt is given by others in his/her efforts to change nutritional behavior. We will use the core measures used in the NCI "5-A-Day" worksite intervention trial to measure social support of family, co-workers and friends for dietary change. (122) Time to complete: 1 minute.

D.10.3.2.2.4. Other Variables Measured on Baseline and One Year Questionnaires*

Following are variables on which we will collect data using questions identical to those in WATCH. These represent variables with which we have considerable experience: Dietary and eating behaviors; Dietary knowledge; Health attitudes; Self-efficacy; Cholesterol measurement history; Weight loss history; Smoking behavior; and Attitudes about physician advice (see Appendix I for baseline assessment).

The following two parameters are measured using separate instruments:

D.10.3.2.2.5. Physical Activity*

Physical activity will be assessed to quantify changes in energy expenditure. We will use an instrument developed in the Five-Cities Project to quantify energy expenditure (Blair/Sallis). (123) Subjects review a list of activities and their intensities and recall time spent in sleep and in moderate, hard, and very hard activities in the previous 7 days. This instrument collects information in all domains of daily activity and provides an estimate of weekly energy expenditure (kcal/kg/wk). The list of activities will reflect winter activities common to the

North-East. The intensity classifications of the list will conform to the metabolic equivalent (MET) activity intensity classifications in the recently compiled physical activities compendium of Ainsworth et al. (124) Time to complete: 5 minutes.

D.10.3.2.2.6. The Beck Depression Inventory*

This instrument is a standard for the assessment of depression. (125) It has well established psychometric properties, including high internal consistency ($\alpha = 0.86$). In studies comparing responses to clinical assessments, the Pearson correlation coefficients are approximately .66. Time to complete: 3 minutes.

D.10.4. Other outcome variables of interest

The following two variables will be measured at baseline and again at the 12-month point:

D.10.4.1. Patient Satisfaction

The Overall Evaluation of Quality Scale will be used to assess pt satisfaction with care. This is a 2-item scale consisting of an evaluation of 1) overall quality of care, and 2) outcome of care. Pts rate their responses on a 5-point rating scale: poor, fair, good, very good, excellent. The score is the mean of the 2 items. This scale compares favorably to other frequently used pt satisfaction measures. (126) Time to complete: 1 minute.

D.10.4.2. Quality of Life

Quality of life will be assessed with the Health Status Questionnaire (SF-36), (127) a self-administered instrument with 8 distinct dimensions including physical functioning, social functioning, role limitations, general mental health, energy, bodily pain, and general health perceptions. A score is calculated for each of the dimensions by summing responses to individual items and converting to a scale from 0 (poor health) to 100 (good health). The SF-36 has been used in numerous health care settings in the U.S. and abroad and has been shown to have acceptable reliability and validity. Time to complete: 5 minutes

D.11. Data Entry, Management, and Analysis

D.11.1. Project Management, Pt and Physician Tracking, and Data Management Procedures (Summary)

Under the direct leadership of the project coordinator, project staff will be responsible for: 1. tracking participants to ensure that all necessary data are collected in a timely and efficient fashion; 2. developing and generating monitoring reports; 3. providing immediate timely and relevant feedback to project staff and leadership regarding the accuracy and precision of data; 4. writing all necessary programs and data screens for the collection of data; and, 5. creating analytic data sets.

As noted in section D.8.4.1., this study will use Lotus Notes for tracking all pt and physician data. This system is ideal for monitoring the progress of study pts and physicians, and alerts the project manager and other study personnel to all study data collection points. The software will also be used to gather and store data which can be shared by individuals both on-site and in remote locations. This includes 24HR call assignments and the status of these and other data which are collected at remote sites and downloaded directly to the Lotus Notes system (see appendix O). It also provides reports of data such as those from the 7DDR, other pt questionnaires, and blood lipids. Storage of such data provides instant access to the pt's diet and other critical information for interventions by the DLMCs. Multiple levels of password protection are utilized to ensure data security. This type of tracking system has been in use for 3 years in other division studies and has proven to be easily learned, reliable, and efficient. (74)

D.11.1.1. Systems for Patient and Provider Contact

Most of the contact required will be fixed to a time of enrollment or related to an event (e.g., completion of a form or attendance at a class). The tracking system will allow notification of study staff to carry out such activities as scheduling of pts for endpoint measurements, or identification of physicians due to receive post-training questionnaires. Additionally, the tracking system will identify pts who have completed assessments or attended classes. This information is necessary in order for the DLMC and the site coordinator, both of whom have access to the tracking database, to make informed and timely contact with study participants.

