Cost-effectiveness analysis of the 2005 Clinical Practice Guidelines for the Management of Dyslipidemia in the Philippines

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ABSTRACT

Background: In 2005, the Philippine Heart Association and the International Clinical Epidemiology Network sponsored the development of the clinical practice guidelines for the management of dyslipidemia in the Philippines. Being a country wanting in health resources, it is important that an economic evaluation of these guidelines be undertaken. This paper determined the cost-effectiveness of the recommendations of the clinical practice guidelines in the management of dyslipidemia in the Philippines using the societal perspective.

Methods: A cost-effectiveness analysis using a societal perspective was undertaken. Costing included cost of health care and patient's resources as well as those consumed from other sectors and production losses. Cost was valued in Philippine 2006 real prices and converted to US$ (1US$ = Php46.00). Effectiveness was expressed as prevention of either fatal or nonfatal vascular events (coronary events, stroke or revascularization) or death from any cause (total mortality). The cost per event prevented or incremental cost per additional event prevented (cost-effectiveness or incremental cost-effectiveness ratio, CER or ICER) was computed using effectiveness data from evidence (primary and secondary prevention trials) cited in the guidelines and available local data. Analysis through Markov models to determine the cost-effectiveness ratios were also performed.

Results: The cost-effectiveness of the recommendations was assessed through the CERs and ICERs obtained for a particular strategy. For primary prevention using non-pharmacologic therapy vs. "do nothing" alternative, the CERs ranged from Php26,980 – 31,234 (0-5% discount rates) for the single cholesterol determination strategy. This increased to Php 76,949 per cardiovascular event prevented if the cost of exercise time was included. Using the same assumptions, the ICER of pharmacologic over non-pharmacologic therapy for high-risk patients using simvastatin were Php2,016,818 – 2,979,768. For diabetics, the ICERs of simvastatin were 1,038,967 – 1,603,195 (single cholesterol determination – cholesterol or lipid profile determination strategy; discount rates 0-5%); for fenofibrate the ICERs were Php2,025,267 – 2,058,009. For secondary prevention, simvastatin dominated the therapeutic options. Using the above assumptions in the calculation of ICERs for diabetics, ICERs of simvastatin for pharmacologic over non-pharmacologic therapy were Php220,409 – 639,977 (US$4792 – 13,913). When Markov models were done, the ICERs were Php458,299 – 703,108 (US$9,9963 – 15,285).

Conclusions: In dyslipidemia, non-pharmacologic management can be considered more cost-effective than pharmacologic intervention. Pharmacologic therapy is more cost-effective as a secondary prevention strategy compared to primary prevention. Among the pharmacologic options included, simvastatin was the dominating alternative.

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I Introduction

A. Importance of conducting an economic evaluation of the local clinical practice guidelines for dyslipidemia

In the Philippines, cardiac and vascular disease accounted for 16.5% (79.1 deaths/100,000 population) and 13.2% (63.2 deaths/100,000 population) of total deaths in 2000, respectively. In terms of risk factors, the prevalence of hypercholesterolemia (using either >200 mg/dl or >240 mg/dl as cutoff levels) increased by two-fold between the 1998 and 2003 national survey.[1] Dyslipidemia (increased cholesterol or other lipid levels), together with smoking, were found to be the two most important risk factors for acute myocardial infarction in a recent global case-control study which included patients from the Philippines.[2] Thus, in the international and local scenarios, it is important that the problem of dyslipidemia be addressed. With the growing literature on this condition as well as variations in its diagnosis and management, clinical practice guidelines (CPGs) were formulated. However, most CPGs on dyslipidemia had been formulated by those from the developed world and applying them to the local setting is also a problem.

The cost of treating dyslipidemia represents an additional economic burden to a population where four out of five live below the poverty line.[1] On the other hand, the national government provision for health care delivery is limited. In contrast to the WHO recommendation of 5% of the gross national product (GNP) to be spent on health care, the national health care expenditure is 3.4% of

GNP in 1997. This even decreased to 3.1% of GNP in 2001.[1] In addition, the existing health care delivery is mostly through out-of-pocket payments. In 2002, out-of-pocket payments represented 60.9% of the total health care expenditures.[3]

Faced with the increasing problems of dyslipidemia as a cardiovascular disease risk factor, the limited health resources of the country, variations in clinical practice as well as the difficulty of adopting foreign clinical practice guidelines (CPGs), the Philippine Heart Association (PHA) together with the International Clinical Epidemiology Network (INCLEN) developed "The Clinical Practice Guidelines for the Management of Dyslipidemia in the Philippines".[1]

Although the guidelines which were published in December, 2005, included some "crude cost analysis", i.e., total costs of the medications to treat a certain number of patients for a particular duration, there has been no attempt yet to embark on a full economic evaluation of the said guidelines.

An economic evaluation is defined as a "comparative analysis of alternative courses of action in terms of both their costs and consequences".[4] Its major tasks are to "identify, measure, value, and compare the costs and consequences of the alternatives being considered". Drummond et al further state that an economic evaluation is synonymous with efficiency evaluation.[4] An economic evaluation of the recommendations of the above clinical practice guidelines is important considering that awareness of the estimated costs and benefits of the recommended treatment are supposed to guide decision-making (based on the efficiency criterion).

B. Types of Economic Evaluation

Three types of analyses fulfill the criteria for a full economic evaluation, i.e., cost-effectiveness, cost-utility analysis and cost-benefit analysis (CEA, CUA and CBA respectively). Cost-effectiveness analysis is the type of economic appraisal whereby cost is measured in monetary terms and benefit is assessed in terms of units or endpoints relevant to the problem. For cardiovascular programs, the benefits can be measured in terms of reduction in myocardial infarction, stroke, or mortality. In cost-utility analysis, cost is measured in monetary terms and benefit in terms of gains in quality-adjusted life years (QALYs), disability-adjusted life years (DALYs) or healthy year equivalents (HYEs). Lastly, a cost-benefit analysis, measures both costs and benefits in monetary terms.

The type of economic evaluation to be utilized in this paper will be that of a cost-effectiveness analysis. Costs will be measured in Philippine peso and the benefits to be assessed are reductions in total mortality or cardiovascular outcomes resulting from the treatment of dyslipidemia.

C. Achieving technical or allocative efficiency with economic evaluations

Variations in the specific goals of CEA exist in the literature. Weinstein and Stason forwarded that CEA's premise is "that for any given level of resources available, society (or the decision making jurisdiction involved) wishes to maximize the total aggregate health benefits conferred".[5] Green and Barker look at CEA as a method for determining the "most efficient way of dealing with a specified health problem" while Mooney views it as a technique which "accepts a

particular objective as given and is then concerned only with how to meet the objective at least cost".[5,6]

Two types of efficiency need to be clarified before further discussion of CEA's role in health care. The first is allocative efficiency which happens when, "given the existing distribution of income, it is not possible to reallocate resources to make one person better off (in terms of their satisfaction obtained from the goods they consume).[7] This state is known as 'Pareto-optimality' (introduced by economist Wilfred Pareto). This state considers the value of the output rather than the quantity.[7] On the other hand, the other type of efficiency is technical (or productive) efficiency which is concerned with attaining the desired/identified outputs (objectives) with the least inputs (costs).

Birch and Gafni stated that the suggested definitions of CEA imply that CEA is consistent with welfare economics of Pareto efficiency. However, they clarified that since CEA measures outputs in physical units, it can achieve only technical efficiency and not allocative efficiency.[5] This is due to the fact that allocative efficiency involves valuation of the outputs by different individuals or groups. In addition, it also includes evaluating the outputs in relation to their opportunity costs. These are considered in CUA (although CUA is limited to cost evaluation only of health services and outcomes pertain only to health) but not CEA.[5,6] On the other hand, CBA tackles allocative efficiency better than CUA since it addresses maximization of benefits from available resources. This analysis, whereby the objectives are not predetermined, answers the question of 'whether' a program should be implemented. Moreover it considers the question

'how much' through marginal analysis.[6] Lastly, it addresses all aspects of costs and benefits of a program irrespective of who will incur or receive it.

D. Application of CEA (theory and practice)

Having confined its objective to technical efficiency, CEA can be looked upon as less ambitious. The problem is not focused on a fixed budget or available resources but on a particular program's resource requirements. It deals with comparing the new program with an existing one with regards inputs and outputs (incremental costs and incremental benefits).

In a CEA, results are expressed as average cost-effectiveness ratio (CER or average CER) or incremental cost-effectiveness ratio (ICER). Average cost-effectiveness ratio of any intervention represents the cost for every benefit obtained from such intervention, while an ICER is the marginal or additional cost for one additional benefit that is obtained with an alternative intervention or program. Their simple formulae are as follows:

$$\text{CER or average CER} = \frac{\text{cost}}{\text{benefits}}$$

$$\text{ICER} = \frac{(\text{cost of alternative} - \text{cost of standard})}{(\text{benefits of alternative} - \text{benefits of standard})}$$

The use of these ratios is demonstrated by the following scenario. Drugs A and B are anti-ischemic medicines used to decrease mortality among patients who suffered a heart attack. Drug A, if given to 100 patients, will prevent the occurrence of 10 deaths. On the other hand, Drug B, given to the same number of patients will lead to the prevention of 7 deaths. Assuming that both drugs have no significant adverse events, and without consideration for the cost, one

will easily choose drug A over drug B, because of its better effectiveness. However, supposing that drug A costs US$1,000 while drug B costs US$500, then treating 100 patients with drug A will cost US$100,000 and lead to 10 less deaths (CER or average CER of drug A = US$10,000/death prevented), while with drug B, treating the same number of patients will cost US$50,000 and will prevent the occurrence of 7 deaths (average CER of drug B = US$7,143/death prevented). On the other hand, the incremental cost for every additional death prevented (ICER) for using drug A over drug B is US$16,667/death prevented. Moreover, if the budget is US$1,000,000, choosing drug A will enable treatment for 1000 patients, resulting to 100 less deaths, while if drug B is chosen, it can be used to treat 2000 patients which will result to 140 less deaths. Based on the above illustration, drug B is the more cost-effective option compared to drug A.

Cost-effectiveness ratios may be used as criteria for decisions whereby the lower the CER, "the higher the priority in terms of maximizing benefits derived from a given health expenditure".[5] The WHO Guidelines on generalized cost-effectiveness analysis has proposed the use of average cost-effectiveness ratios of mutually exclusive interventions to be used in a league table.[8] These interventions can be programs for chronic diseases like hypertension, cancer or infectious diseases like HIV-AIDs. Initially, the CERs of all interventions compared to the null (or "do nothing" alternative) are determined. In the league table, the intervention with the lowest average CER (or ICER compared to the null) appears first on the table followed by the one with the lowest slope with respect to the lowest CER (the first one on the table; this slope corresponds to

the ICER between the options listed as 1st and 2nd in the league table). The third to appear on the league table will be the one with lowest slope with respect to the second intervention, etc.[8]

The simple application of cost-effectiveness ratios as a decision rule is fraught with problems. Birch and Gafni argue that it does not maximize benefits from a fixed pool of resources nor it minimizes the costs to achieve a predetermined objective.[5] They stated that the problem per se is not in the concept of the CER but failure to comply with issues on opportunity cost when dealing with incremental costs of the program. For example, if the new program requires more resources than the existing one, the use of CER presumes that the additional resources can be obtained from other programs. In addition, the marginal cost/benefit (or ICER) derived from these other programs should not be more than the existing program mentioned above.

Although having a unidimensional outcome makes CEA easier to do than a CUA or CBA, this measurement limits the application of CEA to comparison of programs whose outputs are directly comparable. This means that outputs use the same natural units, e.g., reductions in mortality. However, different health care programs have heterogeneous effects which hinder direct comparison[5], e.g., increasing survival rates cannot be compared directly with improvements in functional capacity. In addition, at times, not only one outcome is achieved with certain programs. For example a program may achieve not only reductions in mortality rates but also reduction in stroke or heart attack rates.

On the other hand, non-health effects may also occur in particular, the dyslipidemia guidelines, may have positive and negative non-health effects such as the following:

1) Information/education regarding dyslipidemia and its role as a risk factor for cardiovascular conditions. Dyslipidemia is the focus of the education maneuver; however, related issues such as other lifestyle modification approaches like exercise, cessation of smoking and their link to a better quality and longer life are important components of the education program. This can be seen not only as an important preventive step towards reduction in the incidence of cardiovascular events but further utility can be achieved due to the knowledge acquired by the patients. In addition, well-informed patients can influence other patients in disseminating the good effects of healthy lifestyles among their co-patients and their families.

2) Anxiety. In contrast to the beneficial effect of knowledge as discussed above, a negative effect, i.e., anxiety can also result from the knowledge of having high levels of cholesterol, especially for those who cannot afford pharmacological treatment (if recommended). In addition, some patients may become overly anxious about slight elevations in lipid levels. Lastly, false positive results can occur which may result in undue concern.

These non-health effects ideally should be included in weighing all the effects of an intervention. However, in a CEA, the outputs center on the health effects expressed in units of measurement like lives saved or strokes prevented. In addition, the guidelines focused on the health outcomes such as reductions in

mortality or myocardial infarctions which were the ones measured in the evidence it obtained from the literature, thus a CEA is the more appropriate economic evaluation to undertake.

On the other hand, because of the heterogeneous effects of health care programs, Drummond et al proposed that in a CEA, either one of the following must be met: 1) “that there is one, unambiguous objective of the intervention(s) and therefore, a clear dimension along which effectiveness can be assessed; or 2) that there are many objectives, but that the alternative interventions are thought to achieve these to the same extent”.[4] Birch and Gafni added that the opportunity cost from reducing other programs to fund the more costly option should be considered.[5]

With regards the issue of multiple outcomes, a cost-consequence approach was proposed by Coast.[9] She argued that this analysis will include all the possible outcomes of a given intervention. For instance, results can be expressed as cost of all consequences, e.g., deaths, heart attacks and strokes prevented. However, this type of analysis which came about before the end of 2004, is still surrounded by a lot of controversies.[10,11,12,13]

Despite the issues on CEA discussed above, CEA can still be useful as an economic evaluation. One must always remember though, that present applications do not adhere to welfare economics theory although some would imply otherwise. When a CEA is utilized consistent with its stated goals, it identifies the “full effects of all options” that is not seen in a simple ratio (CER).[5] In addition, CEA helps guide decision-making and does not dictate the decision

to be made.[4] Lastly, as in all economic evaluations, it entails a value judgment, i.e., the willingness to incur the added costs for the additional benefits obtained.

E. Review of Literature

Role of Clinical Practice Guidelines in health care

In 1990, the Institute of Medicine in 1990 defined clinical practice guidelines as "systematically developed statements to help physicians and patients make decisions about appropriate health care for specific clinical circumstances".[14] Its 'birth' and rapid growth was brought about by several factors. These included 1) wide variations in clinical practice, 2) rapid discoveries of new treatment modalities, 3) doubts on the effectiveness of these new interventions in improving health outcomes, and 4) "need to use the available resources in the best possible way".[15]

The emergence of CPGs globally is seen as an important tool and key answer to the informational needs of health care providers. In addition, 17 years after the issuance of the 'official' definition from the Institute of Medicine, advances in guideline development still continue. A major improvement resulted not only to evidence-based guidelines but incorporation of evidence with other factors unique in particular settings, e.g., economic factors and "local buy-in".[15] To date, hundreds of guidelines have been formulated by major organizations or professional associations, some in cooperation with government institutions. Many of these guidelines have been utilized not only as informational tools but as 'guides' in many health policies especially in the western world. On the other

hand, in the local setting, the Philippine National Health Insurance (PhilHealth) is moving towards the use of local CPGs as basis for its reimbursement policies.

Utilization of economic evaluation studies in decision-making

The link between economic evaluation analyses and decision-making in health care had been demonstrated by its role in several policies in many developed countries. This was demonstrated in the United States and the Netherlands whereby evaluation of the costs and benefits guided decisions with regards health insurance package.[16] Furthermore, economic appraisal studies began to play a significant role in the pharmaceutical industry when some countries implemented a policy whereby such studies are needed before a drug can be listed in their national formulary. This was first seen in 1993 in Australia when such a study became a legal requirement before a drug can be listed in its Pharmaceutical Benefits Scheme (drugs included in this list are the only ones subsidized by the Australian government).[16] This policy on pharmaceutical reimbursement also emerged in Canada. On the other hand, reference price systems (although not a substitute for economic analyses) were implemented in Germany, Netherlands, Denmark, Sweden and Norway.[16] It was believed that economic appraisal will aid this pricing system to support decisions on reimbursement limits.

Despite the increasing number of economic evaluation studies in health care, it is recognized that its use is hindered by several problems and limitations. A survey in the United Kingdom showed that some issues were important to consider beforehand. These included issues on timeliness, access, validity of

studies, multiple objectives of decision-makers and difficulties in freeing up resources. Another study involving members of the European member states also identified barriers to the use of economic appraisals.[17] However, despite these obstacles, policy-makers in these countries have recognized the relevance and importance of these studies in decision-making. Unfortunately, in the local setting, economic evaluation studies still has to make its presence felt, before it can influence or guide decision-making. However, in the context of Philhealth's direction towards using CPGs as the basis for reimbursement, an economic evaluation of the CPG would be an essential tool for policy makers.

F. Objectives of the Study

In view of the above issues and problems, this study was undertaken with the following objectives.

General Objective: To determine the cost-effectiveness of the recommendations of the clinical practice guidelines in the management of dyslipidemia in the Philippines using the societal perspective.

The specific objectives were:

1) to determine the costs of managing dyslipidemia following non-pharmacologic maneuvers;
2) to determine the costs of pharmacologic treatment of dyslipidemia; and
3) to determine the average and incremental cost-effectiveness ratios (average CERs and ICERs) of non-pharmacologic treatment compared to the 'do nothing' approach; pharmacologic vs. 'do nothing' approach;

and pharmacologic vs. non-pharmacologic interventions for the management of dyslipidemia as recommended in the guidelines.

