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ROLE OF PHARMACOECONOMICS IN FORMULARY DECISION-MAKING

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2003

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SUMMARY

'Formularies' represent a compendium of pharmaceutical products and services selected by the medical staff of an institution to reflect current drug preferences of healthcare practitioners and patients.

Successful formularies restrict access to or discourage the use of those drugs for which there are lower – cost substitutes available, thereby encouraging the use of more efficient medications.

When compiling and revising formularies, the most frequently used criteria for selecting among alternative drugs are clinical efficacy, risk of adverse effects and daily cost of drug. Too often, such selection processes focus on a search for the least costly alternative, without an explicit analysis of overall cost-effectiveness.

For an institution or organization assessing drug costs however, the more relevant issue is, how much a drug therapy costs in the context of overall patient care for a given disease. As such a reassessment of the role of the formulary and the manner of its implementation is taking place.

The purpose of today's formulary is to promote the efficient use of drugs.

The importance of pharmacoeconomics in formulary decision-making lies in the information provided about the value and efficiency of alternative pharmaceutical products compared with other relevant treatment alternatives when both costs and consequences are considered simultaneously.

However if Pharmacoeconomics is to contribute to formulary decision-making P & T Committees must appreciate the potential role of that discipline in such decisions; at the same time, pharmacoeconomists must demonstrate that their analyses can lead to more efficient allocation of limited resources in the purchase of drugs without compromising the quality of healthcare.

Initial exploratory surveys of pharmacists in Singapore clearly established the need and scope for use of pharmacoeconomics in hospital settings in the country.

Contending that pharmacoeconomics has a definite role in formulary decisions the researcher endeavored to test this hypothesis in the setting of the university hospital through a means deemed appropriate by her. This was to evaluate one or two products for each P&T Committee meeting through 3-4 meetings and submit the evaluations for facilitating P&T Committee decision-making.

An objective measure of the success of the process would be an assessment of the percentage change in the number of P&T approvals and potential cost savings to the organization as a result of pharmacoeconomic assessments. However, due to the inherent nature of the project and a lack of time it was not possible to consider them as primary outcome measures.

Economic evaluations (as proposed and demonstrated by the researcher), in addition to the primarily pharmacotherapeutic (efficacy and safety) based considerations currently taken into account by the P&T Committee at the NUH would entail a more comprehensive or in-depth evaluation of formulary actions (addition or deletion) leading to increased user satisfaction. Hence, the primary outcome measure was taken to be user satisfaction to be measured or gauged by a questionnaire at the end of 3 or 4 P&T committee meetings.

The responses clearly revealed that a majority of the decision-makers expressed satisfaction with the researcher's approach to formulary decision-making and would even be willing to consider a health economist as a member of the committee. Therefore, the researcher was successful in demonstrating to the relevant decision-makers the role of pharmacoeconomics in formulary decision-making. Support for this claim can be found on Page 90: table 19 - P&T Committee members' opinion of the required constitution of the Committee - clearly shows that a substantial proportion (60%) feels that health economists should be considered as 'must be'

members. Though 30% have not unambiguously declared that health economists 'must be' members, they remain unsure about the issue. Only 10% (or 1 respondent) feels that health economists should not be "must-be" members of the committee.

SECTION 1. 'PHARMACOECONOMICS' IN THE CONTEXT OF "COST-CONTROL" IN THE HEALTH CARE SECTOR

1.1 Historical background

1.1.1 The big expansion

In the 50s and 60s in the context of social solidarity, the welfare state and the great society, universal access to health care, generally publicly financed, was seen as a right for all citizens. Health care systems expanded rapidly, as public and private financing supported and helped create new effective demand and delivery system capacity. [1] An important indicator of such expansive growth on the demand side included per capita use of inpatient care* that increased, for example – from 2.1 in 1960 to 3.4 in 1980 in Japan. [2] On the supply side such indicators include – number of physicians per 1,000 capita that increased by 4.2 percentage points on an average (low of 0.9 percent in Austria to a high of 11.6 percents in Finland) for Organization for Economic Co-operation and Development (OECD) member countries between 1960 and 1980.[2]

1.1.2 Growing pain – unbridled expenditure

This expansive growth came about with its own pain – in the form of extraordinary increases in expenditure. Most governments in the early post-World War II era in developed countries felt it their moral and ethical obligation to try and provide universal coverage to their citizens. But, beginning in the 70s and continuing into the 80s, the recessions in most OECD countries engendered by the oil shocks, coupled with rapid increases in health care expenditures, put governments under strong financial pressures. An increasing challenge emanated from the

* as measured by hospital bed-days per person and per year

growing inability of different governments to cope with the increasing expenses and a heightened concern about the sustained capacity to meet the rising demand in health care services. Pressures for health care reform started mounting in most countries. [1- 10]

Among reasons most often cited by analysts, experts and government officials behind these increasing health care costs, the most important ones were an increasing demand for health care (propelled by a rapidly ageing population, technological advancements and a real income growth), the way health care systems were structured and financed, and an emphasis on acute care rather than prevention. [1, 11, 12]

From the 1970s member economies of the Organization for Economic Cooperation and Development (OECD), responding to increasing concern with regard to growth in health care expenditures, conducted several studies,[1-7] which, revealed important facts about health care systems in different countries and firmly established the need for cost-control. It was being felt in most countries that rising health care expenditure had two major aspects associated with it:

1. The 'real' expense levels
2. additional expenditure that could be warranted due to an increasing proportion of 'ageing' population

1.1.2.1 Real expense levels spelt danger

Let us take some figures from 1984 data to see how grave the situation was.

In 1984, 780million citizens in 24 OECD countries consumed over US$800billion worth of health services, approximating greater than $1000 per person. On an average almost 80% of the expenditure was financed by the public sector. Health care expenditure accounted for almost 15% of all public spending and 25% of all social spending* (the second largest social

expenditure item).[♣] Public expenditure on health accounted for 6% of the GDP while overall it accounted for 8% of the GDP.[1]

1.1.2.2 Future forecasts did not show much hope – the ageing population

The projected trends also did not show any significant improvements. Rather, a steep increase was predicted for most countries. Some nations going by projections made then would have had to spend on average some 30% higher on health care by the year 2030, due to population ageing, which seemed unacceptable by any standards.[1, 12] In the face of the demographic configurations of the population and the rapid progresses made in science and technology these projections did not appear too unrealistic.

A statistical estimate of the years 2010 and 2030 in terms of demographics of the young and old looked like this: [1]

Table 1: Trends in Percentage of National population aged 65 and above

	1980	**2010**	**2030**
Switzerland	13.83	20.49	27.49
Germany	15.51	20.35	25.82
Netherlands	11.51	15.13	22.96
Canada	9.51	14.61	22.39
Italy	13.45	17.28	21.92
France	13.96	16.26	21.76
Sweden	16.29	17.47	21.70
Belgium	14.37	15.90	20.78
Japan	9.10	18.62	19.97
United States	11.29	12.79	19.49
United Kingdom	14.87	14.61	19.24
Australia	9.62	12.59	18.22
Ireland	10.72	11.08	14.74
Denmark	14.41	16.67	22.56
Finland	11.98	16.76	23.78
New Zealand	9.73	12.01	19.35
Average	12.62	15.94	21.27

[♣] Social spending would include other spending for societal benefit. This could include expenditure on education, public housing, public transportation, recreation facilities like parks etc.

The above figures meant, substantial ageing of the populations was predicted for most countries. Again, as has been observed old people generally consume more health care resources than younger people. In fact, health care expenditures were observed to be the highest for the very old and the very young. It was noted that medical care expenditures on those 65 and over could on average be 4 times greater than expenditures on those below 65. Expenditures on those 75 and older could be more than 7 times greater than on those under 65. [1, 7, 12, 13]

That meant two things: first, there would be a greater need for health care resources, as an increased proportion of the population was growing 'old'. Secondly, 'increased proportion of old' would mean there would be a decreased proportion of young or productive population to support the older population. Naturally, it was being felt that the burden on the economy would become very high. In addition, the giant strides made by technological and scientific innovations meant that the life expectancy in general, was increasing which was to bring with it additional medical 'needs' and thus additional expenditure.

1.1.3 A case for controlling costs

Given the rate of progress in medical technology, the estimated future demographic change (associated with a higher-than-ever demand) and the anticipated potential future financing constraints, governments started becoming increasingly concerned about their ability to provide universal access to necessary services.[1,11,12] Governments that until the 70s concentrated on expanding the facilities and capacities of their health care systems became increasingly preoccupied with devising various methods of cost control discussed later. [1, 2, 4, 7, 9, 10, 12, 14]

That this concern of different countries was not in vain can be well understood today by looking at the corresponding figures captured: the global health expenditure in 1995 stood at US $1,800 billion just over 8% of the world's total gross product. In the U.K, the inflation-adjusted per capita rate of growth of health care expenditure has been 4%, slightly lower than the US at 5% and only half of the staggering rate of 8% in Japan.[15]

A pertinent question here may be, "Patients are covered by some form of insurance; therefore they do not pay anyway. Why bother?" In reality, however, consumers pay in one form or the other, for example, in the form of reduced pay and greater premiums or higher taxes.[16]

1.1.4 Compelling reasons for cost-control

The most significant reasons for embarking upon cost-control in the health care sector seem to have been the following:

1. ***Higher expenditures did not necessarily correlate to better "quality" of healthcare***

Quality in health care is difficult to measure. [1, 4, 6, 7, 11, 12] It is not easy to evaluate the effects of the many billions of dollars spent in this sector. If improvement in life expectancy or death rate is an index of quality in health care, then increased expenditures can be no guarantee for "better" health.

Among the more developed countries no clear pattern can be discovered between health care spending and life expectancy.[7] For instance among OECD countries, the US, one of the highest spenders on health care in the world, ranked 21st in terms of infant mortality and was in the bottom half in terms of life expectancy at birth. [11] However, countries like Canada, the United Kingdom, Switzerland and Australia while spending less have much better infant mortality rates than the US.[10]

Moreover, although an index such as infant mortality is a meaningful way of evaluating the impact of health care and public health programs in less developed countries, it is questionable whether such crude measures can accurately gauge the impact of health care services in wealthier industrialized nations. In industrialized nations, much of health care focuses on "softer" health outcomes, such as enhancement of functional status and quality of life in individuals with chronic diseases --- aspects of health status more difficult to monitor at the population level than death rates and related vital statistics. Additionally, when evaluating population health, it is usually difficult to disentangle the influence of health care from the impact of such basic social factors as poverty, education, lifestyle and social cohesiveness.[1, 5, 7, 17] Because, health services by themselves can do little to bring about an improvement in the life expectancy of populations, other than by immunization.[7]

2. *'Value' in health care is difficult to measure - Convoluted healthcare delivery chain*

Important questions raised in different countries were: "How is value for money to be measured in the case of health care?" "Which aspects of health systems provide the most value for money and which the least?"[1,7]

Unfortunately, precise answers to these questions could not be given and answers to these questions evade us even to this day. In fact, there was no assurance that the value society was receiving in return for the rapidly rising expenditures was growing in tandem with the costs being paid. Unlike the Fast Moving Consumer Goods (FMCG) market, the health care market is a notoriously "not efficient" market. For most consumer products market, competition (though not perfect) amidst other factors is one very crucial element that determines which products remain in the market. The health care sector however, is distinguished by its inability to have a perfect market competition. This problem results from the fact that consumers who actually consume the products and services of this sector are unable by

themselves to decide what they "need" or to judge whether they can "buy" it. They have to rely on their more knowledgeable health care professionals for this important judgment. Moreover, whether they are willing and able to buy cannot be estimated correctly as they hardly ever pay wholly (out-of-pocket) for the care (especially in developed countries). Exactly what it is that consumers are paying for (in some form or the other) no one knows. And no one knows either, whether the consumer really would want to buy that product if he were given a full understanding about it. Moreover, it is not quite believable that anybody would ever "want" to "buy" health care (if not compelled to do so).

The result is that only a few people (namely, the health care professionals) know what is good for consumers but they do not know whether the product is the 'best value' for the price being paid.