D.11.1.2. Data Entry

All study data are entered into computerized data files, utilizing: Lotus Notes for participant tracking; the data entry screens and utilities from the NDS CATI system for 24HR recalls; MS Excel for creation of spreadsheets, including those necessary for cost-effectiveness analysis; NCS OpScan 5 scanner and Scantools software for optically scannable forms; data on blood lipids transmitted via coded e-mail and downloaded directly into analytic databases (as we currently do in the Seasons study); and Epi Info for double-entry verification of data from paper and pencil forms. We also will use the data manipulation techniques available in SAS (128) as appropriate. Continuous entry will allow for close monitoring of study data.

Each pt will be assigned a unique study ID. We also will enter the UMMC ID into the study record. For the purposes of follow-up, we also collect data on name, name at birth, current address, day and evening telephone numbers, alternate contact name, and social security number. All data that identify an individual pt

will be removed from analytic datasets. All datasets with identifiers are password-protected, and are kept locked in the files room at the Prevention Institute (see Resources and Environment).

D.11.1.3. Quality Control Measures.

All CATI-derived data are entered directly into an NDS database, and then downloaded into SAS data sets. Opscan forms are checked prior to scanning for obvious errors and stray marks. All such checking is blinded as to the identity and study condition of the participant. All data from pencil and paper forms are entered using a double entry format. All of the data entry systems employ automatic checks for values that are out of range or represent errors of faulty logic. These procedures reduce transcription errors for hard copy data to close to zero (<0.5%). Therefore, for telephone interviews we will monitor a random 1% of all 24HR calls. As we currently do for all data collected from transcription error-free methods such as the 24HR, we will conduct frequent exploratory analyses to detect outliers and to assess for adherence to the assumptions of the multivariable analyses, particularly regression modeling, that we plan to use in order to test hypotheses and to measure effect (e.g., normality, linearity, and homoscedasticity). (129)

D.11.1.4. Management of Data Files.

In close collaboration with Drs. Hebert and Stanek, the project's Masters level biostatistician, T. Hurley, will develop the interactive database systems, write the appropriate software programs, and be responsible for quality control measures. Dr. Hebert will have primary responsibility for overseeing the assembling of datasets from pts in the study. Dr. Stanek, in collaboration with Dr. Hebert and Mr. Hurley, will have primary responsibility for structuring primary data sets, code books, naming conventions, and for designing primary documentation of data. Data management will be conducted in the Division of Preventive and Behavioral Medicine in a microcomputer environment. Primary data sets will be shared via FTP with Dr. Stanek at the Umass-Amherst site. Data sets are cleaned, verified and archived, and then read into SAS data sets which also are archived. Access to programs and archival data sets will be denied by password to non-study staff. All analytic and tracking database files are backed up daily. On a weekly, monthly, quarterly and yearly basis complete backups are made of all database files. One copy is saved on-site and one off-site. Separate archival databases are permanently maintained.

D.11.2. Statistical Analysis

There are two primary endpoints in this study based on comparing conditions on:

1. Change in pts' LDL-cholesterol after 12 months in the study.
2. Difference in the level of SFA (% energy) after 12 months in the study.

Additional analyses will be conducted for secondary hypotheses relating to: 1. Difference in total fat intake (% energy) after 12 months in the study; 2. Change in pts' mean body weight; and 3. Difference by condition in the number of intervention steps implemented by physicians (as measured by PEIs).