The dyslipidemia guidelines contain 12 general statements or recommendations which cover both primary and secondary prevention strategies. In addition, a section containing 7 general recommendations is devoted for disadvantaged patients.[1] The guidelines referred to these patients as those who are a) "living below the annual poverty threshold of Php12,267.00 (as of 2003); b) cannot afford laboratory examinations and drug therapy; c) have limited or no access to health care; or d) are undernourished (e.g., people with BMI <18.5)."[1] The specific recommendations of the dyslipidemia guidelines are listed in Appendix 1.

II Methods

Effectiveness data were obtained from randomized controlled trials that were appraised beforehand by the technical research committee of the guideline developers and included in the CPGs. The trials included only those wherein clinically relevant endpoints were the outcome measures considered and not just mechanistic outcomes, e.g., lowering of cholesterol or lipid levels. Furthermore, in answer to the problem of applying results of foreign studies to the local setting, the INCLEN Guideline Development Cycle, otherwise known as the Knowledge Management Plus (KM+) was utilized in the guideline process[1]. KM+ incorporated not only appraisal of the trials' validity but also applicability to the target population, in this case, the Filipinos. This appraisal technique included questions on 'equity lens', i.e., those involving access to a particular health care

intervention. Moreover, once the trials were assessed to be valid, the results were extrapolated to the local setting by using local data. This was done by generating balance sheets of benefits and harm from the literature. Local event rates were calculated by multiplying the local prevalence rates (whenever available) with the relative risk reduction obtained in the trials.

A. Description of Competing Alternatives:

The alternatives analyzed in this paper were comparisons of 1) “doing nothing” versus lifestyle modification maneuvers which refer to adhering to diet interventions for dyslipidemia (low fat diet), and appropriate exercise regimens; 2) pharmacologic therapy for dyslipidemia, i.e., statins or fibrates versus “doing nothing” (placebo) and 3) lifestyle modification maneuvers (non-pharmacologic therapy) versus the pharmacologic treatments, statins or fibrates. These alternatives were the ones chosen because these are the various courses of action~~s~~ that may be taken when presented with the problem of dyslipidemia. Furthermore, the options on non-pharmacologic and pharmacologic maneuvers were the ones identified and appraised in the literature to be effective interventions for dyslipidemia.

For the dietary interventions, the guidelines utilized evidence obtained from a meta-analysis that included 27 studies. In this article, dietary fat restriction or modification was proven to reduce CV events and mortality. Moreover, the recommended daily total fat intake is 30-40% of total caloric intake or total fat intake should be reduced to approximately 35-40 g/day. Furthermore, dietary cholesterol intake is recommended to be from >300mg – 450 mg/day or

to 100 mg/1000 kilocaries/day.[1] Finally, these interventions were adhered to for more than 2 years, implying that compliance to these maneuvers was essential.

Recommendations for regular physical activity, on the other hand, specified that for this to confer benefits (decreased risk of death from cardiovascular and coronary heart disease) must be "vigorous, aerobic, habitual and continuing."[1] The guidelines cited a study where moderately vigorous activity totaling to 3 hours/week equivalent to about 3,500 kilocalories confer protection. Activities referred to above include "swimming, basketball, volleyball, badminton, tennis, jogging and running."[1] On the other hand, walking 35 miles (56 kilometers) or going up 438 flights of stairs (20 steps/flight) will correspond to 3,500 kilocalories.[1]

For the pharmacologic intervention, the possible options consist of any of 5 specific oral anti-hyperlipidemic drugs which belong to the family of statins and fibrates. The medicines found to be effective in reducing cardiovascular end-points in varying rates are the following:

1. Simvastatin 40 mg/day for 5-5.4 years,
2. Pravastatin 40 mg/day for 5 years;
3. Atorvastatin – any of the following daily dose for 3 years, 10 mg, 20 mg, 40 mg or 80 mg.
4. Bezafibrate 400 mg/day for 6.2 years
5. Gemfibrozil 1200 mg/day for 5 years

The dose and duration of the above medications were obtained from the evidence generated and appraised in the guidelines.

B. Identification, measurement and valuation of costs:

Previous literature on costing differentiated costs as direct and indirect costs. However, because of the confusion surrounding this classification, the 3rd

edition of *the economic evaluation of health care programmes* published in 2005 suggested doing away with this classification. Instead, costs were divided into four types which are described below.[4] This classification was utilized in this study, and the costs were expressed in current prices for mid 2007 Philippine peso, (Php) converted in US$ then, as well as the real or nominal prices in 2006 Php.

These costs were:

1) Health care resources consumed.

The health care resources consumed refer to the costs of setting up and running the program, as well as the possible adverse effects or events attributable to the program. Under this category of costs are variable costs (supplies) and fixed or overhead costs (rent, or capital costs). In this paper however, this type of cost was not incurred since there is no need to create a dedicated facility for the screening and management of dyslipidemia. Patients' consultations are done in existing out-patient clinics. Moreover, laboratory examinations for screening and monitoring of lipid levels and transaminases do not require setting up additional laboratory facilities. On the other hand, the costs for clinic visits and laboratory examinations were included in the out-of-pocket payments since the burden of these costs were on the patients or their families (please refer to next section). In addition, the costs of consultation for the lifestyle modification maneuvers were included in the 4th or last category of cost.

With regards the costs of treating possible adverse effects, again no such costs were included since no significant adverse events were reported for simvastatin, atorvastatin, fenofibrate and gemfibrozil.

2) Cost of patient/patient's family resources

This refers to out-of-pocket payments incurred by the patient/s and his family as well as value of resources allotted to the treatment process.

Out-of-pocket payments included cost of medicines, laboratory examinations, doctor's fees and transportation costs of going to and from the doctor's clinics. Some studies recommend using international prices of medicines, while others used the wholesale acquisition costs[18,19] In contrast, in this study the costs of medicines were computed based on the prices obtained from the biggest drugstore chain in the country. These prices were used since these are the real costs borne through out-of-pocket payments. In addition, this drugstore chain which has a nationwide presence, controls 80% of the retail market and claims uniform pricing scheme.[20] This claim was verified by a random survey of prices of some of the lipid lowering agents cited in the guidelines from this drugstore chain located in urban as well as rural areas.

Finally, in the issue of the cost of medicines, is the existence of different brand names or generics for a particular drug. A list of the prices of available brand names of the particular medication was done and a range was obtained from lowest to the highest-priced brand. The lowest price drug was used in the base case analysis.

Bioequivalence of generic/other brands in reference to the innovator drug

The prices of lipid lowering agents used to be very prohibitive. However, because of the emergence of generic as well as other branded medicines (of same generic name), especially in the case of simvastatin, the prices had dramatically gone down by more than 50%. On the other hand, makers of the innovator drugs as well as some sectors (which include physicians and patients), doubt the bioequivalence of these lower-priced medicines.

Bioequivalence refer to the property of a newer drug (which is usually priced lower) to have the same clinical efficacy as the innovator drug. In a similar context, the newer drug should not result to more adverse events in comparison with the innovator drug. Although the local Bureau of Foods and Drugs (BFAD) require bioequivalence studies prior to registration of drugs, this is only mandatory for drugs with reported bioavailability or bioequivalence problems.[21,22] A review of this list did not include any lipid lowering agents, although some (either from the pharmaceutical industry or the BFAD itself) claim that this is required for registration of any new drug. Despite this "requirement", the ambivalence of many regarding bioequivalence still persists. For this paper, the medicines included in the costing (except for gemfibrozil) were those with studies proving their bioequivalence with the innovator drugs (such copies were obtained from the manufacturers).

Cost of laboratory examinations was obtained using charges (charges, rather than real cost, again because these were borne through out-of-pocket payments) surveyed from several hospitals or out-patient private laboratories.

These included those from both government and private hospitals or laboratories. Again, the lowest charge was used for the base case analysis.

Variations again existed in the professional fees of doctors. In addition, patient's consultations entail other patient's concerns (e.g., other concomitant conditions especially in the setting of secondary prevention) and not only those pertaining to dyslipidemia, hence the cost attributed to dyslipidemia was not the total amount paid for the clinical consultation. Consultation fees ranged from P200.00-600.00/visit. The full amount of this consultation was used for the primary prevention strategy except for the high-risk and diabetic patients. This is because of the fact that the consultation time was not used solely for dyslipidemia but for the other concomitant conditions. Assuming that 50% of the consultation time was allotted to dyslipidemia, then computation of the cost will be 50% of the doctor's fees. The lowest range of the doctor's fees was again used for the base case analysis.

Transportation cost was estimated using the charges imposed by a laboratory which conduct home visits for purposes of extracting the specimen for laboratory examinations. The amount charged (P100.00) was considered acceptable even by those patients who belong to the lower socio-economic class since the average transportation costs could be similar or even higher than this.

3) Production Losses

The value of production losses had been referred to as "wealth lost to society due to disease".[24] On the other hand, the term 'productivity cost' was recommended by the US Panel on Cost-Effectiveness in Health and Medicine

which refers to “the costs associated with lost or impaired ability to work or to engage in leisure activities due to morbidity and lost economic productivity due to death.”[23] Earlier policies seem to disagree on the inclusion of this cost resulting from reduced productivity in economic evaluations. This can be seen in opposing views held by health authorities from Australia and Canada (Ontario, Canada) with regards reimbursement of pharmaceutical products. The 1990 Australian guidelines suggested exclusion of these costs while that from Ontario in 1991 suggested otherwise.[24]

Issues for the inclusion of productivity costs in economic evaluations

Arguing for a broader perspective in economic evaluations, i.e., that of a societal viewpoint, is seen to relate to the principles of welfare economic theory. Welfare economics depends on the principle that individuals want to maximize utility and societal welfare consists of the aggregation of utilities or preferences from all individuals.[25,26] This theory indicates that a “policy change may have a series of effects on different individuals and groups, and that an overall assessment of the efficiency of the policy needs to consider all of these implications.”[23] This implies that taking a narrower perspective, e.g., a specific health care system, rather than a societal viewpoint, might lead to the exclusion of non-health costs and benefits of a health care program and lead to inefficient delivery. Furthermore, savings incurred in the use of other resources outside the health care system as a result of an intervention will be of much value if these will be fed back into the health care budget.

On the other hand, the extra-welfarist approach concentrates more on the aggregate health gain rather than individual utility. The focus of this approach on health gain might exclude productivity costs in economic evaluations. However, Olsen's model showed that in maximizing utility from health, productivity gains are justified. This is in view of the fact that giving priority to productivity (implication of including productivity costs/production losses) can be warranted since it could "pay their way by financing extra health care".[23]

The above discussion arguing for the inclusion of productivity costs or production losses in an economic evaluation within a societal perspective rests on efficiency criteria. However, equity issues can also come into play. Those who are opposed to including production losses argue that programs directed to health care of the working people will always result to production gains or deemed more cost-effective compared to programs for the mentally ill or the elderly. Thus, it can be seen to increase existing inequalities in health even if allocation of resources may not be driven by such considerations.[24] Although this argument is important and should be given proper consideration, production losses brought about by illness still affects the wealth of society through its effect on scarcity of resources. In this regard, it should then be included in economic analyses of health care programs.

As stated earlier, society's gain will definitely increase by providing programs to those who are economically active. As such, trade-offs between equity and efficiency, may need to be considered in allocating resources.[24] However, being explicit about these non-health care costs, i.e., extent of the

trade-off will be of better help to decision making rather than implicit assumptions. Furthermore, an analysis that only includes health care costs is not consistent with a societal perspective and will not provide guidance to societal decision making.[27] Finally, the trade-off between efficiency and equity "will largely depend on a society's attitudes to inequality."[23]

Valuation of productivity costs/production losses

Three approaches had been cited in the literature (although there can be some overlap between these approaches) in valuing lost work (and leisure time) due to disease. These are the human capital approach, friction cost method and the US Panel approach.[23,24] The human capital approach had been used to value changes in the quantity of paid working due to sickness or health care programs designed to diminish ill health. This approach which uses the gross wage as the reference unit for valuing changes in paid working time was seen to measure 'potential value of production loss' rather than actual production loss due to illness.

Because of problems in the human capital approach, a group of economists from Netherlands developed the friction cost method for valuing production losses. This method centers on the "valuation of lost time from paid work as a result of illness".[23] In this approach, the "amount of production lost due to disease depends on the time-span organizations need to restore the initial production level."[4] However, friction period varies and is influenced by location, industry, type of work, etc. On the other hand, some studies have shown lower

productivity costs using the friction method approach compared to the human capital approach.

The US Panel proposal listed five components of costs brought about by the effect of illness on productivity. These were 1) effect of loss of work time on sick individual, 2) effect of loss of leisure on sick individual, 3) external effects (via tax), 4) effect on the previously unemployed and 5) effect on employer (recruitment and training). The major problem seen with this proposal was due to the use of a generic preference-based measure of health like QALY as the means of valuation of the effect of disease on productivity.[23]

Comparison of the three approaches on valuation of productivity cost was summarized by Sculpher in the following figure:[23]

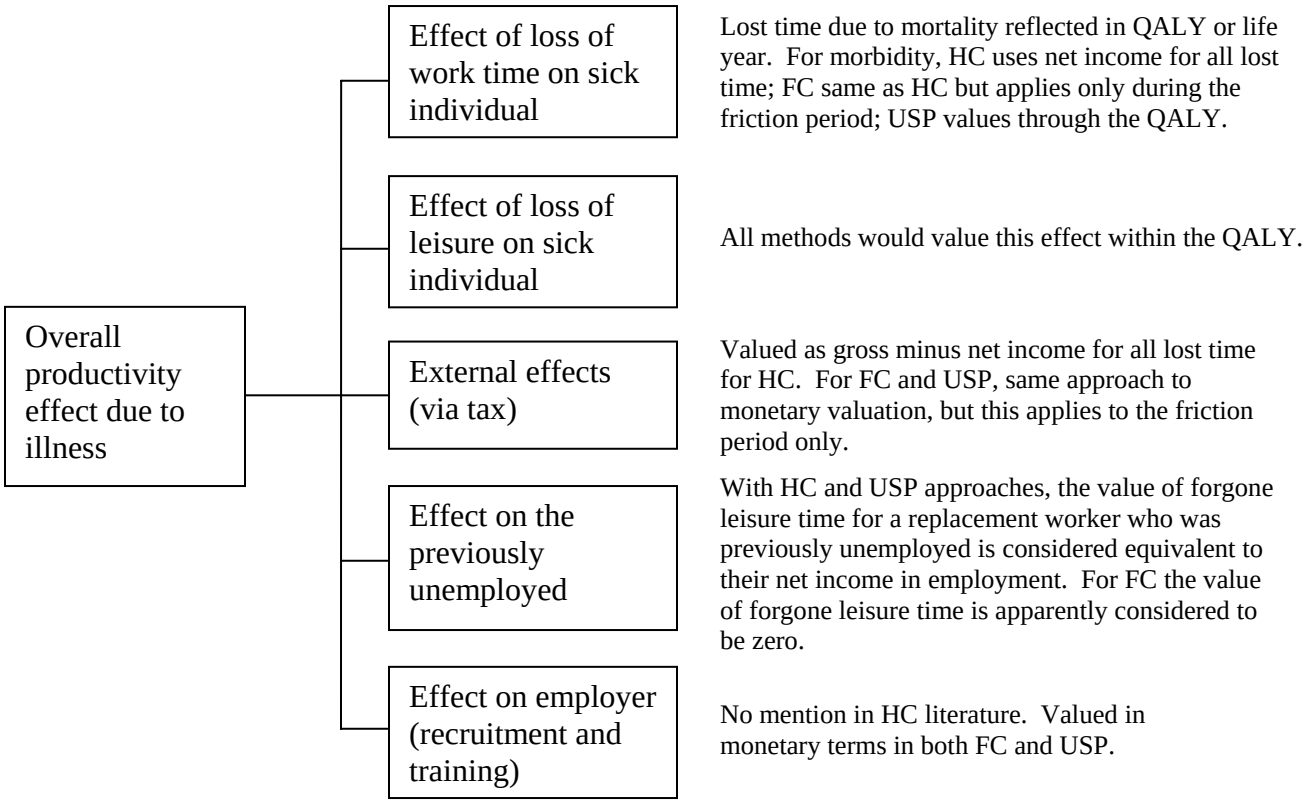


Figure 1 Components of productivity cost and differences between the human capital (HC), friction cost (FC) and US Panel (USP) approaches to valuing each component
(from Sculpher MJ. The role and estimation of productivity costs in economic evaluation. In: Economic evaluation in health care: merging theory with practice (ed. M.F. Drummond and A. McGuire), 94-112. 2001; Oxford University Press, Oxford)

The friction cost method in valuing short-term absences is important in the valuation of production losses brought about by attending programs directed to the management of dyslipidemia which consist of out-patient visits. This is brought about by the fact that dyslipidemia, although considered an important risk factor for the development of possibly fatal outcomes such as strokes or heart attacks, is an asymptomatic condition. Since the management recommendations for dyslipidemia consist of out-patient consultations as well as programs for healthy lifestyle, absences from work usually entail a few hours or at most one day per clinic visit. This time period away from work will enable the

employee/worker to go to the doctor's clinic or medical facility for consultation as well as for the determination of lipid levels.

For short-term absences, variations may exist on how a firm or industry will react to this type of absences of its workers. In view of this uncertainty, Koopmanschap and his group estimated the elasticity of production in reference to changes in labor time in Netherlands. They found this to be 80%, i.e., for every 1 per cent reduction in labor days would lead to 0.8 per cent reduction in production.[24] However, the use of the friction cost method need country-specific estimates of several parameters which can change over time.[23]

On the other hand, in the Philippines, the definition of labor productivity forwarded by the Organization for Economic Cooperation and Development (OECD) as "the ratio of a volume measure of output to a volume measure of input" was adopted.[28] Thus, labor productivity was computed by dividing the Gross Domestic Product (GDP) by the number of employed persons (average of four survey rounds of the Labor Force Survey or LFS).[29,] On the other hand, "GDP refers to the value of all goods and services produced domestically; the sum of gross value added of all resident institutional units engaged in production (plus any taxes, and minus any subsidies, on products not included in the values of their outputs)."[30] Production losses from work due to out-patient consultations/laboratory determinations for dyslipidemia were measured as the daily cost of labor productivity multiplied by the number of days of absences incurred in the treatment period (duration of treatment in the trials cited for a particular drug).