As an example, if there is a medical treatment that can affect the same cure in the same time as a more expensive surgical treatment, efficiency in consumption can be increased by substituting medicine for surgery. If however, the consumer's health insurance scheme pays for surgery but not for medicine, a choice, which is inefficient from society's point of view, is likely to be made. An imperfect market thus is more often the norm in the health care sector .

3. 'Law of Diminishing Returns' in health care

Additionally, "more" may not necessarily be "better" either. In this respect, health care behaves like any other economic good in the sense that, the cost-benefit curve has a diminishing slope as increasing investment of resources yields less marginal improvements in the health of the population (Law of Diminishing Returns).[16, 17]

To summarize, the important findings that mooted the whole idea or contemplation of health-care cost control were the following:

- Health care costs were growing at an unsustainable rate
- To keep pace with such growth meant cannibalizing into other sectors of the economy that also demanded share of the public budget
- The tremendous growth in expenditure was not necessarily translating into superior quality, for two reasons: quality was difficult to measure and whatever indicators were available did not necessarily show any direct correlation with high expenses
- The Law of Diminishing Returns in health care also meant that the concept of "limits in expenditure" was gradually finding appeal to most decision-makers.

1.1.4.1 "Health care cost-control" Ethical/ political hot potato

However, "cost-control" in the healthcare sector was and is, not taken too lightly. There is invariably a degree of suspicion. Will fewer people have access to health care? Can't the government take stock of other sectors? The moment 'cost control' is mentioned it also raises doubts about the issue of 'quality'. Will the quality of care be compromised? Eyebrows are raised about the "ethics" of "controlling" costs in health care.[16] Questions about the quality of care are an integral part of the debate on cost containment policies for health care for the elderly and the consequences of adopted policies.[13] That quality issues in this sector are politically sensitive issues is undoubted.[1, 5, 11, 12]

1.2 The governments' will to change – 'cost control' methods implemented

1.2.1 Demand control methods

1.2.1.1 Restrictions on reimbursement

These measures were based on the philosophy that consumer demand is limitless, unless some kind of restraint is placed on it by way of requiring patients to pay for part or whole of

treatment. When a good is provided "free" it almost always brings with it the issue of moral hazard. People tend to be insensitive to the cost of the good and overuse or abuse it because they "lose nothing" by doing so.

In the health care arena it was being increasingly felt that with virtually "no costs' borne by the patients the issue of moral hazard was a big possibility. Hence, one of the most important policies aimed at patients was that of restrictions on reimbursement (particularly prescription charges). By limiting the reimbursement of products, such policies are aimed at providing an incentive for patients to reduce their consumption of drugs. These could include co-payments that may require patients to pay a proportion of the cost of a prescribed product or a fixed charge. [11, 12, 18] Patient caps constitute limiting the number of reimbursable prescriptions per patient. [11, 18] The withdrawal of reimbursement of a drug may also be used in attempts to reduce prescribing.[18]

Thus in France co-payment requirements were increased either by cutting reimbursement rates or by removing some treatment from coverage. This was most pronounced with prescription medications. A list of reimbursable drugs **(positive list)** was drawn up by the Ministry for Social Affairs, and each year the list kept growing smaller.[11] In some countries like Greece, **negative lists** that provide the list of products that would not be reimbursed.[19] However, it has been suggested that policies to limit the level of reimbursement of drugs reduce the use of essential as well as non-essential drugs and may do more harm than good. [20]

1.2.1.2 Patient co-pays

In the UK changes were implemented in certain areas previously covered for free by the National Health Service (NHS). Patients were required to pay a portion of their bill for medicine and appliances prescribed by the doctor. This measure serves dual purposes. The doctor becomes more cost-conscious and so prescribes only if the situation demands it. The

patient also becomes more sensitive to costs and does not demand extra unnecessary care.[11] However, user charges are perceived as taxing the ill by shifting some of the burden out of government budgets. Such practice is of a regressive nature in the sense that, after a certain stage the expenditure levels tend to be distributed around a mean value. They cannot be decreased any more. Moreover, increasing user charges may reduce government expenditure but not enhance efficient use of drugs.[18]

1.2.1.3 Supply restrictions

The National Health Service was set up to control costs by having the general practitioners (GPs) act as gatekeepers to secondary and usually more costly care, a form of supply restriction. [7, 11, 21, 22]

1.2.1.4 Health service providing organizations and policies

The concept of managed care in the US emerged as a strategy to reduce demand. After trying a number of regulatory approaches during the 70s and the 80s, the cornerstone of cost containment policy during the 1990s has been managed care.[23] It is based on the philosophy that many of the health services provided to consumers are unnecessary or inappropriate and since consumers are not able to evaluate the care given, Managed Care Organizations can act on the consumers' behalf. Use of the term "managed" underlines the fact that the health care sector lacks some of the basic features of a "free" market, such as full consumer information or real pricing mechanisms and competition. Managed care acts to curtail costs by limiting or influencing patients' choice of providers, reviewing and intervening in decisions about health services to be provided either prospectively or retrospectively, and negotiating different payment terms with providers.[7, 11] The two primary types of managed care organizations

Health Maintenance Organizations and Preferred Provider Organizations by engendering competition among the providers relied on the philosophy of free markets to control costs.

In 1983, Medicare began its Prospective Payment System to reimburse hospitals. This system is based on Diagnostic Related Groups (DRG s). Hospitals are given a fixed payment related to the expected costs of treatment for specific diagnoses, for each hospital admission. Should the hospital spend less on caring for the individual, the hospital retains the extra funds. Conversely the hospital is at financial risk for treatment costs beyond the fixed amount. Thus, hospitals have an incentive to operate efficiently and to discharge patients at the earliest medically feasible time. [11] However the down side of this scheme is that, in a bid to make more profits, the hospitals might discharge patients prematurely.

However, it has been seen that piecemeal initiatives tend to leave untouched the full set of forces that give health care spending its momentum.[11]

1.2.2 Supply control methods

1.2.2.1 Generics

On the supply side, attempts were made to place limits on prescribing practices by fostering the use of generic (usually cheaper) substitutes.[11] Use of generic drugs is encouraged in most countries, but only Germany, Denmark, the United States, and the Netherlands allow community pharmacists to substitute generic drugs for proprietary brands.[23] Moreover, generic drugs may reduce spending on drugs, but it can tackle only part of the problem of containing costs as new drugs are patent protected and their increased use will not be affected.[23]

1.2.2.2 Fund holding

In the UK, in the 90s a system of "fund holding" of the GPs came to be practised. [7, 11] In the late 80s hospital and community health services were managed by general managers under the supervision of regional health authorities and district health authorities. However, under the fund holding system, GPs can control their own budgets and bypass the district health authorities in their provision of health care. They can buy treatment from any source whether NHS or private. They are encouraged to shop competitively for hospitals that offer them the best quality and price. Private hospitals compete for patient referrals from the GP s.[11]

One aim of fund holding was to secure better value for money by encouraging general practitioners to scrutinise their prescribing and referral patterns and to shop among competing providers for the best price and quality. Supporters of this approach argue that it constructs an internal market for some types of service and thus incentives to search for cost-effective alternatives. The GP acts as an agent for the patient, helping him to be a better-informed customer than would otherwise be the case. [7] However the impact of changing referral rates on the quality and appropriateness of care is not known. [22]

Another pertinent question could be "Is it time well-spent by the doctors?" Would it be more fruitful spending of time if they did not manage funds and concentrated instead on their clinical practice? As has been truly stated, with such an approach "paperwork grows; patient work shrinks".[21]

Another question that also seems pertinent here is "How can allocation efficiency be ensured under such a system?" In other words, how can we be certain that the GP allocates it properly as per patient needs? In one case, 27% of patients exhausted all the GP's funds.[22]

Hence, fund holding practices constitute methods of cost-control targeted at doctors for controlling pharmaceutical expenditure, and rightly so. After all, until adequate steps have been taken to tackle the health system and clinical behaviour, it is unfair to penalise patients, whose decisions are largely not responsible for health care costs.[24] Other measures aimed at

doctors for controlling pharmaceutical expenditure include, physician authorisation, budgetary restrictions and prescribing guidelines.[25]

1.2.2.3 Physician authorization

In France, social security employs 3,000 physicians who among other duties are charged with granting prior authorizations for certain elective treatment - e.g. cosmetic surgery.[11] Retrospective utilisation reviews of physician practices are conducted. The criteria employed are, numbers of patient visits, number of treatments, number of tests ordered etc. A median is developed and anybody exceeding 50% over the median is given 6 months to rectify or sanctions are imposed against him. Media campaign is widely used to discourage consumers from over relying on medications.[11]

1.2.2.4 Other supply side restrictions

Other policies aimed at doctors include budgetary restrictions, information and feed back to physicians, prescribing guidelines or even control on the prescribing advice disseminated to doctors by the drug industry.

In Germany, ***budgetary restrictions*** were introduced in 1993 that placed a limit on drug costs. The first DM280m spent above this limit was supposed to be paid for out of physicians' remuneration budgets. Regardless of whether such policy could lead to a pronounced reduction in prescribing rate and lead to substantial savings, such an approach does not definitely look into issues of quality of prescribing and hence may not encourage cost-effectiveness in health care.[7, 25]

Prescribing guidelines with strict enforcement mechanisms and suitable incentives for compliance or penalties for otherwise, were instituted in France and were instrumental in a

15% reduction in prescribing of antibiotics in the first six months of 1994 (even though the results may have been confounded due to other factors). [24, 25] However, just using guidelines to inform professional behaviour, including the cost-effectiveness of prescribing as done by the Agency for Health Care Policy and Research in the US or by the Department of Health in Britain may just serve as advisory schemes without clear incentives to reward compliance.[25] Taking a slightly modified approach, in Germany, guidelines were introduced to define the average prescription volume for each medical specialty according to therapeutic use and category of drug.[25] In New Zealand part of the Preferred Medicines Concept aims to give general practitioners information on drugs to provide administrative support to help them develop their own '***preferred medicines lists'*** in a "critical and rational" manner. [25, 26]

1.2.3 Market control methods

1.2.3.1 Price/ budget control

Market controls take the form of price or profit controls or both. However, price and profit controls contain few incentives for improving cost-effective use of drugs, and focus on cost containment and profitability of domestic industry. Without the use of carefully monitored economic evaluation (such as in Australia), price regulation remains a crude method of controlling costs and may result in poorer treatment of patients or increased overall costs to the health care system if expensive but cost effective drugs are discouraged. Carefully monitored economic evaluations could lead to improvements in efficiency and benefits to patients and the health care system.[19]

Special boards and committees decide on price controls in the UK. Under the Voluntary Price Regulation Scheme, price is negotiated centrally to show that profits are fair and reasonable.[11] Companies earning excessive profits (more than 75% of their target 17-21 % rate of return on investment in research and development) may be required to cut prices to the NHS.[19]

Though targeting drug company profits seems an attractive option for all cost cutting measures, such measures will serve to be a disincentive for producing and marketing potentially useful drugs and stifle the industry. Regulation of profits also overlooks the need to identify separately the costs of research and development and other costs for each product.[27] It may result in perverse incentives, in particular by reducing inducements to control costs. It may also conflict with other measures to contain costs by allowing companies to increase prices when profits are threatened by reduced sales. Again, profit regulation, makes no attempt to link prescribing with cost effectiveness.[19]

1.2.3.2 Reference Pricing

In 1989, the reference price scheme for reimbursable drugs was introduced in Germany to reduce pharmaceutical expenditure, which had been steadily increasing in the past. Reference-based pricing is a term describing any system that establishes a common reimbursement level for a group of comparable or interchangeable drugs.[28]

In the Netherlands and Germany, the reference price for each product results from average prices calculated on a basket of four European countries (Germany, UK, Belgium and France). [29, 30, 31] In New Zealand the reference price is that of the lowest priced drug, while in Sweden it is the lowest priced generic drug plus some amount (10% in Sweden). [19] In reference price schemes, each company is free to fix its own price over the cap, with the difference being paid by the patient. There is therefore, a strong constraint on companies' pricing policies. Generally, reference prices are fixed in the lower band of market prices, so companies are effectively forced to reduce the prices of many products that may be priced above the reference price.[30] This occurred in Sweden after the introduction of the scheme in 1993, as companies anticipated that consumers would not pay the higher price.[32] The basic premise of reference-based pricing seems to be that governments can reduce drug costs without affecting quality of care by encouraging the use of less expensive but equally

efficacious drugs while maintaining the freedom of manufacturers to set prices and of physicians and patients to choose the products they prefer.