The analyses will be developed by Dr. Stanek in close collaboration with Drs. Hebert and Ockene, and implemented both at the Umass-Amherst campus and at UMMC. Interchange of analysis results, data sets, analysis programs, and reports will be facilitated by frequent face-to-face meetings, and electronic mail.

As discussed in D.9., measures will be put into place to optimize the rate of data completion. Nonetheless there will be some pts with incomplete data. Descriptive analyses will characterize study completers, and be augmented with ANOVA and chi-square tests as appropriate. Logistic regression analyses will be conducted to evaluate differences between completers and non-completers, focusing on factors that are differentially distributed between conditions. Particular attention will be given to gender and education differences, since these factors appeared to be potential effect modifiers in the WATCH study. Because of missing data, different subsets of pts may be eligible for analyses of LDL-C and SFA (%energy). Complete analyses will be conducted separately for these endpoints. Variables found to both differ between completers and non-completers and to adhere to the assumptions of the regression models will be included as covariables in subsequent primary and secondary analyses to control for possible selection bias. Analyses also will be conducted that allow for unbalanced and missing data, with the logistic regression analyses serving to help guide interpretation of these results.

Change in LDL-C levels (baseline minus one year) will be constructed for each pt and serve as the primary outcome variable for testing hypothesis #1. Since the study design is stratified by physicians, we will conduct primary analyses using physicians as a fixed blocking factor in the analysis. All analyses will make use of PROC MIXED in SAS due to the expanded flexibility of the mixed modeling paradigm. The principal comparison will control for physicians and other important selection variables identified at baseline, while testing for differences in condition. An important covariable that will be included is use of cholesterol-lowering medications (started after baseline). The rate of such medication used, as modified by the intervention, as well as the effect on change scores will be developed, with analyses possibly stratified on medication use. Models

will be compared using likelihood ratio tests based on maximum likelihood estimates, with final model parameters estimated via REML. Subsequent analyses will consider possible effect modification by education, gender, and their interaction.

In addition to the primary analyses using physicians as fixed blocking factors, additional analyses will consider physicians as a random factor, enabling extrapolation of intervention effects to a broader group of physician practices. These analyses will make use of broad inference as described by McLean et al., and summarized by Little et al. (130, 131) Attention will be paid to interpreting the differences between results based on fixed and random effects, so as to distinguish results specific to this randomized trial from results generalizable to other settings.

Additional analyses will be conducted that include the baseline LDL-C value. Because patient eligibility is established via duplicate fingerstick cholesterol measures and baseline LDL-C levels are taken from duplicate venous measures, there should be minimal concern over regression to the mean. Consequently, including the baseline LDL-C value should result in a more powerful test. Although little regression to the mean is anticipated, some regression is possible since due to practical constraints, the second finger stick measure and the first venous LDL-C measures are conducted on the same day (i.e., within 1 hour of each other). Analyses will be developed that identify this possible regression effect. While not affecting the primary comparison between conditions, if regression to the mean is present, it will affect condition-specific estimates. Alternative analysis approaches will be developed if regression to the mean is detected; e.g., analyses that account for the regression, or ones that use only the second venous LDL-C baseline measures.

Models for SFA (% energy) at one-year will be constructed in a manner similar to analyses for LDL-C. Large day-to-day variability within pts results in more powerful analyses that compare group differences between SFA (% energy) at one year, as opposed to change scores when based on 24HR recall data. Randomization to intervention groups guarantees comparability of pts in conditions, with imbalances due to non-response accounted for by inclusion of additional covariables identified via the initial logistic regression analyses. However, the power of these analyses may be augmented by inclusion of pt specific covariates. Such covariates will include education, gender, age (both continuous and categorical) and other patient factors. Model development will proceed as for LDL-C, with physicians treated first as fixed block effects, and then considered as random factors for generalization of study results to other settings.