However, not all employers allow their workers to have their out-patient medical consultations on regular working hours. In these instances, workers spent part of their leisure time for medical purposes, thus the cost of leisure time was also determined (discussed below).

Lastly, compliance rates to the guideline recommendations may vary. For this purposes, the sensitivity analysis (in later section) discussed the effects of differences in patient's compliance rates with regards the cost-effectiveness analysis.

Valuation of Leisure Time

Arguments exist regarding assessment of the market valuation of leisure time. Using the neoclassical theory, "assuming diminishing marginal utility from leisure, an individual will devote time to paid work until the opportunity cost of that time equals the marginal benefit which is the wage-rate (net of taxes and other deductibles) received from employment." If one's time is used for either paid employment or leisure, the opportunity cost of working time is foregone leisure, which at the margin, can be valued as net (take-home) wage.[23]

Another way of looking at the cost of leisure time would be as follows. More often than not, people would prefer to spend their time on leisure rather than work. The value of an hour or a day of leisure is the amount of income that one gives up by not working for that hour or for that day. Thus, leisure can be valued as the hourly or daily wage. Moreover, one may choose to spend his time on leisure until the marginal utility of spending the next hour or day on leisure is not anymore greater than the hourly or daily wage.

Drummond et al, on the other hand stated that the value of leisure time may range "from zero, to average earnings, to average overtime earnings (time and a half or double time)."[4]

Based on the above, i.e., valuing leisure time as the hourly or daily wage, this paper estimated leisure time based on an individual's earnings. These earnings, on the other hand, could be average earnings (net wage) or average overtime earnings.[4] Moreover, the average minimum daily wage and overtime rates in the different regions on the country as promulgated by the Department of Labor and Employment was utilized. Average overtime rates were then calculated as 150% of average minimum daily wage rates.[31]

The three cost categories mentioned above usually make up the majority of the costs relevant to economic evaluations of health programs/services. However, a fourth category which is often left out can still be considered and is discussed as follows.

4) Cost due to consumption of other resources/sectors

This last type of cost measures resources consumed in other sectors including those from volunteer work or those exemplified in the following example. The enactment of the clean air act by the local Congress resulted in the additional processing of crude oil to produce gasoline that will be less harmful to the environment. This added cost resulted in an increase in the price of gasoline that is borne by consumers; such increase in gasoline prices has far-reaching effect on the prices of commodities since the cost of transporting goods and services will likewise increase. Ideally, this fourth category of cost should be

included in economic analysis. However, these costs are often left out because they are insignificant or because of the difficulty in valuing them (as in volunteer work).

For the dyslipidemia guidelines economic analysis, included in this last category is the cost of education programs on lifestyle modifications. The cost of time spent on physical exercise is also included in this category. Some may argue that engaging in activities such as biking, swimming, playing badminton and the like are not only for exercise purposes but more specifically ways of spending 'quality' time with family members or friends from which they derive immense pleasure. Because of these reasons, no monetary cost is attributed to the time spent on exercise. Others, on the other hand, might look at exercise time as a diminution in leisure time. Because of these varying views, the cost of time spent in physical exercise would range from zero (in the base case analysis) to the cost of leisure time (sensitivity analysis).

This last type of cost is included in both pharmacological and non-pharmacological interventions for dyslipidemia. Hence, the effect will be on the average CER but not on the ICER.

The summary of the different components of the costs that were identified in the treatment of dyslipidemia using a societal viewpoint is listed in the following table (Table 1). This table also includes how these costs are measured and valued.

Table 1 Summary of the societal costs of treating dyslipidemia

Costs Identified	Measurement of Costs	Valuation of Costs
1. Health care resources consumed - Costs of treating adverse events	Cost per single adverse event multiplied by the number of adverse events	Depends on the adverse effect identified (no significant ones identified for simvastatin, atorvastatin & fibrates)
2. Cost of patient/patient's family resources		
a) Cost of Medicines	Unit price of specific lipid lowering agent multiplied by the treatment/trial duration*, multiplied by 1000 patients**	prices obtained from the biggest drugstore in the country
b) Laboratory Costs	Unit price (charge) multiplied by frequency of screening tests (trial duration)* x1000**	Unit price/charge from laboratories range; minimum-maximum
c) Doctor's Fees	out-patient fees multiplied by number of visits (during trial duration)* x 1000**	out-patient consultations fees (50 - 100%); minimum-maximum fees
d) Travel Costs	frequency of travel depends on number of visits/laboratory testing x 1000**	transportation charges by laboratory doing home visits
3. Production Losses**		
a) Labor productivity	½ day – 1 day/visit multiplied by number of visits (treatment duration)*	GDP/average number of employed persons
b) Cost of Leisure Time	same time spent as above (for those who will not use work time in doing out-patient consultations)	Average net wage rate – overtime wage rate
4. Cost due to consumption of other resources/sectors - lifestyle modification maneuvers education programs	Number of consultations for lifestyle modification maneuvers, e.g., diet/exercise prescriptions	Charges/consultation on non-pharmacologic treatment, e.g., diet/exercise
- time spent on exercise	Number of hours spent	0 - value of leisure time

*refers to the duration of treatment (follow-up period) of specific trials used in the CPG
** these costs were measured for every 1000 patients treated with each of the pharmacologic agent for easier comparison purposes to come up with x number of endpoints (reduction in heart attack/stroke/mortality) produced; for cost of production losses of 1000 patients, x number will be computed based on labor productivity cost, while (1000-x) will be computed based on cost of leisure time.

Consequences/Outcomes Measured

Clinical endpoints resulting from the above-mentioned treatment which are reductions in total mortality, cardiovascular deaths, strokes, acute myocardial infarctions (AMIs) or revascularizations were the clinical outcomes measured in this study. Table 2 gives a summary of the parameters of effectiveness identified, measured and valuated in this paper.

Table 2 Summary of Consequences

1. Reduction in Heart Attacks (Fatal or nonfatal Myocardial Infarction)
2. Reduction in Strokes (Cerebrovascular Disease)
3. Reduction in Revascularization
4. Reduction in Mortality

Cost-Effectiveness and Incremental Cost-Effectiveness Ratios

A cost-consequence approach[9] was initially done before coming up with the cost-effectiveness ratios, i.e., looking into all the health outcome measures or clinical end-points attributed to a particular drug. These different consequences were summed up as total major events prevented to come up with a single outcome for the cost effectiveness analysis. Average cost-effectiveness ratios (CERs or average CERs) were obtained by dividing total costs by the total number of major events prevented by each of the pharmacologic agents. These were thus expressed as the cost per any major event reported, i.e., either total mortality, cardiovascular death, AMI, stroke or revascularization (although it can

be argued that these endpoints cannot be valued equally). The cost-effectiveness ratios computed in this paper are for 1) non-pharmacologic therapy compared to the "do nothing" alternative, 2) pharmacologic treatment compared to the "do nothing approach", and 3) pharmacologic therapy compared to non-pharmacologic treatment. The corresponding average and incremental cost-effectiveness ratios were computed. Average CER referred to the cost per benefit obtained from the intervention. ICERs on the other hand, refer to the marginal cost for the additional benefit obtained from the alternative treatment. For the non-pharmacologic approach and pharmacologic approaches compared to the "do nothing" alternative, the average CERs of both approaches can also be considered ICERs since the "do nothing" alternative incurs zero cost and zero benefit. Furthermore, aside from comparing the drug therapy to the "do nothing" alternative, the other option was to compare it to non-drug approach, hence the different ICERs of each pharmacologic agent compared to non-pharmacologic treatment were also determined (the usefulness of the average CERs is discussed in the next chapter). Finally, whenever possible (if dominance of an intervention was not present), ICERs between different pharmacologic treatments were computed.

For comparison purposes, the costs and effectiveness (events prevented) computation was for treating 1000 patients.

C. Analysis

1) Base Case Analysis

For the base case analysis, the lowest cost in the range of prices/charges (prices of medicines, laboratory charges or consultation fees) was used. In addition, no discounting was done for both costs and effects in the base case analysis.

2) Sensitivity Analyses

Several one-way sensitivity analyses were done, i.e., changing one variable at a time during computation. First was, still using the undiscounted cost, the highest-priced brand of the specific drugs were the ones used for computation. The next analysis used the highest level of the charges in the other listed items. The other one-way analyses consisted of using the discount rates, 3% and 5% in the computation of costs and effects.

Some multiway analyses whereby two or more different parameters were changed at the same time such as variations in the prices of medicines, charges of laboratories or doctor's fees or valuation of production losses were also done.

Discounting

A 3% discount rate for both costs and effects in the base case analysis and 6% for costs and 0% for effects in the sensitivity analysis is recommended by the WHO Guide for CEA while Drummond recommends using 3% and 5% in the base analysis and include 0%, 3% and 5% in the sensitivity analysis (for both costs and effects).[3,18] In this paper, 0% (undiscounted), 3% and 5% were used in the base case and sensitivity analyses for both costs and effects.

III Results:

The recommendations of the guidelines can be divided into pharmacologic and non-pharmacologic interventions (refer to appendix 1 for the specific recommendations). The non-pharmacologic interventions which are applicable to all consisted of lifestyle modification maneuvers such as dietary advice (low fat diet), cessation of smoking, and appropriate exercise. These were listed in guideline statement numbers 1-3. For the pharmacologic interventions, these were divided into either primary (statements 4-7) or secondary prevention strategies (statements 8-9). The recommended laboratory examination to be used to screen for dyslipidemia again depended whether these were for primary (statements 10-11) or secondary prevention strategies (statement 12).

On the other hand, the cardiovascular (CV) risk factors attributed to in the guidelines are hypertension, familial hypercholesterolemia, left ventricular hypertrophy, smoking, family history of premature coronary artery disease (CAD), male sex, age > 55 years, proteinuria, albuminuria, body mass index (BMI) $\geq$ 25. Patients are categorized as low-risk if they have < 3 risk factors. However, once familial hypercholesterolemia is present, pharmacologic treatment is warranted despite the absence of other risk factors.[1]

A. Base Case Analysis

Table 3 contains the different costs included in providing non-pharmacologic treatment for 1000 patients with dyslipidemia expressed in Philippine peso and US dollars. These consisted of doctor's fees, laboratory examinations, transportation, production losses as well as the education program

package charges obtained from a clinic providing education sessions on nutrition, physical fitness or other related issues. As can be noted from this table, there can be several ways whereby the education packages as well as the laboratory screening can be measured. For the education package, this could either be the 3- or 4-module package. These modules could either include a combination of sessions on high cholesterol levels, hypertension, diabetes or obesity, etc. In the primary prevention strategy except for those with $\geq$ 3 CV risk factors (high risk) and diabetic patients, the 3-module package was selected. In contrast, because of the presence of more risk factors or concomitant conditions, the 4-module package was chosen for high risk or diabetic patients as well as for the secondary prevention strategy.

On the other hand, the guideline stated that laboratory monitoring could either be 1) a single cholesterol measurement or 2) lipid profile monitoring. In addition, monitoring of cholesterol levels instead of lipid profile as a possible option in clinical practice was also included (to be used in subsequent sensitivity analysis). The guidelines though, were not explicit on the number as well as the frequency of consultations. In view of this, as well as the fact that the Heart Protection Study (HPS)[32] was cited both for primary (laboratory parameters for treatment thresholds) and secondary prevention, the frequency of laboratory monitoring utilized in HPS was adopted. In addition, monitoring of transaminases, SGOT and SGPT (or AST and ALT), which were done both in HPS and usual clinical practice were included in the costing. For consistency

purposes, this paper utilized the protocol of HPS whenever there were issues not explicitly stated in the local guidelines.

The effectiveness of non-pharmacologic interventions, on the other hand, was obtained if patients stayed on such management for > 2 years as cited in the meta-analysis of this type of treatment.[33] Since no exact duration for the excess in the two years was specified, several treatment durations were done such as 2.5 years corresponding to 6 months after the second year (to be consistent with the HPS protocol where the next visit after 2 years was 6 months) or 3 years and 5 years. The treatment duration of 3 and 5 years corresponded to the treatment duration of the specific pharmacologic agent used in the drug trials.

Table 3
Cost of non-pharmacologic Intervention and number of events prevented in treating 1000 patients

	2.5 years*	3 years**	5 years**
Doctor's fees	1,400,000.00/30,435.00	1,600,000.00	2,400,000.00
Education Package (3 modules)	550,000.00/11,957.00	550,000.00	550,000.00
Education Package (4 modules)	725,000.00/15,761.00	725,000.00	725,000.00
Laboratory: 1) single cholesterol determination	50,000.00/ 1,087.00	50,000.00	50,000.00
2) cholesterol monitoring	350,000.00/ 7,609.00	400,000.00	600,000.00
3) lipid profile monitoring	1,715,000.00/37,283.00	1,960,000.00	2,940,000.00
Transportation	700,000.00/15,217.00	800,000.00	1,200,000.00
Production Losses**	755,776.00/16,865.00	863,744.00	1,295,615.00
Total Events Prevented (for non-pharmacologic intervention trials)	125 events	125 events	125 events

*in Php/US$(1 US$ = P46.00 as of June, 2007; rounded-off to the nearest Php (Philippine peso)
** in Php as of June, 2007; *** based only on cost of labor productivity (refer to Table 4)

In Table 4a, the cost of the medicines (simvastatin and fenofibrate) in treating 1000 patients who do not have any evidence of atherosclerosis (primary prevention) but have ≥ 3 risk factors for cardiovascular diseases or are diabetics are listed. The corresponding total events prevented are also given. As mentioned in the methods section, these events refer to any of the following: total mortality, cardiovascular death, myocardial infarction, stroke, or revascularization. The treatment duration for each of this drug was based on the length of the particular trial where the efficacy of the drug was proven.

In contrast Table 4b lists the cost of three statins and a fibrate, i.e., gemfibrozil for treating patients with evidence of atherosclerosis (secondary prevention). Again, the treatment duration depended on the length of the study of the particular drug. The cost for simvastatin was computed based on the two treatment trials used for the secondary prevention strategy. These trials were the HPS and the 4S (Scandinavian Simvastatin Survival Study).[32,34] The effectiveness of the drugs was measured as the total events prevented for every 1000 patients treated. The details of these events are shown on appendix 2.

Table 4a
Cost of Medications for 1000 patients*
(Primary Prevention Strategy)

Primary Prevention	Cost	Treatment Duration	Total Events prevented/1000
1. ≥ 3 CV risk Factors			
Simvastatin	35,131,250.00/763,722.83	5 years	17 events
2. diabetics			
Simvastatin	35,131,250.00/763,722.83	5 years	33 events
Fenofibrate	64,331,250.00/1,398,505.43	3 years	31 events

*in Php/US$ (1 US$ = P46.00 as of June, 2007)

Table 4b
Cost of Medications for 1000 patients*
(Secondary Prevention Strategy)

Secondary Prevention	Cost	Treatment Duration	Total Events prevented/1000
Simvastatin; 4S	37,941,750.00	5.4 years	168 events
HPS	35,131,250.00	5.0 years	89 events
Atorvastatin	65,700,000.00	3 years	87 events
Pravastatin	469,025,000.00	5 years	93 events
Gemfibrozil	62,962,500.00	5 years	45 events

*in 2007 Philippine peso

On the other hand, Table 5 lists the costs of out-of-pocket payments that were incurred under the secondary prevention strategy. These included cost of medicines, laboratory examinations, consultation fees as well as transportation expenses for every 1000 patients treated. Computation of the total cost would include the combination of any of the medications with any of the laboratory parameter selected, as well as the corresponding doctor's fees and transportation expenses. The duration of treatment, laboratory screening, consultation and transportation should be consistent with the duration of the specific drug treatment chosen.

The costs in table 5 were given both in mid 2007 nominal prices as well as the corresponding real prices in 2006 Philippine peso. These costs were expressed in 2006 real prices because the most recent available data for the computation of production losses (see below) were in 2006 real prices. Thus, in order for the subsequent computation for the cost-effectiveness ratios to be consistent, all the cost components were computed in 2006 real prices.

Table 5
Costs of patient/patient's family resources consumed in dyslipidemia treatment (secondary prevention)

	Mid 2007 prices	2006 real prices
Cost of Medicines		
1. Simvastatin	35,131,250.00	34,285,912.07
2. Atorvastatin	65,700,000.00	63,979,618.00
3. Pravastatin	469,025,000.00	457,739,190.00
4. Gemfibrozil	62,962,500.00	61,447,479.00
Cost of laboratory examinations;		
A. Cholesterol + transaminases for #s2-4		
1. chol (once)	50,000.00	48,797.00
2. 3 years	1,440,000.00	1,405,350.00
3. 5 years	2,160,000.00	2,108,025.00
4. 5.4 years	2,340,000.00	2,283,694.00
B. Lipid profile + transaminases		
1. 3 years	3,000,000.00	2,927,813.00
2. 5 years	4,500,000.00	4,391,720.00
3. 5.4 years	4,875,000.00	4,757,696.00
Doctor's fees for pharmacologic management; 50%)		
1. 3.0 years	800,000.00 – 2,400,000.00	780,750.00– 2,342,251.00
2. 5.0 years	1,200,000.00 – 3,600,000.00	1,171,125.00– 3,513,376.00
3. 5.4 years	1,300,000.00 – 3,900,000.00	1,268,719.00– 3,806,157.00
Travel costs		
1. 3 years	800,000.00	780,750.00
2. 5 years	1,200,000.00	1,171,125.00
3. 5.4 years	1,300,000.00	1,268,719.00

Consumer Price Index (CPI) for 2006 = 137.9; June, 2007 = 141.3[37]

Table 6 contains the cost of production losses per day for every 1000 workers who absent themselves to be able to consult and have their laboratory examinations done. The cost of labor productivity (per person) was obtained by dividing the real GDP with the average number of employed persons for 2006.[28] The range of daily cost of leisure time lost, on the other hand, was obtained from

the average of the minimum daily wage rates to the average overtime rates which took effect in mid 2006.[31,35,36] These averages were taken from the wages from the 16 regions of the country representing a mixture of urban and rural areas.