However, the key question is the extent to which the policy is reducing inappropriate utilisation and not acting as a barrier to appropriate care.[28]

The pharmaceutical industry has been vehemently opposed to reference pricing, particularly because the strategy deliberately fails to distinguish between branded medicines, which reflect research and development costs, and cheap generic alternatives.[30]

1.3 General Limitations of governments' approaches

Price and profit regulation focusing on cost containment and profitability of the pharmaceutical industry would most likely result in profit losses for companies and eventually might force less investment in Research & Development and prevent advances from benefiting mankind.

Inadequate prescription drug coverage (as is the case for most Medicare enrollees) for outpatient drug expenditures –might result in less overall use of drugs but one must be careful to see that 'less use' does not mean 'less use of clinically important medications'. Important medications when not taken may cause deterioration of health among those with serious and chronic illnesses. This policy could also potentially lead to increased hospitalization therefore incurring more expenses.

Expenditure caps [20] on outpatient drugs (from an experience of Medicare HMOs in Massachusetts) or other kinds of limits such as limits on the number of prescriptions filled each month (as observed in the New Hampshire Medicaid program) [20] should be avoided to prevent unintended effects like increased hospitalization and nursing home admissions.

As a cost-containment measure in November 1992, the UK government intended to ***widen the range of drugs available without a prescription*** to make individuals aware of personal health care as well as provide "significant savings". [11] But at what cost would the government expect to accumulate such savings? The cost could be very high, because patients might take inappropriate medicines. Such measures would serve to just contain costs without keeping the good health of the community in perspective.

Thus we have seen a variety of approaches being used to control health care costs in general. However, none of these approaches can guarantee "better value for money' because they almost always face resistance from potential losers of reform. To be successful, all cost-containment measures must provide incentives to managers at all levels in the system to acquire the relevant knowledge and make the best decisions, taking into consideration all the difficult trade-offs between the various possible uses of resources. It is through improved decisions that health care can be made more efficient, that is, give better value in all relevant aspects for the resources consumed. To improve decisions, continuous monitoring and evaluation of the individual steps taken are also needed.[7]

1.3.1 Focus on pharmaceuticals – in all cost-control methods

A look at the various measures would reveal that "drugs" were important targets in all initiatives. In spite of differences in cost-sharing approaches in the different countries, virtually all countries impose some kind of cost sharing on pharmaceuticals.[23] Indeed, an offshoot of this massive movement to control increases in health care costs was a major war waged against the pharmaceutical industry primarily targeting drugs.[1, 7, 11, 19, 30]

Several factors contributed to the increase in health care costs. In fact, contribution of drug costs to the total health care expenditures is minimal. [1, 11, 12] An important argument could be that drugs have good potential to substitute for other more costly interventions and

therapies.[33, 34] Hence, their use should be increased. Then why is the pharmaceutical industry drawing increasing attention?

There could be several reasons:

- In most of the countries in Europe and Australia, pharmaceuticals, is always a covered benefit.[23] Pharmaceuticals make up a small yet significant portion of the health care sector. As governments try to control costs, expenditure on drugs, therefore, has been a prime target although generally drugs represent only about 10% of health costs. [1,7,11,12]

- In hospitals, pharmacy departments usually operate on a budget that is 5-10% of total hospital costs. Regardless of the percentage of the overall hospital's budget, a pharmacy department's costs – primarily drug supply costs have been increasing at a rate ranging from 9% to 20% annually.[35] For both acute care and ambulatory care settings, the cost of drug therapy is projected to skyrocket.[35]

- Drug expenditures in the US increased by 12.6% annually between 1994 and 97. This represents a more rapid average rate of growth than any other category of health services, almost 4 times the rate of growth of hospitalization expenses (3.4% per year). [20,36] Consequently drug costs and how to use this resource appropriately have become important health care issues.

- New drugs and biotechnology products entering the market often expand the range of diseases treated with the result that patients are less likely to accept that nothing can be done.[8,11, 12] The pressure to treat increases even when the benefit is marginal. In so far as these new innovations are concerned, they unambiguously increase costs.[17, 37] Even if long-term costs may be expected to decrease; initial capital costs certainly go up.[8, 12] Moreover superior technology is almost always designed for "greater access"

and in that sense it decreases "price" (it enables more people to use the product or service by lowering "price") but certainly pushes up "total costs."[7]

- Governments realise that targeting pharmaceutical prices is far easier and less politically sensitive than curtailing number of hospital beds or medical personnel and their services [1, 11, 12].

- Drugs form a conspicuous and easily identifiable component of medical treatment. However, most drugs, especially in chronic illnesses, only promise to prolong life or enhance the quality of life rather than offer an eradication of disease.

- Pharmaceutical companies are seen as aggressive marketeers promoting their products to the doctors who make complete and final decisions about all drugs on behalf of the consumers, the patients. However, the demand-supply situation does not allow the customer to be 'king' like in the other sectors of the economy because demand determination in the health care sector is far more complex than that found in usual market situations.[38] In addition, the environment in which this occurs is further defined by the presence of numerous government agencies and regulatory requirements.[1, 7, 12, 38]

- In other sectors of the economy "over-priced" items get swept out of the market automatically by market dynamics. However in the health care arena, this could be a more difficult proposition. The customer or the ultimate consumer is heavily dependent on the decisions of the medical care provider who must act as an agent for the patient and must recommend the most appropriate product and/or service. However, due to the intrinsic role of the doctor as both the provider and the recommender, with often a financial incentive attached to the decisions, the doctor's recommendations (especially about buying expensive services or products) are also coming under scrutiny.

- Moreover, the fact that the consumer is most often subsidized by the government or by some form of insurance, presents an inappropriate picture of the "true costs" incurred during treatment. Since the consumer pays much less 'out-of-pocket' when subsidized by the government or insurance than he would have paid otherwise, there is a false notion about 'costs' – which policy makers want to draw attention to.

- Drugs constitute an important node or focal point in the network of management of disease conditions. And, pulling at this focal point could set other things to fall in place.

1.4 Emergence of Pharmacoeconomics

To sum up, the following conditions primarily gave rise to a climate conducive to the emergence of pharmacoeconomics.

- The health care sector is distinctively characterised by its *concern with human lives*. The traditional justification for regulating the drug market is a belief that left unregulated, marketeers will mislead clinicians and patients will suffer physical and economic harm from inappropriate prescriptions. [39]

- Secondly, *the distribution of illness* is not in any way related to the ability to pay. Therefore, if producers were left to operate solely under market incentives then certain illnesses (afflicting people with limited ability to pay) may not have had a treatment at all.

However, enabling every kind of treatment to be available and accessible is equally difficult because of the limitation of scarce budgets. Therefore, policies benefiting the greatest number of people are to be implemented. Thus, most governments felt that *intervention in the health*

care sector was definitely necessary to ensure allocative efficiency, fair access and distributional equity. However, this had to be attained with as much efficiency as possible. Hence technical efficiency, which would enable minimum usage of resources in the attainment of the aforementioned objectives, was imperative. It was this growing need for a balance of cost and quality and issues of *allocative and technical efficiency'* that gave rise to the discipline of pharmacoeconomics.

Therefore, pharmacoeconomics emerged primarily as a response discipline to the immense challenge of health care cost control and a changing perspective in the adoption and use of newer and more sophisticated health care interventions (technologies). [11, 14, 40, 41, 42]

The change in perspective was a natural sequel to, or one could say, the product of, the Outcomes Movement that was born in mid 1970s.[43, 44] It was from then that the term 'outcomes' came to be increasingly used to describe the results and value of healthcare intervention. Until then, practitioners had traditionally been mainly concerned with the "clinical outcomes" of treatments. But with increasing costs, concern about resource usage or economic outcomes of health care decisions also started surfacing. Patients on their part started becoming increasingly knowledgeable and involved in decisions regarding their own healthcare.[1, 11, 40] They increasingly wanted to know how their quality of life would be affected or how satisfied other patients with their condition had been with various treatments.[40]

Howsoever necessary cost-control was, the concern for 'quality' could not be overlooked. Determining what was, 'acceptable' quality was a contentious issue. A plethora of definitions exist of the quality of health care, although there appears to be little agreement of how the quality should be measured.[1, 11, 12]

It so appears that some consensus was emerging in this direction at least where pharmaceutical interventions were concerned. Acceptable 'outcomes' (clinical, economic and humanistic) were gradually being regarded as indicative of optimum quality.[1, 11, 12, 40, 42]

A complete assessment of the "true value" of pharmaceuticals began to mean an assessment of outcomes on all the three dimensions – clinical, economic and humanistic – something that pharmacoeconomics is widely professed and believed to do. However, it was not until 1986 that the term "pharmacoeconomics" was formally coined and used by Townsend in the literature.[40] Since then, the term has been defined, re-defined and newly defined so many times that it seems quite an exercise to attempt defining it without consciously or unconsciously plagiarizing! [14, 40, 42]

However, any exposition must begin with the researcher's understanding of the key terms and issues. This would enable a clearer explanation of the researcher's standpoint in view of his/her perceptions about the topic and improve comprehension of the readers. Following is offered as a basic understanding of what "pharmacoeconomics" is all about (no new definitions attempted) in light of the research objective, approach and relevance of findings.

Pharmacoeconomics gives us an idea about what outcomes are obtained from what products and services based on evidence, from which decisions may be made about which products and services to adopt. As such, it gives more rationale to the spending rather than making a decision in a void/vacuum or with insufficient information. The intent of pharmacoeconomics is to facilitate the production, distribution and consumption of pharmaceutical products and other health care interventions in the most "efficient" manner. The word "efficient" implies greatest benefit derived from a particular level of resource usage.

"Pharmacoeconomics, a division of health care economics, is a tool, not a solution, designed to provide users and decision-makers with information about the cost-effectiveness of different pharmacotherapies. It is used in combination with outcomes research, - a process by which different therapies or drug regimens are evaluated to measure the extent to which a goal of therapy or desirable outcome can be reached."[42]

It identifies, measures and compares the costs (resources consumed) and consequences (clinical, economic and humanistic) of different alternatives (drugs, equipment, diagnostic procedures, disease screening, prevention, treatment programs and policy), and thus performs a complete assessment of their potential 'value' in the efficient delivery of healthcare. Thereby, it can assist in choosing between competing treatment alternatives, allowing decision-makers to balance cost with quality and patient outcomes.[42]

Hence, pharmacoeconomics as a discipline gained prominence with most governments in developed countries zeroing in on 'cost-control' as the keyword in the healthcare sector. [16, 45]

1.4.1 How Pharmacoeconomics fits in the healthcare cost-control jigsaw

It is undisputed therefore that "drugs" must demonstrate tangible "value" in terms of all three (clinical, economic and humanistic) outcomes if they are to be accepted by the society at large. Pharmacoeconomics can help in a good assessment of this "value" and place them in proper perspective in the management of disease. Pharmacoeconomics does not profess to bring down health care expenditures, or drug costs per se. Rather, what it does is to supply decision-makers with more information that would enable them to reduce subjectivity and intuition from their decision process. By helping assign 'value' to different products and services pharmacoeconomics enables us decide if what we are paying for is 'worth' the money. Removing subjectivity could also lead to a more scientifically determined price, a price that the drug is "worth" rather than fix price on a predetermined profit margin or cost-plus basis or simply on whims. Resources are scarce. Therefore, it would be wiser to employ available resources for the best possible use thus maximising the value of every dollar spent. Pharmacoeconomics certainly helps in attaining that objective.

1.4.2 Shortcomings

Pharmacoeconomics as a discipline comes with its share of skepticism.