Models for secondary hypotheses will be developed in a similar manner to analyses for primary hypotheses. Models for total fat intake will parallel analyses for SFA (% energy). Analyses of change in body weight will make use of (baseline - one year) change scores, similar to analyses for LDL-C. Analyses of the number of intervention steps implemented by physicians will be conducted using the PEI scores as the outcome variable. When considering PEI scores as an outcome, a covariable will be constructed corresponding to the time-weighted number of patients previously receiving the condition II intervention to investigate possible transfer of the systems-based approach to altering behavior among the condition I intervention pts. Additionally, PEI score will be fit as a potential effect modifier in analyses of the primary outcome variables, LDL-C and SFA.

Additional analyses will be conducted to address other ancillary research questions. Change in fat intake based on the 7DDR will be fit to the Keys and Hegsted equations (65) as we have done previously (79) to predict change in total cholesterol, thus enabling us to evaluate how well, on average, the study patients report their dietary change. Correlation analyses will be conducted to examine whether changes in intake of SFA are independent of intake of other fatty acids; and whether reduction in SFA will predict reductions in caloric density of the diet as well as in total caloric intake. Analyses will be conducted to examine the effect of the GNI on lipid and dietary outcomes. Predicted values of one-year LDL-C levels will be developed from the final fixed effect LDL-C models and used to evaluate the percent of pts achieving their LDL-C goals, and compare these percents between conditions.

D.11.3.1. Cost Measurement.

Costs will be estimated for each of three scenarios: non-intervention (no added study intervention, based on usual care in the study site), control (the study's control condition I, with physician-initiated nutritional interventions), and the study intervention condition II (with "system" initiated interventions). For each condition, costs will be measured on an annualized basis for each pt. These costs will encompass any initial costs of setting up the condition as well as on-going monthly operating costs. Intervention system, professional, and induced services costs associated with additional hyperlipidemia intervention will all be included.

The non-intervention group will consist of patients of the same study physicians who, in the year prior to the study intake period, would have met the other study eligibility requirements and received an LDL-C measurement, as part of regular clinical care, which was in the highest quartile. While this is not a randomized group and is subject to possible selection bias by the provider and patient in receiving a cholesterol test, it

provides a reasonable estimate of a comparable group. We considered the inclusion of a true control group, but this would have introduced an entirely different (and possibly more important) set of biases relating to willingness to be in a study and the effect of obtaining study measurements.

To develop the cost of each of the 2 study conditions and the non-intervention group, we will build on the approaches of Dr. Shepard and co-workers in an ongoing cost-effectiveness study of substance abuse treatment (R01DA08739) and on previous work. (132) All 3 groups entail the cost of identifying patients with high LDL-C as well as determining follow-up services. The cost of identifying a person with high LDL-C will be derived by dividing the total cost of testing by the number of patients eligible for the trial, recognizing that several patients must be tested to find each one with an elevated value.

Both treatment conditions (I & II) require sensitizing physicians to appropriate steps in the detection and management of elevated lipids, performing work-ups to test for hyperlipidemia and providing nutritional counseling. We will estimate direct cost (the personnel, supplies, materials, and education-related costs) by first determining the cost for delivering and receiving sensitization and training and counseling. This entails identifying all staff and personnel involved in study-related tasks, and determining salary information and percentage of time performing these tasks. (133)

The costs of counseling services will be determined by multiplying the frequency of each service times its unit cost per contact hour. Frequencies will be obtained from clinical and study records. Unit costs will be based on patient contact and preparation time for each session. For group sessions, the cost of a session will be prorated over the average number of participants, using procedures similar to those in the above-mentioned behavioral health study (DA08739). Costs of supplies and materials will be estimated by recording the average use of each item per service (e.g., recipes given out at each session). We hypothesize that, while unit costs will remain identical across groups, the increased frequency of testing and counseling in the study conditions will increase total cost. The cost of the system intervention has two components: 1. The initial cost required to set up and "debug" the system (time and materials), and 2. the ongoing cost each month (time and materials) (entering the appropriate data, ensuring that the resulting medical orders are accurate, properly transmitted, and filed). Personnel costs of each component will be recorded through logs and time sheets.

Indirect costs associated with clinical care will be determined by employing the existing Transition Systems, Inc. (TSI) accounting system used by UMMC. This system can supply detailed cost data on both an individual and an aggregate basis (see appendix P for output examples). Indirect costs of services supported under research funds will be determined by applying the institution's current indirect rate approved by the U.S. Department of Health and Human Services.