Table 6 Daily Production Losses

A. Cost of Labor Productivity* (per day x 1000)	
Real or Constant Prices (2006)	*105,370.00*
B. Leisure Time (per day x 1000)	
Average Minimum Daily Rates**; Current Prices (2006)	174,580.00 – 216,140.00
Average Minimum Daily Rates; *Constant Prices (2006)*	*126,599.00 – 156,737.00*
Average Overtime Rates***; Current Prices (2006)	261,870.00 – 324,210.00
Average overtime Rates; Constant or Real Prices (2006)	*189,898.50 – 235,105.15*

*Cost of Labor Productivity - Php 38,460 in 2006[28]; Php = Philippine peso
**Obtained from the minimum daily wage rates from the 16 regions of the country (average), which took effect on July- August, 2006.[35]
***Additional 50% to the average minimum daily wage which took effect on July-August 2006[31,36]
Consumer Price Index (CPI) for 2006 = 137.9; base year - 2000 (CPI = 100)[37]

B. Cost-effectiveness Ratios

Primary Prevention

The cost-effectiveness ratios (CERs) of non-pharmacologic or pharmacologic treatment (either average cost-effectiveness ratios referred to as CERs and incremental cost-effectiveness ratios referred to as ICERs in the subsequent discussion) were determined. As earlier stated, CERs represent the cost for every benefit obtained from the specified treatment strategy. ICERs, on the other hand, refer to the additional or marginal cost incurred for every additional benefit derived from the alternative therapy.

For the base case analysis, the following assumptions were made:

1. comparisons done are either: non-pharmacologic treatment vs. “do nothing” or pharmacologic vs. “do nothing” or pharmacologic vs. non-pharmacologic treatment;
2. all costs were computed for treating 1000 patients;
3. non-pharmacologic treatment was given for a duration of 2.5 years;
4. the lowest prices or rates were used for the following: medications, laboratory examination charges and doctor’s fees;
5. the doctor’s fees for the high-risk patients/diabetics as well as for the secondary prevention strategy were halved (50%) since the patients are consulting not only for dyslipidemia but other conditions, e.g., hypertension, diabetes, etc.; 100% for primary prevention (low risk patients);
6. the lowest-priced medication have the same bioequivalence or bioavailability as the innovator drug;
7. the number of visits (doctor’s visits) over the treatment period followed the protocol of the Heart Protection Study[32];
8. the time spent for each consultation or education session plus the laboratory examination equals one day (to be used for the computation in the production losses);
9. the laboratory screening and monitoring strategies consisted of either a) single cholesterol determination b) monitoring of cholesterol levels and c) lipid profile during the treatment period;
10. monitoring of the liver enzymes (transaminases) SGOT or AST and SGPT or ALT were added to the laboratory examinations whenever pharmacologic treatment is given;
11. transportation cost was based on the charge for blood extractions being conducted at home (home visits) by certain laboratories offering such services;
12. for the production losses: 2nd column in table 5 referred to 100% of production losses derived from cost of labor productivity alone while in the next 2 columns production losses were derived from 50% cost of productivity and 50% from cost of leisure time;
13. costs of leisure time were based from the average minimum-maximum daily and overtime rates from the 16 regions of the country;
14. overtime rates were computed as additional 50% of the daily average wage rates;
15. the cost of education program was derived from charges for a counseling package (3 modules for the non-pharmacologic treatment without medications and 4 modules for those with $\underline{\geq}$ 3 CV risk factors and diabetics);
16. compliance rate to monitoring and treatment was 100%
17. time spent in exercise was not given any cost (see sensitivity analysis);
18. all computations were based on 2006 constant or real prices (Philippine prices).

Table 7 shows the average cost-effectiveness ratios (CERs, i.e., the cost for every benefit in terms of clinical outcomes obtained) in the base case analysis (1st column) as well as the change in the CERs if half of the production losses were derived from labor productivity and the other half from the cost of leisure time. In addition, the cost of leisure time was determined either through the average minimum daily rates or through the average overtime rates.

For the non-pharmacologic treatment, there was minimal variation in the CERs if the production losses were obtained solely from labor productivity or if these were divided equally into labor productivity and cost of leisure time. Likewise, the change in the CERs was minimal between single cholesterol determination and monitoring of cholesterol levels together with the transaminases, SGOT and SGPT (or AST and ALT). However, if the laboratory monitoring utilized was the lipid profile (also with the above transaminases), the difference in the CERs was about Php10,000 per event in treating 1000 patients.

For the pharmacologic intervention, the CER was also not affected much by varying the computation for production losses into labor productivity alone or labor productivity and cost of leisure time. However, the CERs for those with $\geq$ 3 CV risk factors changed considerably (more than Php100,000 – 250,000) if the laboratory screening and monitoring methods were changed. On the other hand, the change in the CERS for patients with diabetes were smaller (< P50,000). The type of pharmacologic agent used for diabetics has a large effect on their CERs (about 1 million pesos!). Simvastatin's lower CER compared to fenofibrate was brought about by its lower cost and greater benefits (see table 4a).

Table 7 CERs* for the Primary Prevention Strategy

	Production Losses (100% from labor productivity losses CERs	Production Losses (50% from labor prod losses; 50% from cost of leisure time**) CERs	Production Losses (50% from labor prod losses; 50% from cost of leisure time***) CERs
Non-pharmacologic a) single cholesterol determination	26,980.98	27,575.39 - 28,419.25	29,347.77 - 30,613.56
b) cholesterol monitoring	29,323.23	29,917.64 - 30,761.50	31,690.02 - 32,955.81
c) lipid profile monitoring	39,980.47	40,574.88 - 41,418.74	42,347.26 - 43,613.05
≥ 3 CV risk factors **Simvastatin** a) Single Cholesterol determination only	2,273,467.89	2,280,960.47 – 2,291,597.41	2,303,301.47 - 2,319,256.75
b) Cholesterol & SGOT, SGPT determination	2,394,598.96	2,402,091.55 - 2,412,728.49	2,424,432.55 - 2,440,387.84
c) Lipid profile & SGOT, SGPT	2,528,933.92	2,536,426.51 - 2,547,063.45	2,558,767.51 - 2,574,722.80
Diabetics **Simvastatin** a) Single Cholesterol determination only	1,171,180.42	1,175,040.24 - 1,180,519.88	1,186,549.24 - 1,194,768.63
b) Cholesterol & SGOT, SGPT determination	1,233,581.28	1,237,441.10 - 1,242,920.74	1,248,950.10 - 1,257,169.49
c) Lipid profile & SGOT, SGPT	1,302,784.14	1,306,643.96 - 1,312,123.60	1,318,152.96 - 1,326,372.35
Fenofibrate a) Single Cholesterol determination only	2,127,229.16	2,129,968.38 - 2,133,857.16	2,138,136.06 - 2,143,969.18
b) Cholesterol & SGOT, SGPT determination	2,170,988.94	2,173,728.17 - 2,177,616.94	2,181,895.84 - 2,187,728.96
c) Lipid profile & SGOT, SGPT determination	2,220,100.65	2,222,839.87 - 2,226,728.65	2,231,007.55 - 2,236,840.66

*CER (average cost-effectiveness ratio) of non-pharmacologic or pharmacologic compared to "do nothing" approach

**minimum - maximum average daily rates all over the country (2006 real prices)

***minimum - maximum average daily overtime rates all over the country (2006 real prices)

On the other hand, Table 8 lists the incremental cost-effectiveness ratios (ICERs) of pharmacologic treatment compared to non-pharmacologic maneuvers for the primary prevention strategy for diabetics and those with $\geq$ 3 CV risk factors. This ratio refers to the additional cost for every additional benefit obtained with drug treatment compared with giving non-pharmacologic therapy only. In the computation for this table, the assumption for the duration of the non-pharmacologic treatment was changed from 2.5 years to the duration of the pharmacologic treatment. This resulted to 3.0 years for fenofibrate and 5.0 years for simvastatin. Furthermore, since the non-pharmacologic treatment was the comparator in the randomized trial, the incremental costs were due to the costs of the medications and the additional laboratory tests. The incremental costs in the laboratory were due to the costs of the monitoring of the transaminases. The costs for either cholesterol or lipid monitoring which were incurred by both treatment arms were excluded from the incremental costs. This resulted to similar ICER whether the laboratory monitoring strategy was either through cholesterol or lipid profile determination.

The above exclusion of some of the components of the costs that went into the computation of the average CER, in contrast to the computation for the ICER, demonstrates that fact that the average CER is useful in terms of giving the information in terms of totality of all the costs for every benefit obtained. This is due to the fact that in the pharmacologic option, the costs of non-pharmacologic maneuvers are also included in the total costs; hence just looking

at its ICER will not give the complete picture of all the costs of this alternative. Thus the average CERs are much higher than the ICERs.

For diabetics, simvastatin is more efficient (technical efficiency) than fenofibrate since its incremental cost per additional clinical benefit (over non-pharmacologic therapy) is less by almost a million pesos. (Appendix 4 gives the details of Table 8).

Table 8 ICERs for Primary Prevention
Pharmacologic vs. Non-pharmacologic Treatment

	Simvastatin	Fenofibrate
With ≥ 3 CV Risk Factors:		
a) Single Cholesterol	2,016,818.36	
b) Cholesterol/lipid profile monitoring	2,106,374.99	
Diabetics		
a) Single Cholesterol	1,038,967.03	2,025,267.48
b) Cholesterol or lipid profile monitoring	1,085,102.27	2,058,008.62

Secondary Prevention

The assumptions for the base case analysis for the secondary prevention strategy are the same as for the primary prevention except when a particular assumption is modified. Such modification will be explained prior to the listing of the corresponding CERs.

Table 9 shows the average CERs (cost per benefit obtained) of the different lipid-lowering agents that can be used for the secondary prevention strategy. These CERs refer to the comparison of the different pharmacologic maneuvers (treatment duration = trial duration) compared to placebo or the "do nothing" approach depending on the type of laboratory parameter used for

screening or monitoring. The production losses included in the computation was derived solely (100%) from productivity cost. A comparison of these CERs revealed that simvastatin has the lowest CERs while pravastatin has the highest CERs. Moreover, simvastatin was the dominant alternative and this was brought about by its lowest cost and highest number of events prevented (least cost and most effective). Because of these, incremental cost for additional benefit obtained (ICER) is not possible between simvastatin as compared to the other medications. Table 2 and appendices 2 & 5 give out the details of the cost and effectiveness of these treatment options.

Table 9 CERs for Secondary Prevention
Pharmacologic Treatment vs. "do nothing" approach

	Simvastatin	Atorvastatin	Pravastatin	Gemfibrozil
Single Cholesterol determination	246,379.93	773,332.42	4,968,841.20	1,462,456.03
Cholesterol & SGOT, SGPT monitoring	258,637.24	788,924.99	4,990,983.45	1,508,216.65
Lipid profile, SGOT & SGPT monitoring	272,230.66	806,424.56	5,015,539.30	1,558,965.41

The following table (Table 10) gives the ICERs of the pharmacologic therapy compared to non-pharmacologic treatment for the secondary prevention strategy. In contrast to the assumptions earlier listed, the duration of the non-pharmacologic treatment for this computation was assumed to be similar as that of the specific drug therapy (instead of the constant 2.5 years in the base case analysis). This was done to correspond with the individual trial treatment period whereby the drug was compared to non-pharmacologic treatment. The resulting

incremental costs included the cost of the medications involved and the additional laboratory screening parameters indicated for the drug treatment. Since the difference in the laboratory parameter only involved the addition of the transaminases, the resultant ICERs were the same whether one would opt to use cholesterol or lipid profile for monitoring. Among the four drugs, simvastatin had the lowest ICER being the most effective with the least cost (the dominant option). In addition, two ICERs were obtained for simvastatin (both for the undiscounted and discounted tables – Table 10 and *Table 10D*), the first one derived its data from 4S and the other one from HPS. These two studies proved the effectiveness of this particular drug. Differences in the ICERs could be due to 1) variability in the calculation of effectiveness and 2) differences in the population of the two trials. In 4S, the endpoints summed up were reductions in total mortality (all-cause mortality) and first-ever myocardial infarctions or stroke or revascularization (total of 168 events). On the other hand, in HPS, the outcomes included were the occurrence of first-ever vascular event which may be fatal or nonfatal myocardial infarctions or strokes and revascularizations (total of 89 events). In terms of population, HPS is composed mainly of patients for secondary prevention strategy mixed with high-risk patients for primary prevention strategy. 4S population, in contrast, is composed only of patients for secondary prevention strategy.

Table 10 ICERs for Secondary Prevention
Pharmacologic vs. Non-pharmacologic Treatment

	Simvastatin	Atorvastatin	Pravastatin	Gemfibrozil
Single Cholesterol determination	220,409.43* 385,234.97**	737,001.24	4,921,926.77	1,365,499.53
Cholesterol or lipid profile monitoring	229,471.71* 402,341.29**	748,667.63	4,938,297.34	1,399,332.04

*derived from 4S data; **derived from HPS data

Discounting

So far, no discounting has been applied in all the analyses that were presented in all preceding sections. In health care, the costs of health programs are not incurred all together in the present time but are spread over in the future. Benefits on the other hand, are achieved after a certain period of time. Discounting makes present costs and benefits worth more, than if they will be obtained in the future due to opportunity cost of spending money in the present and the yearning to experience the benefits in the present time rather than in the future. A hundred pesos (or dollars) now will not be a hundred pesos a year from now if this was invested at a certain rate. If discounting is not done, it would imply that costs and benefits achieved 5-10 years from now would be of equal value to those achieved in the present time. In dyslipidemia management, the costs are spread over several years and the benefits likewise obtained after years of treatment.

The effect of discounting is seen in the following examples. In 1997, an economic analysis of treatment with pravastatin for primary prevention was

undertaken by the West of Scotland Prevention Study group. The authors reported an undiscounted gain of 2,460 years of life, £8,121 per life year gained, or £20,375 per life year gained if benefits are discounted at 6% with the duration of treatment at 5 years.[38] Moreover, in a study of two interventions for hip fractures, discounting changed the conclusions with regards the relative cost per hip fracture prevented by hormone replacement therapy (given to 50 year old women for 10 years which prevents 50% of fractures in 30 years) versus vitamin D and calcium (given to 70 year old women for 10 years which prevents 30% of hip fractures in 10 years time). Before discounting, the cost-effectiveness ratio of HRT was lower (£7,362) compared to that of vitamin D and calcium (£15,646). These ratios became £42,374for HRT and £23,022 for vitamin D and calcium after discounting, thus reversing the initial conclusions.[39]

To demonstrate the effects of discounting in this paper, the change in the CERs and ICERs in tables 8-10 are shown in the following revised tables *(**D** = discounted CERs and ICERs))* where 3% or 5% discount rates for both costs and effects were used (undiscounted in parentheses, discounted in bold font on top of the undiscounted values). Furthermore, the use of discounting further increased the difference in the CER brought about by the sensitivity analysis (discussed in the next section). This led to changing the drug of choice for primary prevention among patients with diabetes (refer to tables 12a & b).

Table 8D ICERs for Primary Prevention
Pharmacologic vs. Non-pharmacologic Treatment (D)

	Simvastatin		Fenofibrate	
	3% D	5%D	3%D	5%D
With ≥ 3 CV Risk Factors: a) Single Cholesterol	**2,554,807.91** (2,016,818.36)	**2,979,768.22**		
b) Cholesterol/lipid profile monitoring	**2,668,253.93** (2,106,374.99)	**3,112,084.56**		
Diabetics a) Single Cholesterol	**1,316,132.35** (1,038,967.03)	**1,535,032.12**	**2,279,446.50** **(**2,025,267.48)	**2,461,805.29**
b) Cholesterol or lipid profile monitoring	**1,374,575.09** (1,085,102.27)	**1,603,195.08**	**2,316,296.78** (2,058,008.62)	**2,501,603.64**

3%D = 3% discount rate; 5%D = 5% discount rate

Table 9D* CERs for Secondary Prevention
Pharmacologic Treatment vs. "do nothing" approach (D)

	Simvastatin	Atorvastatin	Pravastatin	Gemfibrozil
Single Cholesterol determination	**378,504.59** (246,379.93)	**940,020.94** (773,332.42)	**7,341,263.57** (4,968,841.20)	**2,160,720.12** (1,462,456.03)
Cholesterol & SGOT, SGPT monitoring	**397,335.06** (258,637.24)	**958,974.42** (788,924.99)	**7,373,977.84** (4,990,983.45)	**2,228,329.60** (1,508,216.65)
Lipid profile, SGOT & SGPT monitoring	**418,218.14** (272,230.66)	**980,245.95** (806,424.56)	**7,410,258.13** (5,015,539.30)	**2,303,308.86** (1,558,965.41)

*discount rate = 5% (Simvastatin data derived from 4S)

Table 10D* ICERs for Secondary Prevention Pharmacologic vs. Non-pharmacologic Treatment (D)

	Simvastatin	Atorvastatin	Pravastatin	Gemfibrozil
Single Cholesterol determination	**282,524.77*** **332,063.85**** **(**220,409.43*** 385,234.97)*****	**829,497.79*** **895,858.73**** (737,001.24)	**6,234,858.69*** **7,271,949.38**** (4,921,926.77)	**1,729,748.73*** **2,017,470.78**** **(**1,365,499.53)
Cholesterol or lipid profile monitoring	**294,140.97*** **345,716.87**** **(**229,471.71*** 402,341.29)*****	**842,628.35*** **910,039.76**** (748,667.63)	**6,255,596.13*** **7,296,136.23**** (4,938,297.34)	**1,772,606.12*** **2,067,456.95**** (1,399,332.04)

*discount rate = 3%; **discount rate = 5% (first 3 ICERs for simvastatin – used 4S data; last ICER used HPS data)

Sensitivity Analysis

In any economic evaluation, uncertainties regarding any of the parameters or values included in the analysis always occur. This may happen because of "methodological disagreement among analysis, the data requirements of the study, the need to extrapolate results over time, or from intermediate to final health outcomes" or because of "the desire to generalize the results of the study to another setting".[4] In this paper, several assumptions were made for the base case analysis which may not always hold true at the same time. As earlier stated, there were variations in the cost of the medicines, consultation fees, as well as in other cost centers. In view of these uncertainties, a sensitivity analysis was undertaken.