For instance, what perspective should a pharmacoeconomic study take is a contentious issue. Some opine that a societal perspective is the most ideal.[38, 46, 47] But, to a health care system more concerned with its day-to-day survival in an increasingly cost-conscious environment, the provider's or payer's perspective would look most ideal. Again, valuing indirect costs and benefits as also human life, are controversial areas where consensus has not emerged to date.[1, 39, 48] A general criticism levelled against economics is that it offers ample opportunities for choosing assumptions and techniques so as to reach a preselected result. Researchers know what sponsors want to hear and what will affect the probability of subsequent support.[39] This and the absence of any universally accepted methodology and decision criteria or standardised guidelines for studies leave a lot of scope for introduction of bias in the results.[39, 46, 49] There is a great deal of interest in cost-effectiveness studies on drugs but there are concerns that studies can be manipulated.[39] Bias is often suspected by medical journal peer reviewers simply because a study is funded by the pharmaceutical industry, a suspicion fuelled by the lack of standards and guidelines for performing the studies.[39,50] Economic analyses carried out by the pharmaceutical industry are sometimes seen as thinly veiled marketing strategies. [16, 46, 51, 52] Additionally, there is also the concern about whether pharmacoeconomic data derived from clinical trials is generalizable or applicable to real-world situations. This has also sparked off a new line of controversy about the whether the so-called "naturalized studies" are better compared to the traditional clinical trials.[53]

In spite of these controversies, pharmacoeconomics can be potentially useful. Every new thing emerges out of turmoil and confusion. There cannot be a consensus for some time to come. However, some informed decision-making with respect to cost-effectiveness of therapies is better than no considerations of cost-effectiveness at all. A particular critical issue in the success of this subject lies with the decision-makers who must have the skills to

interpret pharmacoeconomic data submitted to them. In the absence of standardised guidelines this task becomes very difficult. Guidelines apart from being methodological standards ensuring scientific rigour lend an element of uniformity in the interpretation of the analyses. Hence more and more countries are developing standards and guidelines that will ensure studies of scientific rigour and simultaneously generate reliable cost-effectiveness data, generalizable to the standard population. Over the past several years, academic researchers, regulatory bodies, a pharmaceutical trade organization and individual countries have published pharmacoeconomic research guidelines [49.] Academic researchers in Europe and the United States have developed guidelines for the proper conduct of pharmacoeconomic studies.[46, 50] These guidelines authored by highly credible health economic researchers had the general aim to develop consensus among the researchers, regulatory authorities, industry, and other interested parties to give credibility and comparability to pharmacoeconomic study results.[54] The Division of Drug Marketing, Advertising and Communication (DDMAC) of the United States Food and Drug Administration (FDA); the Prevention Effectiveness Technical Work Group of the Centers for disease Control and Prevention, and an expert panel commissioned by the United States Public Health Service have all published guidelines on the proper conduct of pharmacoeconomic studies.[54-57] The Pharmaceutical Research and Manufacturers Association of America (PhRMA) has also developed a set of voluntary principles to guide industry members in conducting pharmacoeconomic studies to minimize bias and ensure transparency. [58]

Individual countries, including Australia, Canada, Italy, Spain, Switzerland, Germany, France, and the United Kingdom have developed guidelines for the proper conduct of pharmacoeconomic studies.[49, 59, 60-63, 64]

1.4.3 Role of Pharmacoeconomics in healthcare cost-control

Having firmly understood that costs need to be cut, and cut without accepting sub optimal quality, it is important to bear in mind that pharmacoeconomics lends an element of rationality in decision-making by helping decision-makers make informed choices. Whatever the method of cost-control, be it supply-oriented or demand-oriented, pharmacoeconomics may be used to enhance the process and ensure its success. When used as a decision-aid for different methods of cost-control, it can make them more acceptable by ensuring a 'balance of cost and quality'.

The goal of a good healthcare system is to deliver acceptable and optimum quality of healthcare at reasonable costs. Only then, would cost-effectiveness in health care be ensured. It is the researcher's contention that all cost control methods should adopt the 'value for money' approach and taking pharmacoeconomic considerations into account when making decisions would most certainly facilitate the process. The following examples are used to substantiate the argument.

For instance, instead of setting the reference price arbitrarily, to arrive at a more scientifically determined price based on cost-effectiveness would be a much better option. Pharmcoeconomics can be used for this purpose by arriving at a consensus-based price, one that could be justified by the effectiveness of the drug.

The potential uses of pharmacoeconomics especially with respect to the hospital setting may be understood by looking at a few questions that pharmacoeconomics may help to address, which are as follows –

- *What drugs should be included in the hospital formulary?*

The answer to this question lies in an assessment of the value of pharmaceutical products and services. Such valuation when based on pharmacoeconomics allows a balance of cost with quality (incorporating patient outcomes).

- *What is the best drug for a particular group of patients?*

Some drugs may sometimes have only nominal benefits over existing alternatives for a relatively large increase in the marginal costs. If used in all patients, such products and services only serve to push up costs and unnecessarily tax the ill. Pharmacoeconomic analyses can supply decision-makers with the data regarding these products and services would represent 'value for money' in certain subgroups of patients.

- *What is the best drug for a particular disease (i.e. assessing clinical pathways)?*

There is usually more than one management approach to most disease conditions. Choosing between competing treatment options requires careful consideration of the various benefits offered by different approaches vis-à-vis the resources consumed. Pharmacoeconomics certainly facilitates such decisions by identifying and elaborating the different outcomes (including patient quality of life outcomes) offered by the various treatment modalities and the costs (resource use) incurred by each.

Thus medication use decisions that can benefit from pharmacoeconomics especially in an institutional setting include formulary management, drug use policy, resource allocation and individual patient treatment decision.

In conclusion, drugs apart from being safe and effective must demonstrate good 'pharmacoeconomic value' if they are to be competitive in today's healthcare environment. As our health care environment becomes increasingly cost-conscious, pharmacoeconomics will play an increasing role in drug use decisions.

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SECTION 2: THE SINGAPORE PERSPECTIVE

Singapore – a question closer to home

Having discussed the awakening of most developed countries to the implications of increasing health care expenditures and the important steps being taken in the direction of ascertaining 'value' in health care delivery, it would now be most appropriate to examine whether Singapore faces any potential problems from increasing health care costs and whether policy-makers are taking any steps in that direction.

Background

Singapore is a small country with a total land area of 659.9 sq km. The total population is about 4.0 million, with a resident population of 3.22 million in 1999. Singapore has a relatively young population, with only 11% of the population above 60 years of age. However, the percentage of population over 60 years is projected to increase to 27% by the year 2030. [65] The age composition of the resident population, selected health-related vital statistics and health indicators are shown in Tables 2-4.

Table 2: 3-Year Trend in Age and Race composition of resident population in Singapore*

		1999	2000	2001
Total Population ('000)		**3,950.9**	**4,017.7**	**4,131.2**
Resident Population ('000)		**3,221.9**	**3,263.2**	**3,319.1**
Age	% below 15 years	21.8	21.5	21.4
	% 15 - 64 years	71.1	71.2	71.2
	% 65 years & above	7.1	7.3	7.4
Race	% Chinese	76.8	76.8	76.7
	% Malay	13.9	13.9	13.9

* Health Facts Singapore 2002, Ministry of Health, Government of Singapore

	% Indian	7.9	7.9	7.9
	% Others	1.4	1.4	1.5

Table 3: 3-Year trends in National Health-related Vital Statistics in Singapore[*]

	1999	**2000**	**2001**
Crude Birth Rate	12.8	13.7	11.9
Crude Death Rate	4.5	4.5	4.4
Infant Mortality Rate	3.3	2.5	2.2
Maternal Mortality Ratio	0.9	1.7	0.7
Life Expectancy at Birth (years)	77.6	78.1	78.4
Male	75.6	76.1	76.4
Female	79.7	80.1	80.4

Table 4: 2001 Health Indicators - Singapore[*]

	Year 2001
Hospital Admission Rate per 1000 Population	93
Hospital Beds to Population Ratio	1:348
Doctor to Population Ratio	1:698

Health Status

The infant mortality rate in 1999 stood at 3.2 per 1000 live births while the average life expectancy rate was 77.6 years. Rising standards of living, high standards of education, good housing, safe water supply and sanitation, a high level of medical services and the active promotion of preventive medicine, have all helped to significantly boost the health of

[*] Health Facts Singapore 2002, Ministry of Health, Government of Singapore

Singaporeans. The leading causes of morbidity and mortality are currently the major non-communicable diseases such as cancer, coronary heart diseases, strokes, diabetes, hypertension and injuries. Cancer and cardiovascular diseases together accounted for approximately 62% of the total causes of death.[65]

Healthcare Delivery System

There is no denying the fact that Singapore's health care system is the envy of many countries around the world. Singapore has managed to achieve the health care standards of a developed country at a fraction of the costs, and its health indicators are on par with that of other developed countries around the world. [66] In fact, in the World Health Organization's first ever analysis of the health systems in different countries in the world, Singapore was ranked sixth.[67]

In Singapore, there is a dual system of healthcare delivery. The public system is managed by the Government while the private system is provided by the private hospitals and general practitioners. The healthcare delivery system comprises primary health care provision at private medical practitioners' clinics and outpatient polyclinics, and secondary and tertiary specialist care in the private and public hospitals. Following is a glimpse of health facilities in Singapore:

Table 5: 3-year trend in Availability of Public and Private Healthcare Facilities in Singapore[*]

		1999	2000	2001
No. of Hospitals/Specialty Centers		**28**	**28**	**28**
	Public Sector	14	14	14
	Private Sector	14	14	14
Total No. of Hospital Beds		**11,747**	**11,798**	**11,884**
	Acute Care	7,853	7,849	8,153
	Extended Care	3,894	3,949	3,731
Public Sector Hospital Beds		9,560	9,556	9,274
	Acute Care	6,268	6,264	6,228
	Extended Care	3,292	3,292	3,046
Private Sector Hospital Beds		2,187	2,242	2,610
	Acute Care	1,585	1,585	1,925
	Extended Care	602	657	685
No. of Polyclinics		18	16	16
No. of Public Sector Dental Clinics		205	202	204

The private practitioners provide 80% of the primary healthcare services while the government polyclinics provide the remaining 20%. For the more costly hospital care, it is the reverse situation with 80% of the hospital care being provided by the public sector and the remaining 20% by the private sector. Following are healthcare facilities utilization trends as measured by hospital admission rates by sex and age per 1,000 population:

[*] Health Facts Singapore 2002, Ministry of Health, Government of Singapore

Table 6: 3-year Healthcare Facilities Utilization Trends in Singapore[*]

		1999	2000	2001
Public Sector Hospitals				
Male		**76.0**	**79.3**	**77.7**
Age	0 – 14 years	63.8	69.2	62.7
	15 - 64 years	59.2	60.8	60.5
	65 years & above	306.2	312.4	309.0
Female		**76.3**	**77.1**	**74.7**
Age	0 – 14 years	51.9	56.9	50.8
	15 - 64 years	62.9	60.7	58.5
	65 years & above	266.3	276.1	277.1
Private Sector Hospitals				
Male		**10.9**	**10.2**	**9.4**
Age	0 - 14 years	21.4	20.3	18.1
	15 - 64 years	5.9	5.5	5.2
	65 years & above	30.0	26.5	25.6
Female		**23.3**	**22.6**	**20.4**
Age	0 - 14 years	17.3	15.8	14.3
	15 - 64 years	23.8	23.3	21.1
	65 years & above	34.2	33.4	30.3

Patients are free to choose the providers within the dual healthcare delivery system and can walk in for a consultation at any private clinic or any government polyclinic. For emergency services, patients have access at any time to the 24-hour Accident & Emergency Departments located in the government hospitals. The Singapore Civil Defence Force runs an Emergency

[*] Health Facts Singapore 2002, Ministry of Health, Government of Singapore

Ambulance Service to transport accident and trauma cases and medical emergencies to the acute general hospitals.

Singapore today has about 5,154 doctors for its healthcare delivery system, giving a doctor to population ratio of 1:730. Slightly less than half of the doctors (48%) are in the private sector. About 42% of the doctors are trained specialists with postgraduate medical degrees and advanced specialty training.

There are 942 dentists, giving a ratio of 1 dentist to 4,130 people. About 77% of the dentists are in private practice.

The nurse to population ratio is 1:244, with a total of about 15,947 nurses. 55% of the nurses work in the public sector.