D.11.3.2. Cost-effectiveness analysis.

The cost-effectiveness analysis will examine each of the three pairwise comparisons: no intervention versus condition I, no intervention versus condition II, and conditions I vs. II. Each comparison will be performed at the aggregate level - using the mean for each condition, (134) and will produce a cost-effectiveness ratio which we express here as dollar cost per unit health improvement (quality-adjusted life years or QALYs gained). The QALY, first 20 years ago in a paper co-authored by Dr. Shepard, (135) has become a standard measure of the impact of health programs. In this study, QALYs will be estimated for each patient based on a 2-step process. First, we will estimate how each pairwise comparison would affect LDL-C through a multivariate equation. Second, we will model how the change in LDL-C will affect QALYs.

The second modeling step will use the risk model of Taylor, Pass, Shepard and Komoroff, which now operates on a personal computer. (93) It estimates the change in discounted quality-adjusted life expectancy as a function of the change in the risk factors for CHD (total cholesterol, HDL-C, smoking and blood pressure), using available data from the literature relating risk factor change to clinical endpoints. The change in the first two factors will be estimated as the difference between the actual levels for a patient at the end of the study, compared to the values predicted if they had been in a different study group. For no intervention, the change in risk factors will be small (less than 2 mg per dl), about equal to the change in cholesterol observed in the control group in WATCH. Thus in the comparison of no intervention versus condition II, the net cost is the difference in annualized cost per pt of no intervention (initial detection and often minimal subsequent follow up) compared to the annualized cost per patient of condition II (initial detection and expected substantial subsequent follow up). The net gain in QALYs is the difference in the average expected gain under no intervention (based on the minimal change in risk factors) compared to the expected gain in condition II (which is hypothesized to be large). The cost-effectiveness ratio represents the cost of achieving a year of good health. The lower this ratio, the more cost-effective the intervention. In previous studies of primary care, Dr. Shepard has estimated that nutritional counseling was likely to be reasonably cost-effective, whereas cholesterol lowering drugs, because of their very high cost, were not very cost-effective. (93)

D.11.4. Statistical Power

Power calculations have been performed for the 2 primary patient outcome variables: LDL-C (mg/dl) and SFA intake (% energy). A full description of the assumptions of the analysis and tables of various combinations of sample size, effect size, and difference score versus cross-sectional comparisons are shown in Appendix Q.

Measures used in this study and certain other aspects of design are similar to those employed in the original WATCH study. Hence, variance component estimates from the WATCH were used in designing this study. We anticipate that the patient population enrolled in this study will be similar to that in the WATCH study. Assuming a 75% rate of complete data collection, the study will have 98% power to detect a difference between conditions in the change over time in LDL-C of 5 mg/dl based on a two-sided test. To detect an effect as large as that observed between conditions I and III in WATCH we will have 99% power. For the primary dietary endpoint, this study is designed to detect a difference of 1% energy from SFA between subjects in the two conditions with 91% power, also based on a two-sided test. This power estimate is based on a single 24HR administered at the one-year time point. Because of the large intra-person variability associated with a single 24HR (65), analyzing a change score based on the difference between the one-year and baseline values would result in lower power to detect an effect than would result from using the single cross-sectional measurement. Because we are randomizing at the level of the individual and blocking by age, gender, and physician (see D.11.1.2.), it is very unlikely that an imbalance in baseline dietary intake by randomization condition would counteract the effect of increased variance resulting from the use of a baseline 24HR.

The power calculations for SFA are based on within-subject variance estimates from the WATCH study of 15, and a between-subject variance of 6. Within subject variance for LDL-C is estimated as 242, with between-subject variance estimated at 448. The sample size calculations make use of the duplicate venous bloods obtained at baseline.