The sensitivity analysis showed changes in the CERs and ICERs when different assumptions were made. In the preceding section, the different CERs were shown depending on the cost of the different laboratory parameters, varying discount rates or cost of the production losses, whether these were due to cost of

labor productivity alone or in combination with cost of leisure time. These changes to the CERs resulted from a sensitivity analysis, a one-way analysis, when cost components were being varied one at a time. On the other hand, since the cost of medicines is a significant determining factor in the CERs, changes in this cost brought about by local practices (discussed in a later section) impact significantly on the one-way sensitivity analysis.

Another important consideration to be included in the sensitivity analysis is the costing of the time spent for exercise activities. In the preceding sections, the time spent during physical exercise was not yet given any cost. However, as discussed earlier, it can be viewed that the recommended time of about 3 hours/week to be spent for exercise decreases the time spent for leisure, thus its inclusion in the computation of the average CERs for Tables 7E and 9E (primary and secondary prevention strategies compared to the null or “do nothing” approach). In these tables, it will be noted that there is a marked increase in all the CERs brought about by the significant contribution of this cost. Inclusion of this cost did not affect the ICERs comparing pharmacologic and non-pharmacologic treatments since this cost was incurred in both interventions.

Table 7E* CERs for the Primary Prevention Strategy**

Laboratory Screening/Monitoring Approaches	CERs Production Losses (50% from labor prod losses; 50% from cost of leisure time based on daily rates***)	CERs Production Losses (50% from labor prod losses; 50% from cost of leisure time based on overtime rates****)
Non-pharmacologic		
a) single cholesterol determination	76,949 – 89,547	103,408 – 122,305
b) cholesterol monitoring	79,291 – 91,889	105,750 – 124,647
c) lipid profile monitoring	89,948 – 102,546	116,408 – 135,304
≥ 3 CV risk factors		
Simvastatin		
a) Single Cholesterol determination only	3,007,043 – 3,190,530	3,392,425 - 3,667,654
b) Cholesterol & SGOT, SGPT determination	3,128,174 - 3,311,661	3,513,556 - 3,788,785
c) Lipid profile & SGOT, SGPT	3,262,509 – 3,445,996	3,647,891 - 3,923,120
Diabetics		
Simvastatin		
a) Single Cholesterol determination only	1,549,083 – 1,643,607	1,747,613 - 1,889,397
b) Cholesterol & SGOT, SGPT determination	1,611,484 – 1,706,007	1,810,014 - 1,951,798
c) Lipid profile & SGOT, SGPT	1,680,686 – 1,775,210	1,879,217 - 2,021,001
Fenofibrate		
a) Single Cholesterol determination only	2,368,873 – 2,429,635	2,496,493 - 2,587,635
b) Cholesterol & SGOT, SGPT determination	2,412,633 – 2,473,395	2,540,253 - 2,631,395
c) Lipid profile & SGOT, SGPT determination	2,461,744 – 2,522,507	2,589,364 - 2,680,506

*includes cost of time spent in physical exercise in total cost of the intervention; all the other assumptions – similar to those in Table 7

**CER (average cost-effectiveness ratio) of non-pharmacologic or pharmacologic compared to "do nothing" approach

***minimum - maximum average daily rates all over the country (2006 real prices)

****minimum - maximum average daily overtime rates all over the country (2006 real prices)

Table 9E* CERs for Secondary Prevention
Pharmacologic Treatment vs. "do nothing" approach

	Simvastatin	Atorvastatin	Pravastatin	Gemfibrozil
Single Cholesterol determination	319,852.56 (246,379.93)	858,459.33 (773,332.42)	5,101,565.96 (4,968,841.20)	1,736,753.86 (1,462,456.03)
Cholesterol & SGOT, SGPT monitoring	332,109.87 (258,637.24)	874,051.90 (788,924.99)	5,123,708.20 (4,990,983.45)	1,782,514.48 (1,508,216.65)
Lipid profile, SGOT & SGPT monitoring	345,703.29 (272,230.66)	891,551.47 (806,424.56)	5,148,264.06 (5,015,539.30)	1,833,263.24 (1,558,965.41)

*cost of time spent in physical exercise included in total cost of the intervention (based on minimum average daily rates); all the other assumptions – similar to those in Table 9 (numbers in parentheses are the corresponding CERs in Table 9)

Likewise, two-way and multi-way analyses where two or more parameters were varied at the same time were also done (e.g., type of laboratory screening used and variation in the cost of production losses; cost of medicines, professional fees and laboratory screening parameters). In addition, different discount rates were used as a form of sensitivity analysis.

In the following analyses, from Tables 11 – 12 (a & b), a discount rate of 5% for both costs and effects was used (discounted values shown in bold ink above the undiscounted or values using 0% discount rate in parentheses whenever space considerations allow its inclusion).

Table 11 details the varying CERs of non-pharmacologic treatment (compared to the "do nothing" approach) for primary prevention where costs and effects were discounted at 5%. Moreover, treatment duration and type of laboratory examination used for monitoring were varied. The duration of therapy was either 2.5, 3.0 or 5.0 years while the laboratory examination utilized were a

choice of a) single cholesterol determination b) cholesterol or c) lipid profile monitoring.

Table 11 CERs of Non-pharmacologic Treatment for Primary Prevention (D)*

	Production Losses (100% from labor productivity losses CERs	Production Losses (50% from labor prod losses; 50% from cost of leisure time**) CERs	Production Losses (50% from labor prod losses; 50% from cost of leisure time***) CERs
2.5 years			
a) Single cholesterol determination	**31,233.85**	**31,921.96 – 32,898.84**	**33,973.72 – 35,439.02**
b) Cholesterol monitoring	**33,945.30**	**34,633.40 – 35,610.28**	**36,685.16 – 38,150.47**
c) Lipid profile monitoring	**46,282.39**	**46,970.49 – 47,949.37**	**49,022.25 – 50,587.56**
3.0 years			
a) Single cholesterol determination	**36,667.19**	**37,492.91 – 38,665.17**	**39,955.02 – 41,713.39**
b) Cholesterol monitoring	**38,470.30**	**39,296.03 - 40,468.28**	**41,758.14 – 43,516.50**
c) Lipid profile monitoring	**54,793.21**	**55,618.94 – 56,791.19**	**58,081.05 – 59,839.42**
5.0 years			
a) Single cholesterol determination	**63,393.22**	**64,898.73 – 67,036.06**	**69,387.80 – 72,593.76**
b) Cholesterol monitoring	**69,737.60**	**71,243.11 – 73,380.44**	**75,732.18 – 78,938.14**
c) Lipid profile monitoring	**96,730.05**	**98,235.57 – 100,372.89**	**102,724.63-105,930.59**

*CER (cost-effectiveness ratios of non-pharmacologic therapy compared to "do nothing" approach); discount rate = 5%
**minimum - maximum average daily rates all over the country (2006 real prices)
***minimum - maximum average daily overtime rates all over the country (2006 real prices)

Table 12a shows the CERs for the primary prevention strategy for high-risk patients (patients with $\geq$ 3 CV risk factors) or diabetics whereby pharmacologic treatment was compared to the "do nothing" approach. The analysis for this table utilized the price of the most expensive brand resulting to a marked increase in the CERs. Moreover, in this table, the cost of production

losses was attributed solely (100%) to the cost of labor productivity and the lowest charge for the doctor's fees was used.

Table 12a CERs for Primary Prevention Strategy for Diabetics or Patients with > 3 CV Risk Factors*

	Simvastatin	**Fenofibrate**
*With ≥ 3 CV RF***		
a) Single Cholesterol determination only	**7,035,273.88** (4,761,750.29)	
b) Cholesterol, SGOT & SGPT monitoring	**7,214,239.66** (4,882,881.37)	
c) Lipid profile, SGOT & SGPT monitoring	**7412,713.58** (5,017,216.33)	
Diabetics		
a) Single Cholesterol determination only	**3,624,232.00** (2,453,022.87)	**2,585,660.33** (2,127,229.16)
b) Cholesterol, SGOT & SGPT monitoring	**3,716,426.49** (2,515,423.74)	**2,909,332.82** (2,170,988.94)
c) Lipid profile, SGOT & SGPT monitoring	**3,818,670.63** (2,584,626.59)	**2,698,546.21** (2,220,100.65)

*compared to "do nothing" alternative; used price of the most expensive drug/lowest charge for doctor's fees/100% of production losses due to labor productivity
**CV RF = cardiovascular risk factors;
discount rate = 5% for CERs in bold ink, 0% for CERs in parentheses

On the other hand, in Table 12b, the highest charge for the doctor's fees was used instead of the lowest in the range. The price of the most expensive brand was used and the assumption regarding production losses remained constant.

Table 12b CERs for the Primary Prevention Strategy for Diabetics or those with ≥ 3 CV Risk factors*

	Simvastatin	**Fenofibrate**
*With 3 CV RF***		
a) Single Cholesterol determination only	**7,544,181.37** (5,106,198.91)	
b) Cholesterol, SGOT & SGPT monitoring	**7,723,147.16** (5,227,330.00)	
c) Lipid profile, SGOT & SGPT monitoring	**7,921,621.07** (5,361,664.95)	
Diabetics		
a) Single Cholesterol determination only	**3,886,396.47** (2,630,466.10)	**2,738,725.94** (2,253,156.61)
b) Cholesterol, SGOT & SGPT monitoring	**3,978,590.96** (2,692,866.97)	**2,791,916.23** (2,296,916.39)
c) Lipid profile, SGOT & SGPT monitoring	**4,080,835.10** (2,762,069.82)	**2851,411.82** (2,346,028.10)

*compared to "do nothing" alternative; used price of the most expensive drug/highest charge for doctor's fees/100% of production losses due to labor productivity
**CV RF = cardiovascular risk factors;
discount rate = 5% for CERs in bold; 0% for CERs in parentheses

In the preceding 2 tables, it can be seen that for primary prevention for diabetics where the cost of the medicines and doctors' fees were varied, simvastatin was not the dominant option anymore (with the cost of the medicine being the predominant reason for the change). Instead, fenofibrate has a lower cost-effectiveness ratio compared to simvastatin using any of the monitoring strategies. This is more emphasized when discounting was applied.

Apart from the change in the cost of medicine, the other significant factor that led to the shift, i.e., fenofibrate having a lower ICER than simvastatin rather than the other way around, was the effectiveness of the drug. Fenofibrate prevented 31 events during the trial duration of 3 years, while simvastatin prevented 33 events over a period of 5 years. Hence, when the values were

discounted, the difference between the ICERs of fenofibrate and simvastatin became bigger (as stated earlier in the section on discounting, there is a preference to experience benefits in the present or earlier time rather than far into the future).

In the base case analysis (discounted or not), the shorter duration of treatment to attain the benefits was not enough to overcome the advantage of simvastatin (being priced much less than fenofibrate).

Local practices directed to lowering costs of medicines

The CERs can also change by the common practice of splitting a higher strength tablet into two to come up with the required daily dose of the drug in order to lower the cost of the medicine. For example, if the daily dose for simvastatin is 40 mg/day, an 80-mg tablet is divided into two. Whereas a 40mg tablet costs either Php 37.75 or 43.00, depending on the brand, splitting the 80-mg tablet which costs either Php 39.00 or 43.00 will reduce the cost of treatment per day to Php19.50 or 21.50. (The innovator drug lowered its price and adopted the same price for both the 40 mg and 80 mg tablet. This similar pricing scheme for all strengths/doses of the innovator drug, including the 10 mg/tablet, came after the entry in the market of a lower-priced simvastatin from a local pharmaceutical firm.)

For the analysis involving the lowest-price brand for the 40 mg/tablet dose and the brand whose 80 mg/tablet costs Php39.00, the resultant change in the CER brought by the above practice was minimal. This was brought about by the resulting price difference of only Php0.25 (the lowest price of the 40 mg/tablet being Php19.25 and the resulting price of the halved 80 mg/tablet to be P19.50).

However, the CER for the most expensive brand, i.e., the innovator drug, will markedly change since the cost of the medicine will be halved (from Php43.00 to 21.50). In this case, the resultant change in the choice of drug (fenofibrate over simvastatin) will not hold true anymore!

Another recent practice being promoted by some multinational drug companies whose drug prices (baseline) are markedly higher than most of their counterparts is the use of discount cards for certain medicines including drugs for dyslipidemias. These discounts which may range from 25% - 50%, will definitely bring down the costs of the medicines. However, these are not available to all, thus the possible effect in the CER was not included in the sensitivity analysis.

The senior citizens' discount of 20%, on the other hand, can be availed by all patients aged 60 and above since it is mandated by the government. The law requires these patients to acquire identification cards and relevant papers from their respective government units. Since the effect on the costs will be uniform for this age group, the change in the average CERs and ICERs applies to senior citizens.

Patient's compliance

An important consideration to take into account in the sensitivity analysis is the patient's compliance to either his lipid-lowering medications or to the non-pharmacologic treatment. In addition, compliance also refers to whether the patients are following their schedules with their physicians as well as the monitoring/attainment of the laboratory parameters. The previous computations were done on the assumption of 100% compliance. This rate or near perfect

rates can be attained in a clinical trial set-up where compliance and follow-up are significantly better than the real world scenario. Thus, it is reasonable to expect significant variations in the CERs due to different compliance rates.

C. Markov Model for the dyslipidemia treatment strategies

All the analyses in the preceding sections have so far calculated the CERs simply by dividing the total costs (relevant components identified) by the effectiveness parameter in terms of the number of cardiovascular events prevented by a particular intervention. Variations in the CERs were noted either by changes in the assumptions of one or two of the parameters incorporated in the costs. These calculations, however, were based as if the events and costs all happened at the same time right after the duration of a particular trial. In contrast, the costs and clinical events were incurred in different time intervals or distributed throughout the trial duration. Furthermore, the 95% confidence intervals of the point estimates of the event rates were not yet included in the analysis. Lastly, many of the assumptions were based on randomized clinical trials which might reflect the ideal scenario, thus miss the other facets of health care delivery. With randomized trials comprising only one of the sources of essential information, there is a need to incorporate those from other databases, e.g., cohorts, population registries, in order to simulate a more realistic scenario. With this in mind, economists have turned to the use of decision-analytical models.

"A decision model is usually developed to assist decision-makers in making choices relating to the evaluated options. Typically, the objective of a

decision model is to obtain a clearer understanding of the relationships between incremental costs and their consequences".[40] In addition, it is viewed as an "explicit, quantitative, prescriptive approach to medical decision-making and allows both clinical and economic consequences of medical actions and attitudes to be analyzed under conditions of uncertainty".[41] In contrast to randomized controlled clinical trials which are limited by the trial duration, models are used to assess the impact of therapy on costs and its effectiveness and should simulate as much as possible the real life setting of the disease. In addition, models incorporate or extrapolate data not only from clinical trials but also observational studies as well as other databases. Although modeling is not easy, "economists often build models that make simplifying assumptions to make the problem tractable, but hopefully capture sufficient detail to provide reasonably valid predictions of future events."[42] These models may either be the simple decision-analytical trees or the Markov models.[41,43,44]

Since the introduction of Markov models by Beck and Pauker in 1983 to determine prognosis in medical applications, they have been utilized in many decision analyses.[43] Markov models are often used "to represent stochastic processes" which are, "random processes that evolve over time".[44] One of the strengths of Markov models is its ability to deal with both costs and outcomes simultaneously hence they are suited to estimate the long-term costs and consequences of chronic conditions as well as the resulting effects of a particular intervention.[44] This is done 1st by dividing the disease condition into separate states (known as Markov states) and assigning transition probabilities for moving

between these states over a certain time (known as Markov cycles). The estimated costs and outcomes are then attached to these states and transitions in the model, after which the model is run over a large number of cycles.[4343,44]

There are two requirements of a Markov model - patients should only be in one state at any one time and that transition probabilities should not be dependent on the previous state of the model ('memoryless' feature of Markov models known as the 'Markovian assumption'). Moreover, two types of Markov models can be obtained depending on the form of transition probabilities. The first refers to the Markov chains where all the transition probabilities are constant over time while the other is known as the time-dependent Markov processes. Although the first one can be simply represented through a transition matrix or matrix algebra, it is hard to assume that transition probabilities from one health state to another is constant, e.g., it is inappropriate to assume that the risk of death is constant between two states, alive and dead. Moreover, matrix algebra cannot incorporate discounting. On the other hand, although time-dependent Markov models are harder to be represented by matrix algebra, the transition probabilities in these models can vary over time. In addition these models are more adaptable to modeling of chronic conditions.[43,44] Thus these models were used for the decision analytic modeling in this paper on dyslipidemia which is a significant risk factor for the occurrence of cardiovascular events.

Based on the dyslipidemia guidelines where the recommendations were segregated depending on the absence or presence of atherosclerosis, three models were constructed, two for patients without established atherosclerosis

(primary prevention strategies, Figures 2 - 3) and one for patients with established atherosclerosis (secondary prevention strategy, Figure 4).

The first model constructed is for patients without atherosclerosis and have < 3 risk factors for cardiovascular disease. The model is composed of several states represented by the ovals and the possible transitions between these states are depicted by the arrows joining the states. The first state is the asymptomatic phase or the state whereby patients do not have any evidence of atherosclerosis and the risk factors for CV disease is less than 2. From the asymptomatic state, patients may move to the 'first non-fatal cardiovascular (CV) event' - either myocardial infarction/stroke or to the 'dead' state (transition probability equals death from all causes minus from the CV events). The backward bending arrow in the first state, i.e., asymptomatic, mean that it is possible that patients will remain in the states they were in the previous cycle before they move to the 'dead' state. After incurring the first CV event, patients may either have a recurrence of such events (progressive disease) then go to the dead state or they may remain in the condition of having survived the said event before proceeding to the 'dead state'.

The transition probability of moving from the asymptomatic phase to the development of the first CV event is assumed to be time-dependent. In the same context, the risk of death from all causes is also assumed to be an increasing function of time.