Following table provides the trends in number of healthcare practitioners over the last few years:

Table 7: 3-Year trends for availability of Healthcare Workforce in Singapore[*]

	1999	2000	2001
Total No. of Doctors	**5,325**	**5,577**	**5,922**
Public Sector	2,535	2,586	2,794
Private Sector	2,606	2,809	2,925
Not in Active Practice	184	182	203
Doctor to Population Ratio	1:740	1:720	1:700
Doctor per 1000 Population	1.3	1.4	1.4
Total No. of Dentists	**942**	**1,028**	**1,087**
Public Sector	167	193	209
Private Sector	726	755	775
Not in Active Practice	49	80	103
Dentist to Population Ratio	1: 4,190	1: 3,910	1: 3,800
Dentist per 1000 Population	0.2	0.3	0.3
Total No. of Nurses/Midwives	**15,947**	**16,611**	**17,398**
Public Sector	8,692	8,927	9,297
Private Sector	3,872	4,166	4,224
Not in Active Practice	3,383	3,518	3,877
Nurse to Population Ratio	1:250	1:240	1:240
Nurse per 1000 Population	4.0	4.1	4.2
Total No. of Pharmacists	**1,043**	**1,098**	**1,141**
Public Sector	219	238	297
Private Sector	598	638	619
Not in Active Practice	226	222	225
Pharmacist to Population Ratio	1: 3,790	1: 3,660	1: 3,620
Pharmacist per 1000 Population	0.3	0.3	0.3

[*] Health Facts Singapore 2002, Ministry of Health, Government of Singapore

Healthcare Philosophy

The Government ensures that good and affordable basic medical services are made available to all Singaporeans through the provision of heavily subsidized medical services at the public hospitals and government clinics. The Singapore health care delivery system is based on individual responsibility, coupled with Government subsidies to keep basic health care affordable. Patients are expected to pay part of the cost of medical services and pay more when they demand a higher level of services. The principle of co-payment applies even to the most heavily subsidized wards to avoid the pitfalls of providing free medical services (moral hazard).[65]

To help Singaporeans pay for their medical expenses, the Government has put in place a financing framework, consisting of **Medisave, Medishield, ElderShield** and **Medifund.** [65]

Medisave, introduced in April 1984, is a national medical savings scheme, which helps individuals put aside part of their income into their Medisave Accounts to meet their future personal or immediate family's hospitalization, day surgery and certain outpatient expenses. Under the Medisave scheme, every working person is required by law to set aside 6-8% of his income into his personal Medisave Account.

MediShield, introduced in 1990, is a low cost catastrophic illness insurance scheme. It is designed to help members meet the medical expenses from major or prolonged illnesses for which their Medisave balance would not be sufficient to cover. MediShield operates on a co-payment and deductibles system to avoid the problems associated with pre-paid insurance. The premiums for MediShield can be paid with the funds in the individual's Medisave account.

ElderShield, introduced in 2001, is an affordable severe disability insurance scheme designed to help Singaporeans meet with expenses incurred in the event of severe disability. The

premiums of ElderShield can also be paid with the funds from the individual's Medisave accounts.

Medifund is an endowment fund set up by the Government in April 1993 to help needy Singaporeans who are unable to pay for their medical expenses. This is a safety net for those who cannot afford the heavily subsidized charges despite Medisave and Medishield. Medifund was established with an initial capital of S$200 million. Capital injections will be made when budget surpluses are available. The capital sum currently stands at S$800 million. Only the interest income from the capital sum maybe used.

Therefore, no Singaporean is denied access into the healthcare system or turned away by the public hospitals because of the inability to pay.

National Healthcare Expenditure

In 1999, Singapore spent about S$4.3 billion or 3% of GDP on health care. Per capita health care spending was S$1,347. Government subsidy on the public health care services was S$1,089 million.[65]

In 2000, Singapore spent about S$ 4.8 billion or 3% of GDP on healthcare. Out of which, Government expenditure on health services was S$1,212 million or 0.8% of GDP.

Table 8: 3-year National Healthcare Expenditure trends in Singapore*

	FY99	**FY00**	**FY01**
Recurrent Health Expenditure (S$m)	936	1,072	1,446
Development Health Expenditure (S$m)	153	140	146
% Recurrent Health Expenditure/GDP	0.7	0.7	0.9
% Of Total Government Health	4.3	4.3	5.7
Total Government Health Expenditure per	338	371	480

* Health Facts Singapore 2002, Ministry of Health, Government of Singapore

Major Concerns and Future Challenges

Based on the previously mentioned observations there are enough reasons to believe that the Singapore health care system is well managed and pretty much state-of-the-art. On the other hand, the future brings with it new challenges and concerns for the Singapore government. Among the challenges facing the government are advances in medical technology and knowledge, rising expectations and demand of the public, changes in disease patterns, shortage of manpower, the aging population and the rapidly escalating health care costs.

The two particularly crucial concerns,

- The demographic concern of an increasing proportion of the elderly (thereby increasing the aged dependency ratio): the proportion of those 60 years and above is estimated to increase from the present 10% to 27% by the year 2030 and,

- The challenge of living up to increasing expectations of the public: even under the circumstances of an increased proportion of the elderly in the future, the government must accept responsibility for providing high-quality care at affordable prices and live up to the expectations of the increasingly affluent and more-informed society.

  Following are glimpses of a 6-month period average bill sizes in public hospitals based on Medisave claims submitted by the hospitals. The table shows data only for the class C inpatient charges (least of the lot). Notable point here is that the minimum average bill only for inpatient care is only marginally less than the per capita expenditure. Therefore, the scenario including higher expenditure classes and diseases (despite a higher co-payment) will most likely be more expensive.

Table 9: Minimum 6-Month Average Medical Bills at Public hospitals in Singapore[♣]

Room	Class C (Open Ward)			
	MEDICAL SPECIALTIES			
Hospitals[*]	**Average Per Day ($)**	**Average Total Bill ($)**	**Total Bill at 90th Percentile**	**Total Bill at 95th Percentile**
AH	91	668	1,303	1,917
CGH	108	731	1,353	1,997
KKH+	121	635	810	1,869
KKH++	108	378	546	876
NUH	160	979	2,326	3,829
SGH	118	910	1,783	2,775
TTSH	88	684	1,252	1,978
NHC	375	1,807	4,459	5,465
NNI	105	793	1,458	2,062
	SURGICAL SPECIALTIES			
Hospitals*	**Average Per Day ($)**	**Average Total Bill ($)**	**Total Bill at 90th Percentile**	**Total Bill at 95th Percentile**
AH	101	583	1,263	1,955
CGH	150	786	1,575	2,361
KKH	185	611	1,258	1,539
NUH	191	1,111	2,220	3,919
SGH	136	982	2,038	3,051
TTS	123	778	1,653	2,548
NHC	191	2,696	4,921	8,053
NNI	124	999	2,446	3,828

[♣] Data for Jan 2002 – June 2002, Hospital Statistics 2002, Ministry of Health, Government of Singapore

[*] AH: Alexandra Hospital, SGH: Singapore General Hospital, NUH: National University Hospital, KKH: KK Women's and Children's Hospital, CGH: Changi General Hospital, TTSH: Tan Tock Seng Hospital, NHC: National Heart Centre, NNI: National Neuroscience Institute

This would mean that though there are no imminent problems from increased health care expenditures, there is also no room for complacency. Systems and processes should be reviewed continually to ensure maximum value from every dollar spent to avoid making the same mistakes made by other developed economies. This calls for a greater awareness of cost-effectiveness issues and only then would the best-informed decisions be made for its population.

Government's responses to the aforementioned Challenges

The Government of Singapore is very proactive in its approach to these challenges. In order to maintain the medium to long-term sustainability and viability of the healthcare system, plans are proposed to revamp geriatric care. In addition, immediate actions were implemented to improve the efficiency of the existing healthcare delivery within the public sector.

Care for the Elderly:

To address the concerns on increasing health needs by the rapidly ageing population, the Inter-Ministerial Committee on Health Care for the Elderly (IMC) was set up in 1997 to put in place policies and strategies for the adequate provision of health care for the elderly, and to ensure that their long-term care is affordable to the individual, family, community and country.

The IMC has recommended a two-pronged approach to looking after the health care needs of the elderly. Firstly, they have recommended health promotion and disease prevention to enable the elderly to remain healthy and active in the community. Secondly, when disease and disability set in, the system must be able to provide appropriate and cost-effective health care

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[+] Includes neonatology

according to each elderly person's need, so as to achieve maximum functional capability. As the elderly generally want to live with their families, they are to be cared for in their own homes for as long as possible. Institutionalization of the elderly would be a measure of last resort.

The key recommendations cover health promotion and disease prevention, screening and early detection of illness and disability, better training in geriatric care for medical undergraduates and general practitioners, development of long-term care facilities and services in partnership with Voluntary Welfare Organizations (VWOs), ensuring standards of health care services, and measures to finance long-term care.

Using Diagnosis Related Groups (DRGs) for Hospital Funding

Funding of hospitals may be based on several approaches. The simplest approach known as historical funding simply provides each hospital with the same funding it received the previous year, with allowances for inflation or a well-argued request for additional funds. [1, 11, 12] Hospitals may also be funded according to the population size and mix of their catchment area. A formula may be used to determine how much each hospital should receive according to the population taking into account other factors such as age, gender and socio-economic status.

However none of these approaches directly funds or pays hospitals for the work they actually do, and therefore, does not encourage hospitals to do the work more efficiently and effectively.

A funding system, which uses case-mix, can overcome this deficiency.[40, 68, 69] In a case-mix funding arrangement, a funding authority may set a price to pay for each case of a particular diagnosis based on its cost. For example, the average cost of a certain surgical procedure may be $10,000. A funding authority may decide to pay hospitals $10,000 for each of these

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[++] Excludes neonatology

procedures regardless of the actual cost for performing these procedures at individual hospitals. Therefore, hospitals that can perform these procedures with less than the pre-specified amount may use the surplus to subsidize more expensive forms of health care. Hospitals that need more money to perform the same operation will need to absorb the difference. They will find it necessary to examine their cost structures, their resource use, and/ or their work practices in order to work within the assigned budget if they are to provide better and more efficient treatment to their patients.

As such, case-mix-funding arrangement would be a more rational way of allocating of scarce resources with financial rewards for efficiency in service delivery.

Case-mix funding signifies a shift from the traditional historical funding formula to an activity- based funding-formula for health care. "Case-mix" simply refers to the range and type of patients a hospital or health service treats. However, in health care policy and planning it has become a generic term for an information tool, which can be used to scientifically plan and manage health care. In general, it is the use of resources in treating patients, which is the key to understanding case-mix as a measure of hospital output and activities.

Diagnosis Related Groups (DRGs) is the best known and most widely used case-mix classification used to classify in-patients receiving acute hospital care according to their principal diagnosis. They consist of a manageable number of distinct classes, which have been identified based on their clinical meaning and resource-use homogeneity. The DRG system was developed in the US to provide data for prospective payments for hospitals. [70]

The goal of the government in using such DRG system is to allocate public financial resources among hospitals in a way that better reflects their genuine level of activity.

However, in the opinion of the researcher, in order for the case-mix funding to be a success, pharmacoeconomics needs to be incorporated routinely into decisions about health care

interventions if Singapore is to at least sustain the same standards of medical care even in the future. The role of PE in case-mix funding environment is discussed in the next section.

Relevance of Pharmacoeconomics in the new case-mix funding environment

Some might argue that since every item has been assigned a cost according to resource consumption patterns, there is very little in the way that the application of pharmacoeconomic evaluation can change or improve this. However, the DRG system in itself has some problems. The DRG system necessitates the government to set prices based on average costs. This vestige of the regulated price model based on average costs is less efficient than pricing decisions made by individual providers on the basis of marginal costs. Hence, government will find adjustments for quality improvement and technological change difficult to arrive at. There may also be a tendency to bypass needed increases in DRG prices in order to hold down government fiscal outlays for health.