The overall effect size on which we base our sample size and statistical power is approximately that which we observed in condition III– condition I of WATCH. It is approximately 40-50% of the effect observed in attendees of ≥ 3 GNI sessions in that study. (2) In the present study we expect that as few as $\frac{1}{4}$ of the pts in cond II will receive the entire GNI (see attendance estimates for other more recent studies in C.2.4. and C.2.5.). If the effect size is as large than that seen in WATCH, i.e., 15.4 mg/dl LDL-C, this will result in an observed reduction of 3.9 mg/dl averaged over the entire group. Though there are few empirical data to guide us, we estimate that the combination of pt tracking with programmed lipid measurements, pt-centered telephone counseling by the DLMC, and other interventional materials (videotapes, newsletters) will produce an effect as large as that of condition III in WATCH (i.e., 6.9 mg/dl.) The net effect size is a reduction of 9.8 mg/dl.

The study has sufficient power to also allow for adjustments due to multiple comparisons in post-hoc analyses of study data. In particular, we are especially interested in analyses looking at the effect of gender and level of education on our primary outcomes.

Table D.11.4. Statistical Power for various sample sizes comparing difference scores and simple differences post-test scores by condition for SFA intake (% energy) and LDL-C (also see Appendix Q)

| Pts / Group | SFA (1.0% energy) | | LDL-C (5.0 mg/dl) | |
|-------------|-----------------------|-----------------------|----------------------|------------------------|
| | Post-test Comparison* | Change Score Analysis | Post-test Comparison | Change Score Analysis* |
| 300 | 76 | 61 | 64 | 90 |
| 350 | 82 | 68 | 71 | 93 |
| 400 | 87 | 73 | 77 | 96 |
| 450 | 91 | 78 | 81 | 98 |

*Model of choice for this analysis

D.12. Race, Gender, And Issues Of Generalizability

The study will enroll men and women in equal numbers. The population of Worcester County is approximately 7% minority, with the largest part of this group being Hispanic (appendix M). The UMMC primary care clinics, however, have a pt population that is 12% minority, in large part because of vigorous attempts to meet the needs of diverse pt groups. We thus expect the percentage of minority recruitment to exceed the percentage of minority individuals in our area.

D.13. Administrative Organization

The study will be administered by a steering committee which includes Drs. Ira Ockene, James Hebert, Judith Ockene, Abigail Adams, and Robert Nicolosi, and Mr. Philip Merriam. This committee will meet weekly during year 1 and bi-weekly during years 2 and 3.

E. Human Subjects

Two consent processes are required in this study. Pts will initially be invited for a screening fingerstick cholesterol via a telephone call from a member of the research staff. The research assistant will briefly explain the nature of the study, obtaining oral consent, and will also explain that a high cholesterol level will result in further information. If the pt's screening cholesterol is elevated, he or she will have an immediate repeat fingerstick which will be analyzed using the Cholestech lipid profile cassette. If the pt remains eligible by LDL-C and other criteria, full informed consent will be obtained by the research site coordinator, who will explain the project, note the need for several blood tests and for the pt to fill out a number of survey instruments, and explain potential risks (the small risk of a venipuncture) and benefits (improved management of cholesterol, both for the individual (half randomized to the systems-based intervention) and for society).

In general, the study is low-risk, with most of the necessary study blood tests (two fingerstick and three venous measurements over the 12 month period of a patient's involvement) being studies which are clinically indicated by the National Cholesterol Education Program guidelines. Institutional Review Board approval for this continuation of our previously approved WATCH study is presently pending.

F. Vertebrate Animals: none.

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H. Consortium/contractual arrangements

Dr. Robert Nicolosi's laboratory at the University of Lowell, Lowell, Massachusetts, will carry out all the lipid profile analyses done for this project, and Dr. Nicolosi also will provide expertise in the area of lipid screening and intervention. Likewise Dr. Stanek of UMass-Amherst will provide statistical expertise. These will be organized via subcontract arrangements. Details of the subcontracts are included in the budget package.

I. Consultants

Drs. Don Shepard and Carl Schulz will consult to the project as experts in the implementation of cost and cost-effectiveness protocols. Their letter of support and biographical sketches, and a complete discussion of their role, is included in the budget justification.