Because of the Markovian assumption (no memory), the transition probability from the disease state to the 'dead state' cannot be made dependent

on the time the patients stayed in the disease state. Thus, tunnel states or temporary states were constructed. "Tunnel states are a series of temporary states that must be visited in a fixed sequence."[44] Furthermore, "temporary states are required whenever there is an event that had only short-term effects" and "are defined by having transitions only to other states and not to themselves."[43] So instead of just a single oval representing state of 'CV disease' or 'progressive disease state', several tunnel states – 'first CV event state' and several progressive stages of the disease were delineated. Thus the model in the figure 2 satisfies the Markov model requirements of having the Markovian assumption and being in one state at any one point in time.

Finally, the Markov cycle terminates with the 'absorbing state', i.e., the state that the patient cannot leave. In the medical field, this is represented by the 'death state' since this is the only state that no further transition can occur.

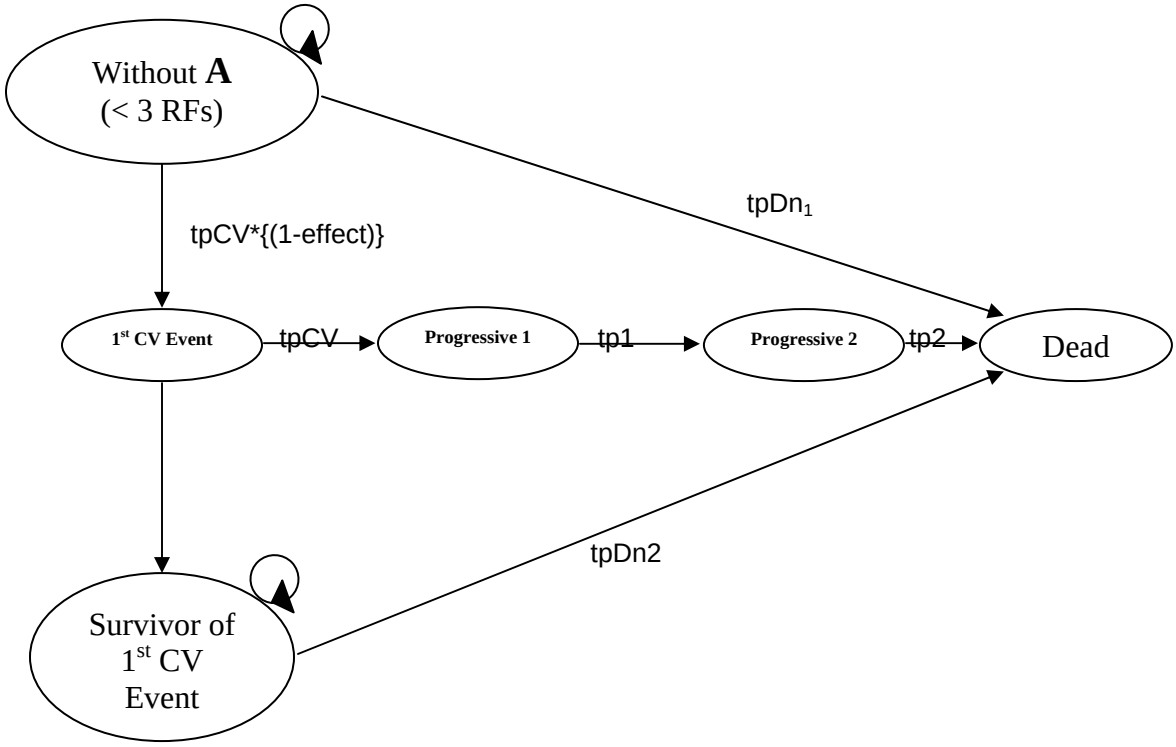


Figure 2 Markov model for the primary prevention strategy for patients with < 3 RFs (risk factors) for cardiovascular disease.
Without A = no evidence of Atherosclerosis
$tpDn_1$ = transition probability to death state due to natural causes; tpCV = transition probability to the first CV event; effect = effectiveness of intervention in terms of reducing disease progression; tp = transition probability; tpS = transition probability to state of surviving 1st CV event (remaining asymptomatic after such event); $tpDn_2$ = transition probability to death from natural causes after surviving a first CV event

The model in Figure 3 is similar to Figure 2 except that although the initial state also begins with patients without established atherosclerosis, this time their risk factors for CV disease are $\geq$ 3 or patients in this category have diabetes mellitus.

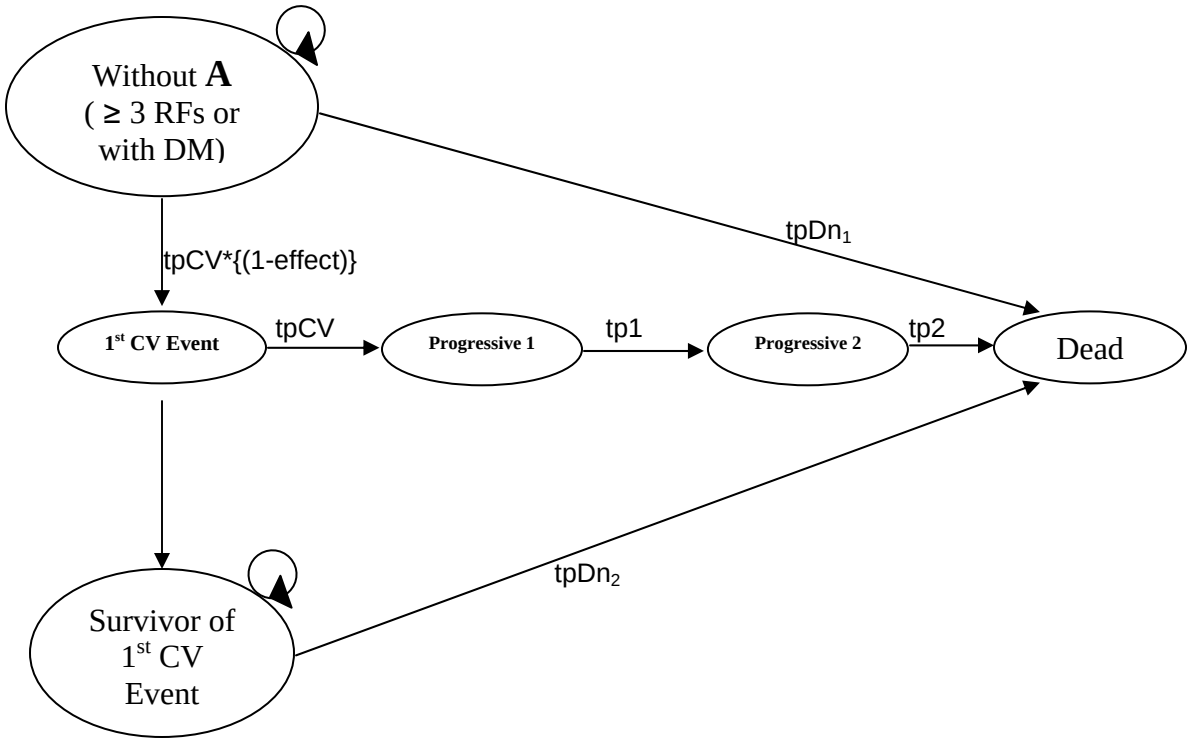


Figure 3 Markov model for the primary prevention strategy for patients with ≥ 3 RFs (risk factors)or diabetes mellitus for cardiovascular disease or with diabetes.
Without A = no evidence of Atherosclerosis
$tpDn_1$ = transition probability to death state due to natural causes; tpCV = transition probability to the first CV event; effect = effectiveness of intervention in terms of reducing disease progression; tp = transition probability; tpS = transition probability to state of surviving 1st CV event (remaining asymptomatic after such event); $tpDn_2$ = transition probability to death from natural causes after surviving a first CV event

The Markov model in Figure 4 is for patients with established atherosclerosis (secondary prevention strategy). It starts in the state whereby patients either have acute coronary syndrome, previous myocardial infarction or unstable angina, peripheral arterial disease, stroke or transient ischemic attack or there is evidence of coronary artery disease or revascularization.[1] Thus, patients in this category may either be symptomatic or asymptomatic. Asymptomatic patients may remain in this state (represented by the backward bending arrow) for the previous cycles before moving to the 'dead state'.

On the other hand, patients may move from the first state (with evidence of atherosclerosis, either symptomatic or asymptomatic) to the progressive states (tunnel states), signifying the occurrence of another cardiovascular event or a progression of the previous events before proceeding to the 'dead state'.

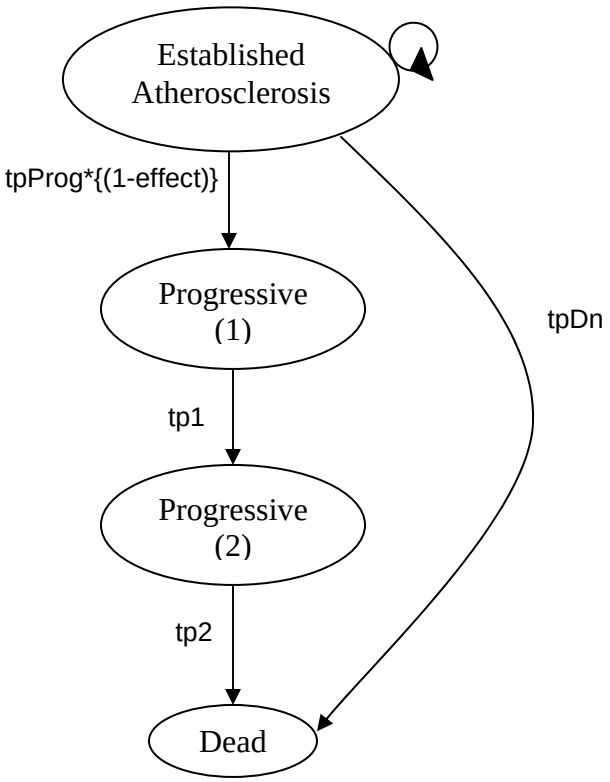


Figure 4 Markov model for the secondary prevention strategy for patients with established atherosclerosis
tp = transition probability; effect = effectiveness of intervention in reducing disease progression; tpDn = transition probability to the death state from natural causes;

The transition probabilities

In the primary prevention models (Figures 2-3), 4 states are illustrated. Transitions from each of these states are assumed to occur in every cycle of the model. Although the possible transitions between these states is equal to *k x k* transition matrix, in reality, the transitions that can take place are: a) without

atherosclerosis or asymptomatic to occurrence of 1st CV event; b) asymptomatic to dying from causes other than CV disease or unrelated condition; c) 1st CV event to the progressive states of the disease (tunnel states) to dying because of CV etiology; d) 1st CV event to asymptomatic survivor of CV event; e) survivor of 1st CV event to dying from an unrelated condition after surviving a CV event. Transitions from dead to asymptomatic state, or dead to progressive state of CV disease and transitions of a similar nature are not possible (notation of 0 in the table on transition matrix). In addition, all the probabilities of moving from one state to another must sum up to 1 due to the requirement of a Markov model that patients should be in only 1 state at any given time. Thus, the probability of being in the same state at any given cycle is equal to 1 minus the probability of leaving that state. The transition matrix is seen in the following table (Table 13).

Table 13 Transition matrix for the primary prevention model

Transition from	To					Total
	Asymptomatic	1st CV	Progressive	Survive CV	Dead	
Asymptomatic	1-tpCV-tpProg-tpDn1	tpCV	tpProg	0	tpDn1	1
1st CV Event	0	0	1-tpS-tpDn1	1-tpProg-tpDn1	tpDcv	1
Survive 1st CV	0	0	0	1-tpDn2	tpDn2	1
Dead	0	0	0	0	1	1

tpCV = transition probability to the 1st CV event; tpProg = transition probability to the progressive states of the disease; tpDn1 = transition probability to death from non-CV causes (no history of CV event); tpS = transition probability of to surviving the 1st CV event; tpDn2 = transition probability to death from non-CV causes after surviving the 1st CV event.

The transition matrix for the secondary prevention model is simpler since the model consists only of 3 states, namely with established atherosclerosis, progressive and dead states. Consequently, the transition will consist of

a) staying in the asymptomatic state (1st state), b) symptomatic patients in the 1st state moving to the progressive states of the disease or recurrence of another CV event leading to death, and c) from 1st state to the dead state from causes not related to the CV disease. The transition matrix for this model is illustrated in Table 14.

Table 14 Transition matrix for the secondary prevention model

Transition from	To			Total
	With A (asymptomatic)	Progressive	Dead	
With A (asymptomatic)	1-tpProg-tpDn	tpProg	tpDn	1
Progressive	0	1-tpDn	tpDcv	1
Dead	0	0	1	1

tpProg = transition probability to the progressive states of the disease; tpDn = transition probability to death from non-CV causes or etiologies not referable to the CV disease; tpDcv = transition probability to death due to CV disease

Analysis of the Markov models for dyslipidemia

The Markov models and decision trees were analyzed using Microsoft® Excel™ and the TreeAge Pro 2007 software.[45] The models were constructed (in Excel spreadsheet) using data of the Heart Protection Study (HPS). This study was selected (compared to other trials) because of the availability of data that are needed for the modeling illustration. In this trial, high risk patients who were randomized to either simvastatin or placebo (non-pharmacologic therapy) were monitored for the occurrence of first ever major vascular events during the 5-year duration of the study.[32] On the other hand, the local data incorporated in this model were the latest available (2005) life tables of Filipino men and women aged 35 years and above.[46,47]

There were two terminal nodes for this model. One was the occurrence of the first ever major vascular event, i.e., any coronary event (fatal or nonfatal myocardial infarction), fatal or nonfatal stroke or revascularization. The second one was the occurrence of death from other causes (non-vascular etiologies).

The cost-effectiveness ratios derived from the above model (through deterministic analysis) were computed using the assumptions used for Table 10. In addition, these values were converted to US$ and enclosed in parentheses (1US$ = Php46.00 as of June, 2007). The resulting ICERs were higher in contrast to the ICERs in earlier sections where decision-analytic modeling was not used as shown in the following table, Table 15.

Table 15 ICERs of Simvastatin vs. Non-pharmacologic Therapy (Secondary Prevention Strategy*)

	No Modeling	*Markov Modeling CEA*
Single Cholesterol Determination 0% discount rate	*385,234.97 (8,374.67)*	*458,298.80 (9,9963.02)*
3% discount rate	*487,997.02 (10,608.63)*	*533,283.65 (11,593.12)*
5% discount rate	*569,169.21 (12,373.24)*	*673,609.49 (14,643.68)*
Cholesterol or lipid profile monitoring 0% discount rate	*402,341.29 (8,746.55)*	*478,709.85 (10,406.74)*
3% discount rate	*548,706.24 (11,928.40)*	*556,790.49 (12,104.14)*
5% discount rate	*639,976.66 (13,912.54)*	*703,107.68 (15,284.95)*

*data derived from HPS; CEA = cost-effectiveness analysis;
1st value in Philippine peso, 2nd value in US dollars, enclosed in parentheses, 1 US$ = Php46.00

IV Discussion

A. The cost-effectiveness of dyslipidemia management in the local setting

This paper evaluated the recommendations of the 2005 clinical practice guidelines for the management of dyslipidemia in the Philippines through a cost-effectiveness analysis using the societal perspective. This perspective is chosen since it reflects a more thorough evaluation of both costs and effects of an intervention or program. An evaluation using the patient's perspective though, important, will be limited to costs of resources incurred by the patient and his family and the consequences attributable to them. In contrast, a societal perspective is a broader perspective, incorporating both non-health and health care costs and is therefore able to give a more comprehensive picture of the resources consumed. Thus this paper included the costs of health care and patient's resources as well as production losses brought about by managing dyslipidemia in the Philippine setting.

On the other hand, effectiveness was expressed in terms of reduction in cardiovascular events (fatal or nonfatal myocardial infarctions or strokes and revascularization) or total mortality. These data were culled from randomized trials which provided evidence of effectiveness for treating dyslipidemia, whether for primary or secondary prevention strategies. Because of the different clinical outcomes achieved by pharmacologic treatment in randomized trials, a cost-consequence approach was initially done. Although one's valuations of these outcomes may differ, these were summed up to come up with cost per major clinical event prevented in the simple cost-effectiveness analysis (total costs

divided by total clinical events prevented). On the other hand, in the decision-analytic modeling through Markov model, the annual costs of treatment, the probabilities of the occurrence of the outcome of interest as well as the life tables were incorporated in the model to come up with the cost-effectiveness results.

The cost of the treatment forwarded in the recommendations of the local guidelines as well as its effectiveness were considered through "crude cost analysis".[1] This referred to the cost of medications given to a required number of patients (number needed to treat) to prevent the clinical endpoints identified. The duration of the trial served as the number of years that the cost of medications needed to be multiplied and 100% compliance to the medications was assumed. The cost derived from this computation served as the cost of a particular pharmacologic treatment for the specified population, e.g., cost of primary prevention strategy using statin or fibrate for diabetic patients (cost needed to achieve the reported clinical endpoints). In this analysis, it can be seen that other costs such as cost of laboratory examinations, consultations, etc. were not included. Furthermore, no cost was considered for the non-pharmacologic treatment which forms part of the recommendations for drug therapy. The following table showed the summary of the "crude cost analysis" stated in the guidelines.

Table 16 Summary of "Crude Cost Analysis" of Guideline Recommendations

Recommendation	Cost	Effectiveness
Primary Prevention Patients ≥ 3 risk factors Statin Therapy	Php 20 million	Prevention of 1 stroke, 2 MIs and 2 CV events for every 300 given treatment for 5 years
Diabetics Statin Therapy	Php 3.9 – 5.3 million	Prevention of 1 MI, 1 revascularization and 1 CV event per 90 patients treated for 5 years
Fibrates	Php 0.88 – 1.0 million	Prevention of 1 adverse CV event per 32 patients treated for 3 years
Secondary Prevention Statins	Php 2.9 million	Prevention of 1 death, 4 CV events, 1 MI, 1 stroke and 1 revascularization for 5 years (did not state number of patients needed to receive treatment to achieve above outcomes)
Fibrates	Php 2.1 – 2.7 million	Prevention of 1 MI and 1 stroke after 5 – 6 years of treatment (did not state number of patients needed to receive treatment to achieve above outcomes)

MI – myocardial infarction; CV - cardiovascular

In comparison, the analysis in this paper (using the societal perspective) took consideration of other cost centers, details of which were given in the methods and results section. The cost-effectiveness ratios for primary and secondary prevention strategies on the management of dyslipidemia were then calculated after identification, measurement and valuation of relevant costs and consequences. The results were obtained through either using direct application of the CER or ICER formulae or through Markov modeling. Moreover, the costs

and effects were computed for treating every 1000 patients (given specific treatment option) to enable comparison of cost for every major cardiovascular event prevented among the different alternatives.