DRGs also set a prospective rate once a patient is in for treatment but do not offer incentives for physicians to be more cost-conscious about hospitalising patients in the first place. [71]

Though such payments are expected to provide incentives for efficiency by attempting to equate reimbursement to "output", they are more difficult to establish technically and can result in administrative problems when several physicians are involved in treating a particular case.[1]

In addition, a deeper thought would reveal that any shift in clinical practice in drug therapy, especially with newer drugs introduced in recent years increase the pressure on the pharmaceutical budget. For instance, an increase of 20% in drug cost over baseline (at which the drug cost is, say about 10% of the total cost) would increase the total cost by around 2%. As each DRG episode is paid a fixed amount by the funding authority, the hospital either has to absorb the extra cost, or other components of the DRG episode, for example, pathology or

nursing care have to receive less cost as a compensation for overrun in drug cost. However, if the other components cannot be controlled, increase in drug costs will result in a proportionate increase in absolute dollars allocated for that DRG. Such an impact on all DRGs and in all episodes treated in a hospital would result in increase in dollar expenditure that could be potentially devastating for any health care budget.

Obviously, none of the above is a sustainable alternative. Therefore, any less than optimal use of drug therapy in treating patients is going to have an impact on the treatment cost.

When properly conducted, pharmacoeconomic analyses:

- Can assist hospitals in choosing more cost-effective drug therapies without sacrificing the quality of care
- Can help physicians, pharmacists and hospital administrators in establishing meaningful guidelines for appropriate use of individual drugs
- Can help in creating an environment for interdepartmental “global” budgeting.

Therefore, besides providing a means to assist in the choice of optimal drug therapy, pharmacoeconomics can serve the purposes of quality assurance and budget allocation. In essence, the practice of both pharmacoeconomics and case-mix involves the principle of optimising efficiency within the health care system. Based on these considerations, rather than becoming obsolete, pharmacoeconomics is going to be more relevant in the case-mix funding environment when there is increased need to be more accountable and more effective for every dollar spent.

SECTION 3. REASONS FOR CHOOSING 'THE FORMULARY' AS RESEARCH FOCUS

There has been little research regarding the ways in which decision-makers use pharmacoeconomic studies in their practice.[72]

The same feeling has been echoed in some published papers on the use of pharmacoeconomics. For example, following discussions with representatives of several pharmaceutical manufacturers and other health care entities, Frank Sloan and Henry Grabowski organised a two-day conference held at the Duke University on December 3-4, 1995 on "Use of Cost-effectiveness Analysis in Decision-Making". Studies presented as papers during the conference revealed that while cost-effectiveness analysis played a minor role in pharmaceutical decision-making in hospitals, whatever little was being used (and/or was being considered for use) either in the US, in Australia, UK or France, was mainly for making drug formulary decisions.

Having felt that pharmacoeconomics could be potentially useful in health care decision-making in Singapore, the researcher wanted to demonstrate and "showcase" the utility of this subject in one decision-area. The "formulary" was chosen for this purpose because the best example of the potential utility of pharmacoeconomics in Singapore - in the opinion of the researcher - is provided by the formulary. The "formulary" whether at the national (Australia), institutional (HMO) or state (Ontario) level is where, the subject has been most successfully used to date. Especially, Australia, the first country to have made a routine use of cost-effectiveness analysis a requirement in its "national formulary" (the Pharmaceutical Benefits Scheme) coverage decisions for pharmaceuticals, provides the best example. [59, 23, 73,74,75,76]

Use of pharmacoeconomics in hospital settings is usually restricted to creating and modifying formularies. Among some of the reasons cited for less use of pharmacoeconomic studies

especially in hospital settings is inadequate in-house capacity to evaluate the quality of such studies.[23]

However, if use is to be increased, expertise is to be built. This would require potential users of information to be convinced of the utility and scope offered by of such information in facilitating decision-making. Of course, if that is to be, the end-users must not be confused by technical jargon. But, most pharmacoeconomic studies published in the literature do not take it to the end-user level.[74] Therefore, if the issue of its use in actual practice needs to be addressed well, studies must be conducted and results elaborated in a form understood by the end-users. "… since, the ultimate utility of socio-economic assessments will depend as much on their being understood by decision-makers as upon their methodological rigour."[74]

Therefore, it was decided that using practical demonstrations in a formulary in a hospital setting would actually take it to the users. It would convince the end-users (the P&T Committee in this case) that pharmacoeconomics has very good potential to sharpen drug-related decision-making in a hospital setting making it a cost-effective centre for health care delivery in the long-run.

In the view of the researcher, the formulary, reflecting major drug-related pharmacy decisions, could be an important instrument for attaining the dual goals of efficient and quality health care delivery and customer (doctor and patient) satisfaction provided it incorporates the cost-effectiveness (pharmacoeconomic) principles. If, the relevant decision-makers realise this, they will start a process of learning about the subject, knowing more and trying various ways and means to use such information. This will set into motion a new framework for formulary decision-making and will definitely encourage growth of pharmacoeconomics. Therefore, it is imperative that the decision-makers be convinced of the potential utility of the subject at least in the context of the formulary.

SECTION 4: THE ROLE OF PHARMACOECONOMICS IN SHARPENING THE FORMULARY- AN INSTRUMENT FOR HEALTH CARE COST CONTROL IN THE HOSPITAL CONTEXT

4.1.1 Importance of Formulary Management

Good and effective formulary management has an immense potential to add a whole new dimension to healthcare delivery in the current fiscal climate – that of ensuring standard and appropriate care while reducing costs – 'quality healthcare at affordable costs'.

4.2 The Formulary: its traditional role and drawbacks

Formularies have been an important governing instrument in hospitals for many years.[35] Formularies represent a compendium of pharmaceutical products and services selected by the medical staff of an institution to reflect current drug preferences of health care practitioners and patients.[77] Regarded most often as cost-containment tools, they lower costs by limiting choice, which, is not viewed favorably by practicing physicians. With its emphasis on "cost" "the formulary" has rendered itself unacceptable to the practitioners who do not feel the need to comply unless compelled to do so. The formulary decision-making bodies on their part, being more concerned with the survival of their institution in this increasingly competitive and cost-conscious environment feel that they are justified in their 'cost-approach' to selection of drugs.

The net result thus has been that there has traditionally been a 'this was expected' attitude of the health care practitioners towards the 'formulary committees' and vice-versa. The doctors have a feeling that they are deprived of their right to prescribe at will, to do what is 'best' or 'clinically most effective' for their patients and the formulary committees feel that it is virtually impossible to satisfy the doctors. In reality, however, both are concerned in their own way about the patient's benefit, albeit, on different levels. The doctor is more bothered about the patient on a one-to-one or individual level and the committee about the majority of

the patients on a more macro level. That is precisely the reason why drugs used by the wide majority are most often subsidised by the formulary. In order to enable more patients, to benefit from the subsidy, quite often the so-called 'cheapest' generics when available are chosen. [35 77, 78] Cheaper brands are also often resorted to. However, whether these truly turn out to be 'cheap' is a different question altogether because sometimes these so-called cheaper brands may have potential costs associated with their use. Such costs could include drug, laboratory and medical personnel costs of retreating treatment failures and treating any adverse drug reactions identified with this agent.

Thus, the major drawback with the traditional formulary decision process has been an undue emphasis on 'cost' resulting in a simple shifting of costs from one cost centre to another and a complete unwarranted overlook of the comprehensive effects of introducing a drug or intervention into the health care system. [78,79, 80, 81]

However, the "true value" of any medical intervention should be assessed in terms of its impact on total health care utilisation and cost. Pharmaceuticals are no exception; to view them in isolation might be penny wise and pound-foolish.[81] Medical care providers are becoming increasingly aware of this fact and have started to examine the cost consequences of their actions.[82]

The physicians on their part must broaden their perspective to balance the needs of individual patients directly under their care with the overall needs of the population served by the health care system whether the system is an HMO or the nation's health care system. Professional ethics will have to incorporate social accountability for resource use and population health, as well as clinical responsibility for the care of individual patients.[17]

4.2.1 The Need to optimize value: The rational formulary

The value of a drug depends on the perspective from which it is viewed. From the perspective of the doctor the "clinical value" of a drug is most important; to the patient the "value" of the drug in improving the health-related quality of life is important and to the institution the drug's economic "value" or the ability of the drug to achieve the desired goals with optimal use of resources, is important.[84] A good formulary at the institutional level however, should aim to optimize 'the value' on all these fronts from the institutional perspective. In the process, it may also be reasonably expected to serve the logistic function of inventory control other than helping manage the institutional drug expenditures effectively. Most importantly, it would allow only the most cost-effective options to diffuse into the respective health care system. Such formulary among other things can better convince the prescribers whose compliance is essential to its success. A successful formulary in the long run can hope to contribute to lowering the overall system costs.

4.2.2 Pharmacoeconomics: A tool to help in assessing 'value' in formulary decision

Appropriate application of pharmacoeconomic evaluation facilitates systematic quantification of the 'value' of pharmaceutical products and services. From the available literature it seems that the role of pharmacoeconomics in formulary decision-making is being increasingly recognized and so pharmacoeconomic assessments of formulary actions are becoming increasingly common and standardized part of formulary decision-making at local, national and international levels.[77, 83, 84, 85, 86,87]

Apart from knowing extra costs incurred for certain extra benefits obtained from new drug treatments, decision-makers increasingly want to know by how much their annual budget is likely to increase or decrease if a specific drug is added to or deleted from the formulary and what annual health benefits are likely to be associated with this budget increase or decrease. [88]

This can be achieved only through a systematic and conscious effort to integrate pharmacoeconomic concepts into decisions.

Some researchers propose that formularies may actually lose importance over time as pharmacoeconomic results increasingly guide practice and management. [77, 85] However in the researcher's opinion, the "formulary" is "a scientific and comprehensive listing" of drugs while pharmacoeconomics is a "science". Pharmacoeconomics cannot actually "substitute" for the formulary. Rather by acting as a research tool, pharmacoeconomics will increasingly inform formulary decision-making.[89, 90, 91, 92, 92]

4.3 Evolving role of the formulary especially at the Institutional Level in the changing context of health care delivery

A discussion about the evolving role of formulary remains incomplete without a discussion of the new concept of disease management and the role of the 'Formulary' in the light of the changing circumstances.

In today's world, health care delivery in a piecemeal fashion is simply not affordable. It has been seen that most health care dollars are spent on small numbers of persons requiring multiple episodes of care often in the last stages of chronic diseases.[94] Prompted by the mounting financial pressures, a paradigm shift in providing health care – from 'treating' or 'curing' individual patients to 'managing' whole disease conditions, has taken place. This new evolving model of disease management is a systematic population-based approach to certain disease conditions that can deliver equal or even better outcomes at lower costs than the conventional approaches. It offers population-based, disease-focussed solutions that will redefine the organisational approach to diseases.[81] Along the way, the existing roles of key players such as hospitals, physicians and pharmaceutical companies will change. Specially,

the hospital, being a cost centre and a place for extreme intervention, is drawing increasing attention.

Disease management aims at cost-effective strategies whereby more resources are allocated to disease conditions that are more serious and widespread (i.e. where they are more needed) and less to less important areas.[81]

A well-built formulary (based on pharmacoeconomics) can assist decision-makers by identifying the most efficient use of pharmaceuticals (or even allied services) in a disease state management program and therefore act as a concise guide to prevalent treatment patterns thereby ensuring that drug management is being placed in the framework of total health care management. Health care organizations that incorporate the tenets of economic analysis into their decision making are likely to build more efficient disease management programs leading to improved patient outcomes and lower costs.[81]

With health care organizations increasingly moving towards the more holistic disease management programs the expectations from a formulary are changing. It is expected that a formulary would typically include only those drugs or interventions, which can demonstrate a 'net increase' in 'value' to the disease management programs. In order to live up to these changing expectations, the formulary decision process has to have a changed approach.

4.4 The Formulary: what should be its changed approach

First and foremost, the formulary should have certain clear-cut objectives that it intends to achieve in the current context of integrated healthcare delivery. Its most important objective should be to help the hospital in reducing the burden of illness as efficiently as possible. For this, the hospital must first identify the major areas of illness treated at the institution. Then it must calculate the costs incurred for treating those illnesses per budget period. The next step would be to set optimum and achievable targets in terms of outcomes of therapy that would

enable reduction in the burden of illness. The formulary must now aim to include such drugs and interventions, which are more efficient in helping attain those targets. Pharmacoeconomics can help in deciding which drugs to stock by telling the efficiency of the drug in achieving an outcomes target under a given level of resource usage. Pharmacoeconomics generates and/ or synthesizes and interprets available evidence to give useful information on efficiency of various interventions in helping achieve particular outcome targets of therapy. Therefore, a good formulary including decisions based on pharmacoeconomic principles can contribute to the wider societal goal of reducing the burden of illness by ensuring judicious management of healthcare, and thereby societal resources.

But, one of the first things formulary-framing bodies should do is to convince prescribers that it is evidence-based so that it becomes more acceptable. This is because it is the doctor who takes the day-to-day decisions about drugs and prescriber compliance to the recommendations made by the formulary is an essential pre-requisite to its success.

Cost-control is an important objective of the formulary. But sheer cost-control aimed simply at containing costs without evidence of cost-effectiveness of drugs or other health care interventions may not just fail to improve efficiency in prescribing or health care delivery, they may deprive the patient population of the benefits of good drugs that may be worth the additional cost.

A rationally built formulary can go a long way in actually assuring prescribers that it is offering the ‘best’ of interventions for their patients and thus ensure compliance while also controlling costs for the institution.

SECTION 5. EXPLORATORY STUDIES CONDUCTED TO IDENTIFY 'NEED' FOR PHARMACOECONOMICS IN FORMULARY DECISIONS

The premise of our current argument runs as follows:

If the expectation is "A formulary must help control drug costs but not just promote 'cheap' drugs (i.e. compromise on quality of care)", there clearly exists a 'need' for Pharmacoeconomics in formulary decision-making.

To understand if such an "expectation" and "need" exist in Singapore, and how confident pharmacists would be if asked to use pharmacoeconomics to aid in formulary decision-making, an exploratory study was conducted. The purpose was to identify the need (if any) and once done, to demonstrate the role that pharmacoeconomics could play in formulary decision-making, in one major public hospital, the National University Hospital in Singapore. The reason why pharmacists were chosen was that, pharmacists are the ones who are supposed to have the most information about drugs and they are the ones who dispense these drugs to the patients.

5.1 METHODOLOGY

Data were gathered through a survey questionnaire administered in 1998-99. The sample consisted of all practising pharmacists (except the DIS pharmacist and the pharmacy manager) in five major public hospitals in Singapore. These hospitals were identified as study centres. In view of the structure, financing and administration of the health care system in Singapore, public hospitals were chosen over private hospitals, as the latter do not operate under as stringent budget controls as the former.

Consent to participate in the survey was obtained from the respective pharmacy managers at the above hospitals either over telephone or in person.

Hard copies of the survey questionnaire[*] were circulated to all practising pharmacists in these hospitals.

Questions addressed respondent background information, which included demographic information like age, race, gender and professional history like experience, current and previous area of experience and experience in the P&T committee. Questions in the main body were framed to draw out broadly the following information:

- ✓ Whether practicing pharmacists (in the institutional settings) in Singapore have any idea regarding the expenditure incurred for drugs in their respective hospitals
- ✓ Are aware of the concern globally regarding increasing drug expenditures
- ✓ Know about and have any suggestions regarding how to control these increasing costs,
- ✓ Know anything about the formulary, its role and decision-making process for the formulary,
- ✓ Whether they are aware of the potentially useful role of pharmacoeconomics in the formulary decision-making process and if required to use pharmacoeconomics how confident they would be.

The various statements expressing different opinions about the formulary, its functions and decision criteria of the formulary were based on our own judgment formed from a reading of the literature. The questionnaire was not pre-tested on any pharmacist. First the respondents were asked to identify which factors they considered important for decision-making of the formulary and then asked to rank the same in order of importance, 1 being for most important and 5 for least important. The other questions did not involve any ranking and usually required answers in the affirmative or the negative.

[*] See Appendix 1 – Survey Questionnaire - Pharmacists

If after 2-4 weeks, the response rate was lower than 50%, a reminder (via e-mail) and a second circulation of the questionnaire was made. This was done to maximise responses without unduly offending the respondents.

All respondents were administered the same questionnaire – without any personal explanation to the extent. Every query was uniformly handled over telephone to ensure no bias was created in the response. If any clarification or completeness follow up was required, the respondent was contacted over telephone and his/ her response was recorded ad verbatim.

Analysis of all responses was done using Microsoft Excel. Raw data were entered into sheets, which were linked back through a custom-made analytical model to cross-tabulate and accumulate data individually and across all hospitals.

Results were analyzed by individual hospitals and as a cumulative picture of all 5 hospitals. These were further analysed into various segments based on demographics, educational background, type and length of professional experience. Each of these segments was analysed to understand their level of familiarity and comfort with formulary and related cost control processes as well as their awareness with respect to potential contribution of pharmacoeconomics in management of the same.

5.2 RESULTS *

With a response rate that ranged from 50% to 85% in the individual hospitals and an overall average of ~ 64% (70 of 110 identified pharmacists responded) our findings delineated the following picture in Singapore. Majority of the respondents fell into the 25-35 age group (60%) and were predominantly Chinese (96%) with a female preponderance (78%). Most of the respondents graduated within less than 5 years (57%) and were less than 5 years in practice (64%). Thirty-nine percent (39 %) of the respondents' current area of practice was

outpatient while 29% had previously worked for retail. Only one member had previous P&T Committee experience.

5.2.1 Idea about average annual expenditure

An overwhelming 84% of the respondents did not have any idea of the average annual drug expenditure in their respective institutions and as expected, 74% could not say whether the expenditure was 'too high'.

5.2.2 Acquaintance with different terms of cost containments in drug use

84% and 77% of the respondents were acquainted with the terms 'formulary restriction' and 'DRG' respectively. 'Prescription restriction' happened to occupy the third slot (67%) in order of awareness of cost containment methods. However, only 19% and 27% respondents were acquainted with the terms 'Fund Holding' and 'Capitation'. None of the respondents was acquainted with all the terms. Details of the response are shown in Table 10.

Table 10: Pharmacists' acquaintance of 'tested' terminology

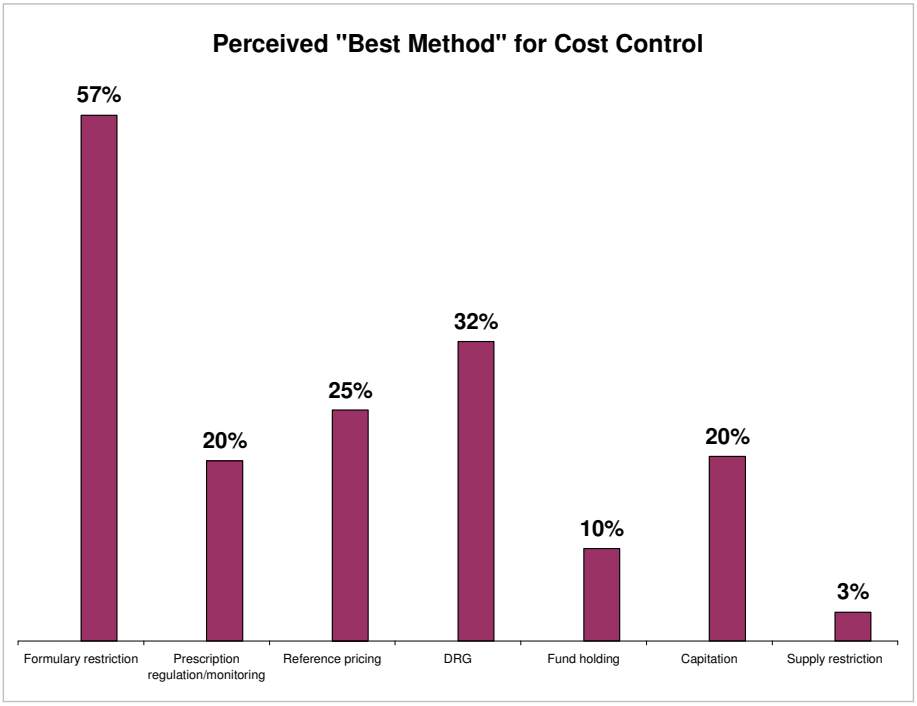
Terms	Response	
	Yes	**No**
Supply restriction	67%	33%
Formulary restriction	84%	16%
Reference pricing	36%	64%
Prescription regulation/monitoring	61%	39%
DRG	77%	23%
Fund holding	19%	81%
Capitation	27%	73%

[*] See Appendix 2 – Pharmacist responses

However, no effort was made to evaluate the actual level of understanding of each term specifically except that a question was asked to rate the methods in order of importance with respect to methods of cost control.

5.2.3 Perceived best method of controlling drug costs

Chart 1. Pharmacists' perception of 'best method' of cost control



'Formulary restriction' was ranked the best method for controlling drug costs by 57% of the respondents whereas 'DRG' was ranked as the no. 2 method by 32% of the respondents.

A question was included asking for explanation for choosing the method. Major reasons cited for choosing the above method, were 'Forces prescribers to adhere to guidelines' (51%), 'Forces prescribers to work within a limited/pre-assigned budget' (47%) and 'Limits choice

of drugs' (41%). Though this did not clarify if the respondent understood each term specifically, the explanations given do indicate that at least 'formulary restriction' and 'DRG' are well understood.

5.2.4 Opinion about 'the formulary' and its ideal purpose

Nearly all of the respondents (99%) claimed that their institution had a 'formulary' or 'drug list'.

In the response to their opinion of what is a formulary (Chart 2), 77% of the respondents called the formulary 'a list of most essential drugs', 31% opined it was a 'list of most used drugs' with only 10% calling it 'a list of the cheapest alternatives'.

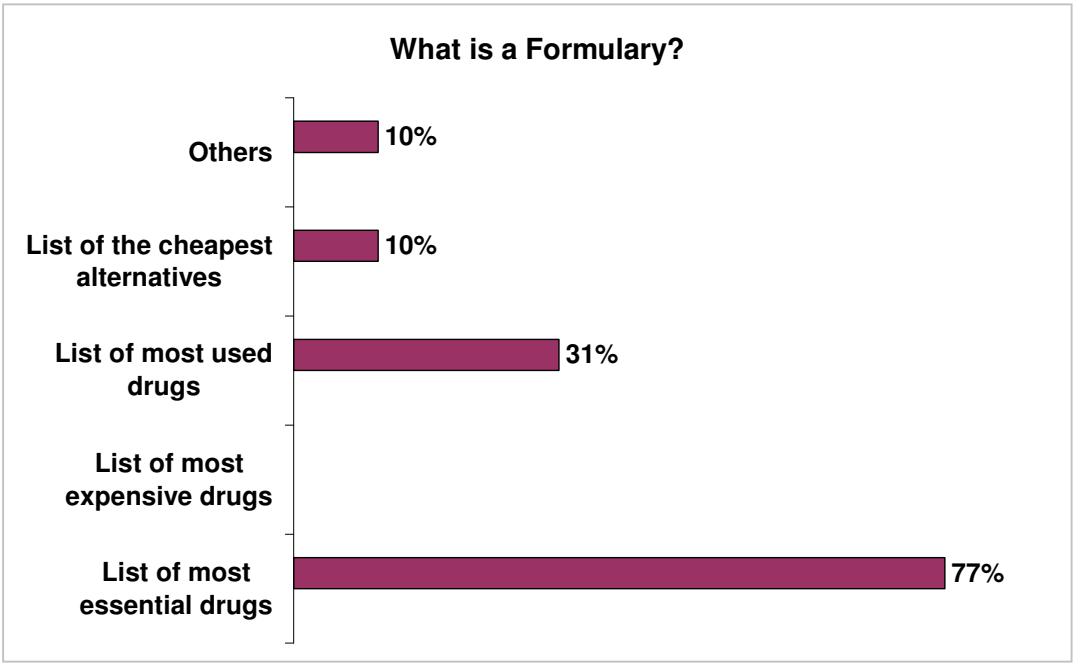


Chart 2: Pharmacists' opinion on Formulary

As to the ideal formulary (Chart 3), 'the ideal formulary' was considered by most respondents to serve 'In promoting the use of the "best" drug/intervention' (71%), 'In

controlling the hospital budget' (57%), 'In subsidising life-saving medicines' (47%) followed by 'In restricting the use of drugs' (34%).

Therefore, it may be reasonably inferred most pharmacists considered 'a formulary' should ideally promote the use of the best drug or intervention while simultaneously controlling the hospital budget.