As shown in the preceding discussion, the “crude cost analysis” has many limitations. Although it is definitely difficult to come up with perfectly accurate estimates (CERs or ICERs), it is imperative not to miss the important factors that should be included in its measurement. This is in view of the fact that missing on them may lead to incomplete estimates and ultimately inappropriate decisions.

On the other hand, estimation of the ICERs was done through simply dividing the total costs over effectiveness or through decision-analytic modeling. As shown in this paper, these two approaches came up with different results. This difference must be given due considerations especially if it is large enough to affect decisions in choosing the best option possible. Since the decision-analytic modeling tries to simulate more realistic estimates then considerable weight should be given such results from such models.

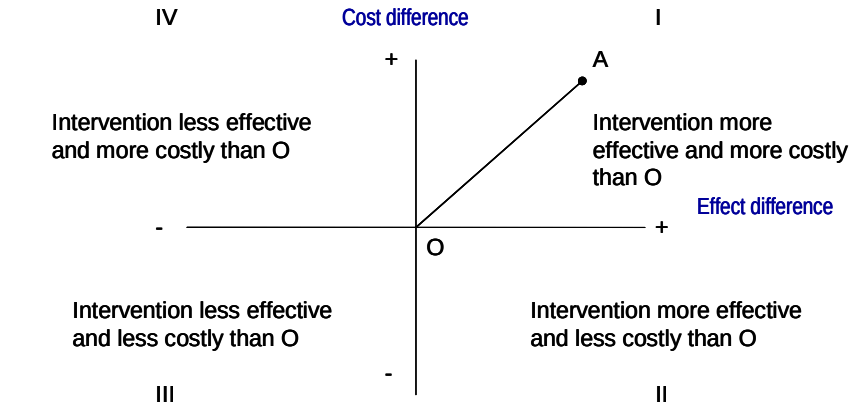
Lastly, for the pharmacologic option, the average CERs of the particular agents (compared to the null) are expectedly greater than the corresponding ICERs considering that the costs for this intervention included even that of the non-pharmacologic maneuvers. The costs that go into the average CERs represent the total costs that society has to pay for every benefit that will be incurred. On the other hand, the cost component of the ICERs of the specific drug for dyslipidemia only included the medications and the laboratory examinations not done in the non-pharmacologic option.

The Cost-effectiveness Plane, Dominant Option & Threshold Ratio

The cost-effectiveness plane (Figure 5) obtained from Drummond et al's *methods for the economic evaluation of health care programmes* is a simple diagram which illustrates differences in costs and effects of several alternatives and the possible decision one may opt to make.[4] The horizontal axis corresponds to the difference in the effect between the intervention being considered (A) and the relevant alternative (O) while the vertical axis corresponds to the difference in cost.

Decisions can easily be arrived at if point A is in either quadrant II or IV. In quadrant II, A, the intervention being considered, is more effective and less costly than the alternative, O, thus A dominates O. In quadrant IV, the reverse is true, i.e., O dominates A. However, in quadrants I and III, the decision depends on the maximum cost-effectiveness one is willing to accept, i.e., for quadrant I, the increment one is willing to pay for the additional benefit, while for quadrant III, the decrement in the effectiveness for the decrease in cost. The slope of the line OA corresponds to the cost-effectiveness ratio.[4]

In addition, an alternative is dominated if it lies above and to the left of another strategy. On the other hand, the strategy below and to the right is referred to as the dominant or dominating one.[45]



Adapted from Black (1990)

Figure 5 The cost-effectiveness plane from Drummond et al. Methods for the Economic Evaluation of Health Care Programmes 3rd ed. 2005

The use of this plane was demonstrated using the TreeAge Pro decision tree.[45] For this figure, the ICERs of the secondary prevention strategies where 4 pharmacologic therapies were compared to the non-pharmacologic maneuver were plotted. In this illustration, the assumptions utilized were similar to those in Table 10, i.e., lowest cost medicine, single cholesterol screening for the laboratory parameter, however a discount rate of 5% for total costs and 0% discount rate for the effectiveness were used. As stated in the previous section, simvastatin dominated all the other options because it was more effective and less costly compared to the 3 other strategies. This dominance was also shown in Figure 6. In this figure, there were no lines connecting the lowest cost option (simvastatin) to the other alternatives since it dominated all of them (or the 3 other alternatives were dominated by simvastatin).

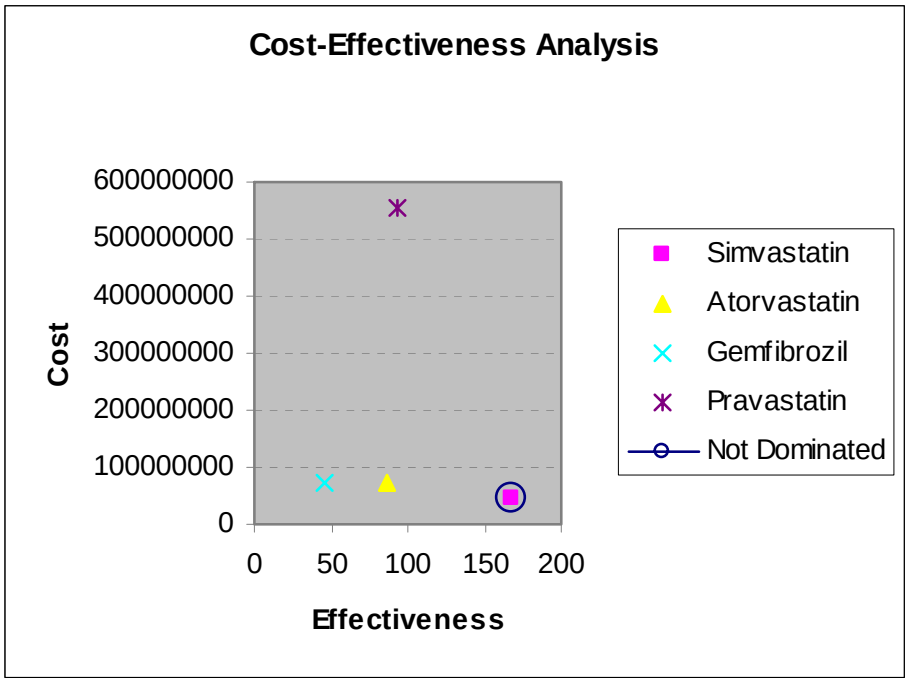


Figure 6 Cost-Effectiveness Analysis of Secondary Prevention Strategies (Pharmacologic vs. Non-pharmacologic Therapies)

In the Philippines, there is no explicit threshold ICER (willingness-to pay or ceiling ratio) to determine the cost-effectiveness of any intervention (although Philhealth's allowed reimbursement is only about Php100,000/year/confinement for the same illness). In the above diagram, if there is no threshold value indicated, the choice would be Simvastatin, the option with the lowest CER/ICER (plotted in quadrant II and is the rightmost and below all other options). Options using atorvastatin, pravastatin and gemfibrozil were all dominated. Likewise, if a threshold analysis is done, e.g., Php300,000/event prevented or <US$10,000/event prevented is used as the threshold ICER, no pharmacologic intervention would be recommended. On the other hand, if this is increased to about Php500,000/event prevented (about US$11,000/event prevented), then simvastatin would be the only pharmacologic agent that will be recommended.

On the other hand, valuation of the costs of the outcomes prevented – myocardial infarction, stroke, revascularization or mortality will definitely lead to varying results. Not only will this be due to valuing the costs of preventing the above illnesses but also how much value is given to saving a life. For those who have the ability to pay, their threshold or ceiling ratios might be much higher, then the above ICERs might be regarded as to be worth paying for. However this scenario will compound the problem of inequity (equity issues are discussed in a later section).

The threshold value (threshold or ceiling ratio) stated in the preceding paragraphs represents the "shadow price per unit effectiveness in the absence of a market."[48] This decision rule means that programs with ICERs below this threshold can be recommended for implementation while those above it will be deemed not acceptable. Some authors argue that interventions that cost less than $20,000/QALY can be deemed appropriate for using society's resources.[5] Other authors meanwhile, opined that the National Institute for Clinical Excellence (NICE), which provide guidance to the National Health Service (NHS) of the United Kingdom on the cost-effectiveness of new health technologies, utilize a threshold value of about £20,000-30,000 per QALY gained. On the contrary, others argue that NICE has no clear and explicit threshold. [49]

Birch and Gafni argued against the threshold value approach by illustrating the following example: Suppose that in the absence of budget constraint, a policy maker is willing to fund programs with ICERs of $20,000 per

QALY or less. Corollary to this, a hospital is planning to replace an existing intervention which provides 2 QALYs for an annual cost of $100,000 with an alternative intervention with an annual cost of $110,000 for every 3 QALYs gained. Using the above approach, the new program would be adopted since its ICER is $10,000 for every QALY gained. But the average CER of any of the two programs is more than $20,000 per QALY gained, thus from a societal perspective, neither program should be funded.[5] (Apart from demonstrating the problem in the threshold value, the above example also demonstrated usefulness of the average CER. A similar scenario is presented by the average CERs and ICERs of a dyslipidemia program since the ICERs of therapeutic intervention compared to non-pharmacologic treatment does not represent the total costs that society must pay to attain its effects.)

On the other hand, other authors claim that there is no clear acceptable ratio since budget constraints may not permit the implementation of programs that will meet the above threshold.[5] Moreover, Sendi and colleagues, enumerate the following reservations: 1) the threshold value also known as the 'critical ratio' represents the shadow price of the constrained budget or opportunity cost of health care resources. However, this value cannot be determined in instances where the budget constraint is difficult to determine. This occurs under some perspectives like the societal perspective; 2) the above approach assumes that the size of the budget for health care does not affect the marginal opportunity cost of health care resources. "It assumes that the value of benefits forgone would be the same for every dollar taken from other sources and that the

marginal opportunity cost of resources is constant for all levels of resource consumption and for all settings"[48]; 3) the cost-effectiveness acceptability curve does not take into account the stochastic nature of the ceiling ratio. Instead it defines the probability that a program is more cost-effective using a deterministic approach and not for a distribution associated with the ceiling ratio; 4) the ceiling ratio approach is dependent on the implicit assumptions of constant returns to scale and complete divisibility of health care programs.[48] Complete divisibility assumes that the program can be bought in infinitely small increments while constant returns to scale mean that the ICER is independent of the size of a program.[5] These assumptions do not hold true for many health care programs such as those that require high capital costs, e.g., programs that need expensive technologies such as equipments for revascularization procedures like angiography/angioplasty.

Because of the difficulties encountered with using a threshold value as a decision rule, several alternatives have been proposed. These include Birch and Gafni's decision rule as well as the use of the 'decision making plane' instead of the cost-effectiveness plane.[5,48] Moreover, Bayesian methods in cost-effectiveness analysis have also been proposed to account for uncertainty. In this technique, costs and effects are considered as stochastic parameters.[50]

On the other hand, Murray and co-authors recommended a different approach.[51] Through a standard procedure, they have identified a set of interventions that a region must buy in order to obtain the greatest benefit for different budget levels. In line with the WHO Commission on Macroeconomics

and Health definition with regards cost-effectiveness, they identified three broad categories for their recommendations. A country's gross domestic product per head served as the basis for their recommendations.[51,52]

B. Cost-effectiveness Analyses of lipid-lowering therapy in other countries

The global burden of cardiovascular disease (CVD) is predicted to increase tremendously, e.g., a 3-fold increase in coronary artery disease is expected in Latin America, the Middle East and sub-Saharan Africa in the next 2 decades.[53] Because of this, there is much concern on the costs and benefits of treatment for CVD prevention. One of the identified strategies for CVD prevention is the use of cholesterol or lipid-lowering agents for which a number of economic evaluations have been done in several countries. In this context, a systematic review of economic evaluations of lipid-lowering therapies which aimed to analyze the quality of these articles was recently published. Of the 1390 articles identified (published up to October 2005) in the review, only 23 passed the inclusion criteria.[54] These 3 criteria specified that studies should be 1) full economic evaluation of drug therapy for hypercholesterolemia; 2) effectiveness data should be taken from randomized controlled trials on long-term outcomes like strokes, MI, etc.; and 3) cost-effectiveness and cost utility must be defined as life-year gained or costs per QALY gained. Moreover, a number of articles were excluded based on 4 exclusion criteria.[54] The quality of the included articles was then graded using Drummond's checklist for the appraisal of economic evaluations.[55] The authors were disappointed with the overall quality score per study which was 2.7 – 7.7 (average of 5.5).[54] However,

a trend in the improvement of scores with time was noted. In addition, the scores of articles published in medical- and economics- oriented journals were 5.3 and 6.3, respectively. Lastly, only two studies were identified as having done a well-performed incremental analysis.[54]

On the other hand, an economic analysis of the 2nd National Cholesterol Education Program (NCEP II) evaluated the cost-effectiveness of cholesterol-lowering strategies among patients with different risk factors (240 risk subgroups) using a societal perspective.[56] Furthermore it used the Coronary Heart Disease Policy Model and all costs were converted to the 1997 U.S. dollars using the Medical Care Component of the Consumer Price Index as reference. Costs and effects were discounted at an annual rate of 3%.[56]

The NCEP II guidelines recommended step I diet therapy as well as drug treatment for all with LDL of $\geq$ 4.9 mmol/L ($\geq$ 190 mg/dL) and for persons with LDL cholesterol levels of 4.2 – 4.9 mmol/L (160 – 189 mg/dL) and 2 or more risk factors.[57] In a somewhat similar context, low fat diet is recommended for all in the local guidelines. However, pharmacologic recommendations differ in terms of recommending drug therapy for primary prevention for the high-risk group of patients as well as a different cut-off level in terms of LDL levels (see appendix 1 for details of the recommendations of the local guidelines.

The incremental cost-effectiveness ratios for the NCEP recommendations on the step 1 diet for primary prevention was US$1900-500,000 per QALY gained depending on the risk subgroup. Meanwhile, the ICER for primary prevention with a statin compared to diet strategy was US$54,000-1,400,000 per

QALY. Secondary prevention with a statin, in contrast cost less than US$50,000 per QALY for all risk subgroup. This study concluded that primary prevention with step I diet may be more cost-effective for some risk subgroups but less cost-effective for healthy young women (with no or just one risk factor). Moreover, primary prevention with a statin may also be less cost-effective for some groups who have few risk factors. Lastly, it concluded that secondary prevention with a statin seems to be more cost-effective for all 240 subgroups identified in the study.[56]

For the secondary prevention strategy, literature review centers on the economic evaluations of the Scandinavian Simvastatin Survival Study (4S) and the Heart Protection Study (HPS). This was done because these studies were the basis for the recommendations for the secondary prevention strategies of the local guidelines.

The Scandinavian Simvastatin Survival Study (4S) was the focus of two economic analyses, one using the setting of Sweden alone, and the other included 5 European countries (which includes Sweden) and the United States.[58,59] The societal perspective was used in the first study while the second one did not mention the viewpoint of the study.

In addition, the economic analysis referred to above as the first study calculated costs based on Swedish prices in 1995 and converted it to U.S. dollars at the 1995 exchange rate of 7.30 kronor to one U.S. dollar. In addition, a discount rate of 5% for both costs and effects was used. Two ways of measuring costs were reported, i.e., net costs (cost of savings due to the reduction in

morbidity from coronary causes deducted from the cost of intervention) with and without cost of production losses attributed to morbidity from coronary causes. Costs of health care because of increase in the years of life gained were however not included. In addition, estimates were done for varying ages for men and women (35-70 years) and total cholesterol levels (213-309 mg/dl). The cost of each life year gained was from $3,800 for a 70-year old man having a cholesterol level of 309 mg/dL to $27,400 for a 35-year old woman with a cholesterol level of 213 mg/dL.[59] When the costs of production losses were included, it resulted to savings in the youngest patients to a cost of $13,300 for every year of life gained in a 70-year woman with a cholesterol level of 213 mg/dL. The analysis concluded that simvastatin was more cost-effective among the population and cholesterol levels included in the study.[59]

The economic evaluation using Sweden alone as its setting, on the other hand, reported the cost per life year saved with simvastatin was 56,400 Swedish kronor (£5502) based on direct costs only.[58] Because of variability in coming up with economic evaluations, “there is no absolute standard for an acceptable CER”.[58] However, a comparison with another economic analysis of anti-hypertensive treatment (moderate elevation in blood pressure) with the same methodology showed that this CER is within the range of the CERs of the other study. Furthermore, a U.S. Survey had reported a median CER of about US$19,000 for 310 life-saving medical interventions. It thus concluded that the cost per life year saved with simvastatin in patients with coronary artery disease (post-myocardial infarction and those with angina) is within the range of values

considered appropriate or acceptable[58] (please refer to the concept of threshold value discussed earlier).

The economic evaluation using the HPS data, on the other hand, used the perspective of the UK National Health Service with costs reported in 2001 UK pounds (£) and CERs reported using a discount rate of 3.5%.[60] The results showed that during the treatment period averaging 5 years, a significant reduction in hospitalization costs for all vascular events for patients treated with 40 mg of simvastatin/day. The absolute reductions in vascular event cost/person were UK£264 - 847 (cost in the lowest risk group – highest risk group). Meanwhile, the cost of preventing a major vascular event was UK£4500 – 31100 among patients with 42% and 12% risk (respectively) of 5-year major vascular event rate.[60] Finally, it concluded that treatment with statin was more cost-effective for patients with vascular disease or diabetes.

The above discussion showed the different CERs and ICERs obtained in economic evaluations of dyslipidemia treatment in several countries. Variation in the CERs may be due to: 1) difference in the identification, measurement and valuation of costs from country to country and 2) changes in disease prevalence leading to differences in magnitude of effects of the intervention. Inevitably, this would lead to different CERs and ICERs in different settings. Moreover, if a threshold ratio is adopted by some sectors (despite the issues raised earlier), the adoption of a similar threshold becomes very problematic in a developing country setting like the Philippines.

C. Reducing the Cost of Medicines

It would be noticed that for the pharmacologic interventions, the dominant factor in the CERs was the cost of the different drugs for dyslipidemia. Thus, marked changes in the costs of these drugs will bring about significant changes in the corresponding CERs. Moreover, in the local setting, where health care is attained mostly through out-of-pocket payments, reduction in the cost of medicines may translate to increased access (please see section on equity issues). This is where the reduced CERs will translate to better clinical outcomes since low CER does not always equate to affordability. This can be exemplified by effective but expensive medicines, access to which is limited to those who can afford them.

The cost of medicines, identified as one of the out-of-pocket payments, was measured using the retail prices of a drugstore chain which controls 80% of the retail pharmaceutical market in the country.[20] Any changes in the prices of drugs will have a significant impact on the costs of medicines. Thus, the availability of similar drugs (same generic, different brand names) marketed by both local and multinational companies have resulted in the lowering of prices. A bill currently being deliberated in the local Senate and House of Representatives, the “Cheaper Medicine Bill”, is expected to further cut the cost of medicines in the country through government imposed price regulation as well as mandatory “generic only” prescriptions. However, for the CERs to go down (due to the decrease in the cost of medicines), the effectiveness of these drugs should be the same. This equality in effectiveness can only be true if they have the same

bioavailability as the innovator drugs. "*Bioavailability* denotes the extent to which a drug reaches its site of action or biological fluid from which the drug gains access to reach its site of action."[61] Two drugs then are deemed bioequivalent if their rates and extent of bioavailability of their active substances are not significantly different from each other under appropriate conditions. Bioavailability will thus affect effectiveness as well as possible side-effects. Decreased bioavailability will redound to lesser effectiveness while increased bioavailability might lead to increased side-effects especially for drugs with narrow therapeutic index.

Although the local Food and Drug Administration Board (BFAD) requires tests for bioavailability/bioequivalence before registration, this holds true only for drugs included in their List B' and not for all drugs.[21,22] In addition, such tests are conducted not by BFAD itself but by accredited testing centers through the Department of Health, located locally or outside of the country. Unfortunately, despite such requirements, supposedly similar drugs but with different bioavailabilities have been allowed to be marketed in the country albeit, with different prices. In one instance, a significant difference in bioavailability (lesser bioavailability) was demonstrated which may result in reduced clinical effectiveness of the drug as compared to the innovator drug.[62] In contrast, another study showed higher bioavailability which may affect the incidence of side-effects. Fortunately, because of the latter drug's wide margin of safety, this increased bioavailability may not be clinically significant.[61]

On the other hand, lipid lowering agents are not included in the BFAD's List B' mentioned above. However, some pharmaceuticals conduct bioavailability studies to assure patients and physicians of the bioequivalence of their products with the innovator drugs. In order that only the costs and not the effectiveness will be affected in the CERs in the sensitivity analysis, the drugs included in this paper's analysis were those with studies proving their bioequivalence to the innovator drugs (except for one where the said study was not available).

Lastly, many lipid lowering agents are available in several strengths of preparation (i.e., mg/tab), the prices of which are only a few pesos apart, e.g., simvastatin is available in 10, 20, 40 or 80 mg/tablet preparations. The increase in prices is not correlated with the strength of preparation, i.e., doubling the strength does not mean doubling the price, the price difference between the lowest strength preparation and the strongest strength preparation amounting to about less than 30% for some drugs. Moreover, the innovator drug for simvastatin has adopted a scheme of having only one price for all its preparations – from the 10 mg to the 80 mg/tablet. Thus, it has been a local practice to buy the higher-priced preparation and split the pill into two to cut on costs. This practice is even advocated by some physicians especially if the drug comes in scored tablets, thus splitting the tablet will mean not only an exact reduction of the dose of the drug by half but of the cost of the drug as well. However, this may not always be true for some drugs.

It is noteworthy that the trials where the beneficial effects of lipid lowering medicines were proven represent the “ideal setting”. Compliance with treatment and monitoring is higher in trials than the real setting. This is observed not only in the local setting but also among patients in developed countries.[63,64] Furthermore, patients in the local setting usually utilize doses lower than those in the trials to lower down the cost of medicines. Because of these, effectiveness of therapy obtained in the trials will most probably not be the same in the setting of decreased compliance.

D. Equity Issues

In contrast to most guidelines, the local guidelines on dyslipidemia devoted a separate section dealing with recommendations for the disadvantaged segment of the population. These groups were identified as those “who live below the annual poverty threshold of Php12,267.00 (as of 2003), cannot afford laboratory examinations and drug therapy, have limited or no access to health care, or are undernourished (body mass index < 18.5).”[1] Differences in the recommendations for this segment of population center on the pharmacologic recommendations especially for those patients without evidence of atherosclerosis but have $\geq$ 3 risk factors (high-risk patients). The options on pharmacologic treatment to these patients depended on cost considerations since the cost of the medications largely determined the burden for this type of treatment. In addition, options regarding monitoring of lipid levels as well as the laboratory examinations for screening dyslipidemia were also listed, again, because of cost considerations. Recommending screening and subsequent

pharmacologic treatment for the disadvantaged population might be unrealistic and might just add undue financial burden to these groups of people who can hardly afford the more basic necessities of living such as food and shelter.

As noted earlier, the cost of the drugs was a determinant factor in the CERs. In addition to the above-mentioned ways of bringing down the cost of medicines, multinational companies have resorted to some measures in order to compete with the makers of lower-priced similar generic products. Makers of the innovator drugs are presently offering discounts in their medicines (although their prices net of discounts are still higher than other brands). These are made possible through the issuance of discount cards given by the product or medical representatives to physicians in their out-patient private clinics. These clinics usually belong to specialists and some general physicians. Unfortunately, access to these clinics is limited by one's ability to pay. On the other hand, such discounts cannot be availed of in all drugstores all over the country but instead mostly through the biggest drug store chain in the country or a few bigger drug stores located in urban centers. This set-up compounds the problem of inequity defined as unequal access for equal need. It is thus ironic that the beneficiaries of the discounted prices are those in the higher socio-economic strata compared to the poor.

In addition to the above problem, not all lipid lowering agents are available in all drug stores in the country. Even the biggest drugstore chain of the country does not carry the same stock of lipid lowering agents in all its branches as documented by a random visits/inquiry by the author of some of its branches.

Moreover, a uniform pricing scheme of prices (lower prices) is true in the national capital region and nearby suburban areas but not in some provinces. A random survey of prices of some lipid lowering agents revealed higher prices in a province located 170 km southeast of Metro Manila (foremost urban center of the country) as well as another province located 795 km southeast of Manila. This unequal availability and pricing set-up further add to inequity considering that those in the higher socio-economic strata usually reside in the urban areas. Ironically again, they are the ones who can readily avail of these lower prices compared to poorer patients in the provinces.

The Philippine National Health Insurance (PhilHealth), on the other hand, is advocating the use of clinical practice guidelines (CPGs). One of its efforts is the identification of CPGs that will serve as basis for quality assurance and accreditation. So far through this effort, 15 have been identified. Moreover, PhilHealth has undertaken an initiative whereby compliance to these CPGs will serve as basis for reimbursement (claims payment).[65]

At the present, the guidelines on dyslipidemia are not yet included in PhilHealth's list of CPGs. In addition, majority of PhilHealth's claims are for in-patient illnesses whereas the mainstay for the management for dyslipidemia is through out-patient services as well as maintenance oral medications.

In 2006, Philhealth estimated that 79% of the total Filipino population as its beneficiaries. During this year, majority of its members were from the indigent and private sectors, corresponding to 36.3% and 34.2%, respectively.[66] However, despite a bigger percentage of membership coming from the indigent

group, the biggest chunk of PhilHealth payments (>40%) went to private patients as can be seen in the following table.

Table 17 PhilHealth Payments by Sector as of 2006

Sector	Amount	Number
Private	43.5%	40.86%
Government	22.5%	22.81%
Retirees	6.9%	5.78%
Indigents	12.6%	15.5%
OFW	0.0%	0.02%
IPP	14.4%	22.81%

OFW – Overseas Filipino Workers; IPP – Individual Paying Patients

Despite the supposed thrust of the government to reach out to the indigent population, it is unfortunate that this group of patients comprise only 15.5% (12.6% in terms of total amount of claims) of those that availed of PhilHealth benefits. This low Philhealth usage is probably attributed to the inability of this sector to make the large co-payments or out-of-pocket payments. In 2002, it was estimated that the national average out-of-pocket payments was 60.9% of the total health expenditures.[3] Thus, patients who benefit most from PhilHealth are not the poor but those who can afford to pay (the larger co-payments) inadvertently increasing inequity!

Furthermore, it is unfortunate that the September 2007 data showed that Philhealth's actual beneficiaries (61.12 million) is only 67% of the total population, a far cry from the estimated 79% in 2006. It also showed that

members from the private sector increased to 38.9% whereas those in the indigent sector (presently known as the sponsored program) decreased to 25.2%.[67] From this data, it would be no surprise if claims from the indigent sector become much lower compared to the private sector further reflecting inequity!

V Conclusions, Limitations and Recommendations

This study presented the economic evaluation of the clinical practice guidelines for the management of dyslipidemia in the Philippines. The analysis reported the cost-effectiveness ratios (average or incremental) of the treatment options, non-pharmacologic therapy compared to no treatment ("do nothing") or pharmacologic treatment vs. no treatment or non-pharmacologic vs. pharmacologic therapy.

In the primary prevention strategy comparing non-pharmacologic treatment for 2.5 years with the "do nothing approach", the cost-effectiveness ratio ranged from Php 26,980 – 31,234.00 per cardiovascular event prevented (discount rate of 0 – 5%) using the single cholesterol as the only laboratory parameter utilized. This increased to Php 76,949 per cardiovascular event prevented if the cost of exercise time was included. When the screening and monitoring strategy adopted was that of a lipid profile determination, the CERs were from Php 39,980 to Php 46,282 (0 - 5% discount rates) and Php 135,304 if exercise time was included in the cost.

Among the pharmacologic agents compared (3 statins and 2 fibrates) simvastatin was shown to have the lowest cost per desired clinical effect

(reduction of cardiovascular events), whether for primary prevention (high-risk patients) or secondary prevention strategy.

For primary prevention for patients with > 3 risk factors for cardiovascular disease (high-risk patients), the incremental cost of adding simvastatin to non-pharmacologic treatment was Php2,016,818 – 2,979,768 (ICER for base case analysis using 0 - 5% discount rate) for every major clinical event prevented (cardiovascular event or total mortality) using the single cholesterol determination strategy. There was minimal change in this ICER if the monitoring strategy was through cholesterol or lipid profile monitoring (highest ICER of Php3,112,085). Using the same assumptions for diabetics, this could range from 1,038,967 – 1,603,195). On the other hand, if fenofibrate instead of simvastatin was the option chosen for diabetics, the ICERs could range from Php2,025,267 – 2,058,009 (using the above assumptions).

For secondary prevention, the ICER of simvastatin could range from Php220,409 – 639,977 (US$4792 - 13,913) using single cholesterol determination or screening and monitoring through cholesterol/lipid profile examination (0 – 5% discount rates). When decision-analytic modeling through Markov models were undertaken, higher ICERs were obtained. These ranged from Php458,299 – 703,108 (US$9,9963 – 15,285).

Locally, no explicit threshold value exists at the present time and setting one might still be problematic. In view of this, in terms of the efficiency criteria for the dyslipidemia problem, programs with the lowest average CERs and ICERs might be deemed to be the appropriate options. In a setting where access to

health care is limited by one's ability to pay, the cost of non-pharmacologic treatment in reducing major cardiovascular events and total mortality could readily be considered more cost-effective compared to the other alternatives included in this study. For pharmacologic treatments, secondary prevention approach is more cost-effective compared to primary prevention.

This paper is limited by the availability of data from published results of the randomized trials which were conducted in the western population. In addition, there is paucity of data in the local population leading to assumptions derived from foreign data. Likewise, there is much variability in the cost of medicines for dyslipidemia, which, on the other hand is a determinant factor in the cost-effectiveness ratio. Moreover, there is a rapid change in the conversion rate of Philippine peso to US dollar in the past few months (the peso has appreciated >10% in the past 5-6 months which could be a reflection of improvements in the local economy or the decline of the US$ due to the economic problems in the United States).

Despite the above limitations and faced with scarce health resources, it is recommended that the results of this analysis guide policy makers, clinicians as well as patients to arrive at a sound clinical decision in the management of dyslipidemia. Furthermore, once more local data become available a re-computation of the CERs and ICERs can be made using the structure/model given in this paper in order to provide a more realistic estimate. In addition, the framework of this paper could be used for the economic evaluation of the three other lipid lowering agents (rosuvastatin, niacin and ezetimibe) in the local

setting. (These medicines were not yet included in the guidelines due to either lack of evidence of clinical effectiveness or unavailability of the drug in the local market at the time the guidelines were crafted.)

Lastly, it is also recommended that during any clinical practice guideline development (especially in a developing country setting like the Philippines), an economic evaluation of its recommendations be undertaken in order to assist its intended users in coming up with the possible best course of action to undertake.

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Appendix 1
Recommendations of the 2005 Clinical Practice Guidelines for the Management of Dyslipidemia in the Philippines

Statements:

Statement 1. "To reduce overall CV risk, all patients, regardless of their present morbid condition or risk profile, should be advised on the need for the following: smoking cessation, weight management, regular physical activity and adequate blood pressure monitoring and control."

Statement 2. "For patients at any level of CV risk, especially those with established atherosclerosis, a low-fat low-cholesterol diet is recommended for life."

Statement 3. "In poorly nourished and elderly patients, correction of nutritional deficiencies can be achieved even with a low-fat, low-cholesterol diet."

Statement 4. "For low-risk patients without evidence of atherosclerosis, drug therapy is not recommended, regardless of lipid levels."

Statement 5. "For patients without established atherosclerosis but with $\geq$ 3 risk factors and total cholesterol $\geq$ 190 mg/dL or LDL $\geq$ 100 mg/dL, statins may be recommended."

Statement 6. "For diabetic patients without evidence of atherosclerosis and with total cholesterol $\geq$ 190 mg/dL or LDL $\geq$ 100 mg/dL, statins are recommended."

Statement 7. "Fibrates may be recommended as an alternative to statins in diabetic patients with HDL $\leq$ 35 mg/dL and LDL $\leq$ 90 mg/dL."

Statement 8. "For patients with established atherosclerosis and total cholesterol ≥ 190 mg/dL or LDL ≥ 100 mg/dL, statins are recommended."

Statement 9. "Fibrates may be recommended as an alternative to statins if HDL < 35 mg/dL and LDL of ≤90 mg/dL."

Statement 10. "In patients without risk factors, history or symptoms of established atherosclerosis, the screening of lipid levels is not recommended."

Statement 11. "In patients without established atherosclerosis but with ≥ 3 risk factors, lipid profile may be recommended."

Statement 12. "In patients with established atherosclerosis or diabetes, the use of lipid profile for screening is recommended."

General recommendations for disadvantaged patients:

1. "Regardless of risk and lipid levels, patients should be advised on smoking cessation, weight management, a low-fat, low-cholesterol diet, correction of nutritional deficiencies, regular physical activity and adequate blood pressure control to reduce overall CV risk."

2. "No drug therapy is recommended for patients with <3 risk factors and without established atherosclerosis."

3. "Costs should be considered for patients with ≥ 3 risk factors but without established atherosclerosis, as statins may be recommended for primary prevention. Screening with a lipid profile to identify the presence of total cholesterol ≥ 190 mg/dL or LDL ≥ may also be recommended after careful consideration of costs."

4. "Statins are recommended for patients with diabetes but no established atherosclerosis (if total cholesterol ≥ 190 mg/dL or LDL ≥ 100 mg/dL). Fibrates may be recommended as an alternative to statins (if HDL ≤ 35 mg/dL and LDL ≤ 90 mg/dL)."

5. "Statins are recommended for patients with established atherosclerosis and total cholesterol ≥ 190 mg/dL or LDL ≥ 100 mg/dL, while fibrates may not be recommended as an alternative to statins in patients with HDL ≤ 35 mg/dL and LDL ≤ 90 mg/dL."

6. "Candidates for drug therapy who are chosen on the basis of the above recommendations may be screened using a lipid profile to identify the presence of specific lipid derangements (e.g., total cholesterol 190 mg/dL, LDL 100 mg/dL or HDL 40 mg/dL). However, the decision to screen and the method of screening should be made after careful patient education and cost consideration. Patients who choose not to be screened may still be given the option to make an informed choice to initiate statin therapy."

7. "Monitoring of lipid levels may be recommended. Patients should be provided with proper and adequate information and education regarding monitoring options to be able to make an informed choice. If patients choose total cholesterol for screening, statin therapy may be initiated at fixed dose. Monitoring may be foregone OR it may also be done using total cholesterol, to be conducted at the soonest after 6 weeks. Dose titration should aim for at least 20% reduction of total cholesterol from baseline."

Appendix 2 Number of events prevented with the different lipid-lowering drugs.*

Secondary Prevention						
	Total Mortality	**Cardiovascular Death**	**Myocardial Infarction**	**Stroke**	**Revascularization**	
Drug						
Simvastatin (total= 168)	33	32	62	14	59	
Pravastatin (total=93)	23	20	27	9	34	
Atorvastatin (total=87	20	23	38	NS	29	
Bezafibrate/Gemfibrozil	NS	NS	21	24	NS	
(total= 45)						

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*Modified from files from "The Clinical Practice Guidelines for the Management of Dyslipidemia in the Philippines