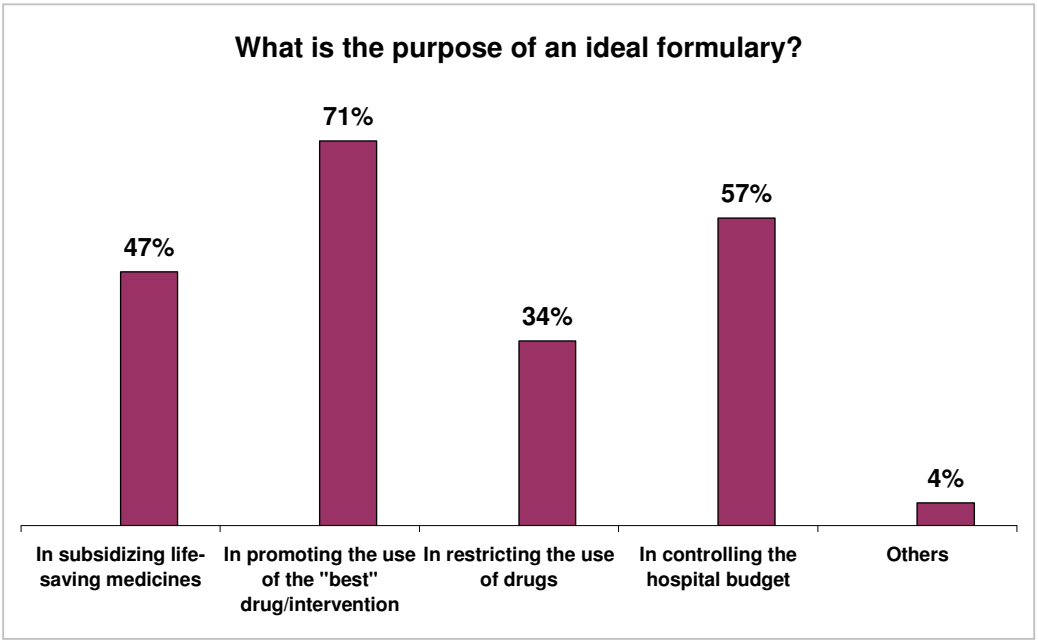


Chart 3: Pharmacists' opinion on purpose of an ideal formulary

But when the pharmacists were asked whether they considered their hospital served the "ideal" purpose to their satisfaction, only a minority (35%) considered it to be so. Most of the respondents either had the negative view (30%) or could not opine on this (35%). The reasons stated involved 'No knowledge of the decision-making process' (24%), 'Formulary is too open' (19%), 'Drugs included solely on cost-basis' (16%) and 'No consideration of drug quality' (10%). This was quite understandable in view of the negative and uncertain responses. The breakdown of the response is shown in Table 10. More than one answer was

allowed on some questions. Therefore, percentages on some questions may add up to more than 100.

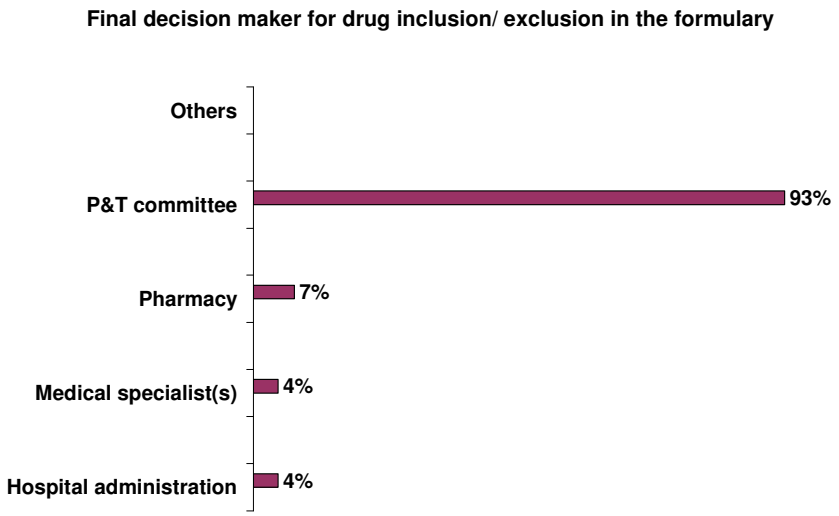
Table 11. Pharmacists' opinion on why 'their formulary' is not 'ideal'

Reasons	% of Response
Formulary is too open	**19**
Drugs included solely on cost-basis'	**16**
No consideration of drug quality	**10**
No knowledge of the decision-making process	**24**
Others	**36**

5.2.5. Formulary Decision Process

Although, nearly half of the respondents (49%) have no knowledge of the factors considered in the formulary decision-making process, most of them considered the P & T committee to be final decision maker for their hospital formulary (Chart 4). However, when asked what factors would be most important if the respondents had to make formulary decisions themselves the factors they would consider (in order of importance) for formulary decision-making would be drug effectiveness, safety and acquisition cost. 64% of them would consider drug effectiveness as the most important factor followed by safety (34%) and then acquisition cost as the next important factor (33%). The factors that they would consider as least important would be politics and hospital budget followed by drug/pharmacy budget.

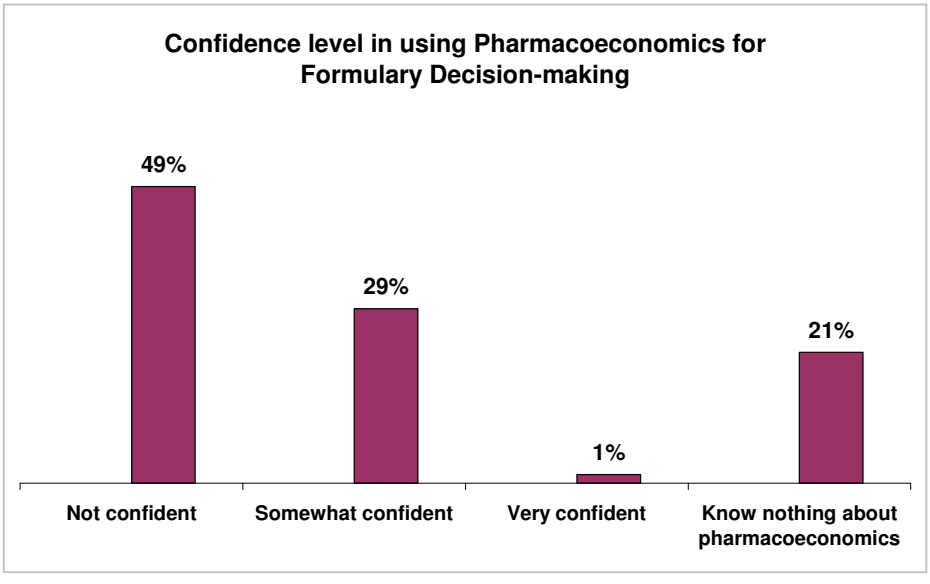
Chart 4: Pharmacists' opinion on decision makers for 'their formulary'



5.2.6. Confidence of Using Pharmacoeconomics

On being asked how confident pharmacists would be if asked to use pharmacoeconomics, 'not confident' was the response given by 49% while 21% of the respondents felt they knew nothing about the subject. However, 1% felt very confident about being able to use pharmacoeconomics to aid their decision-making, if asked to do so (Chart 5).

Chart 5: Pharmacists' confidence on usefulness of Pharmacoeconomics



There is therefore, a definite but unstated need for use of pharmacoeconomics in the formulary setting; however, there is clearly a lack of capability to fulfil the need.

Sorting pharmacist responses with respect to years in practice, we observed that 11% of respondents less than 5 years in practice, 9% of those between 5 and 10 years in practice, 33% of those between 10-20 years in practice and 50% of those over 20 years in practice, had an idea about the average annual expenditure on drugs. Therefore, to test whether years in practice and knowledge were independent of each other, or whether there was any statistically significant association between years in practice and knowledge of drug expenditure, the chi-squared test was used.

The results obtained from the survey of the pharmacists were further analysed to search for trends in the response obtained. The results of these analyses are shown in Tables 12 – 16.

Table 12: Chi-Squared test of 'Years in practice' vs. 'Knowledge of Drug Expenditure'

laving information on drug expenditure is independent of years in practice

Experience	Observed Counts		Total	Expected Counts		Total
	Has info on exp	*No info on exp*		*Has info on exp*	*No info on exp*	
Less than 5 yrs	5	40	45	7	38	45
5 - 10 yrs	1	10	11	2	9	11
10 - 20 yrs	4	8	12	2	10	12
More than 20 yrs	1	1	2	0	2	2
Total	**11**	**59**	**70**	**11**	**59**	**70**

X^2 = **5.67**
p = *>.10 with 3 degrees of freedom*

The test clearly shows that there is no statistically significant association between knowledge of drug expenditure in their respective institutions and years of practice.

Sorting pharmacist responses with respect to age we observed that 8% of respondents aged less than 25, 12% of those between 25 and 35, 29% of those between 35 and 45 and 50% of

those over 45 had an idea about the average annual expenditure on drugs. Therefore, to test whether age and knowledge were independent of each other, or whether there was any statistically significant association between age and knowledge of drug expenditure, the chi-squared test was used.

Table 13: Chi-Squared test of 'Age' vs. 'Knowledge of Drug Expenditure'

H_0 = Having information on drug expenditure is independent of age

Experience	Observed Counts		Total	Expected Counts		Total
	Has knowledge	*No knowledge*		*Has knowledge*	*No knowledge*	
Less than 25 yrs	1	11	12	2	10	12
25 - 35 yrs	5	37	42	7	35	42
35 - 45 yrs	4	10	14	2	12	14
More than 45	1	1	2	0	2	2
Total	**11**	**59**	**70**	**11**	**59**	**70**

X^2 = 4.48
p* = *>.20 with 3 degrees of freedom

No association could therefore be found between age and knowledge about drug expenditure.

Similarly, to examine the association between age and knowledge of factors involved in the formulary decision-making process, the following chi-squared test was performed.

Table 14: Chi-Squared test of 'Age' vs. 'Knowledge of formulary decision factors'

H_0 = Knowledge of factors considered for formulary decision making is independent of age

Experience	Observed Counts		Total	Expected Counts		Total
	Has knowledge	*No knowledge*		*Has knowledge*	*No knowledge*	
Less than 25 yrs	6	6	12	6	6	12
25 - 35 yrs	19	23	42	22	20	42
35 - 45 yrs	9	5	14	7	7	14
More than 45	2	0	2	1	1	2
Total	**36**	**34**	**70**	**36**	**34**	**70**

X^2 = 3.47
p* = *>.20 with 3 degrees of freedom

The test clearly demonstrated that no association could be found. Therefore we accept the null hypothesis that knowledge of factors considered for formulary decision-making is independent of age.

To test the association between knowledge of factors considered for formulary decision-making and years in practice a chi-squared test was performed.

Table 15: Chi-Squared test of 'Years of Practice' vs. 'Knowledge of formulary decision factors'

H_0 = Knowledge of factors considered for formulary decision making is independent of yrs of practice

Experience	Observed Counts		Total	Expected Counts		Total
	Has knowledge	*No knowledge*		*Has knowledge*	*No knowledge*	
Less than 5 yrs	22	23	45	23	23	45
5 - 10 yrs	4	7	11	6	6	11
10 - 20 yrs	7	5	12	6	6	12
More than 20 yrs	2	0	2	1	1	2
Total	**35**	**35**	**70**	**35**	**35**	**70**

X^2 = 3.17
***p* =** *>.20 with 3 degrees of freedom*

The results clearly show that there was no statistically significant association between knowledge of factors considered for formulary decision-making and years in practice. Therefore we accept the null hypothesis**.**

Similarly, a chi-squared test was performed to test the association between knowledge of factors considered for formulary decision-making and area of practice.

Table 16: Chi-Squared test of 'Area of Practice' vs. 'Knowledge of formulary decision factors'

H_0 = Knowledge of factors considered for formulary decision making is independent of area of practice

Experience	Observed Counts		Total	Expected Counts		Total
	Has knowledge	*No knowledge*		*Has knowledge*	*No knowledge*	
Inpatient	4	10	14	7	7	14
Outpatient	18	16	34	16	18	34
Clinic	5	5	10	5	5	10
Laboratory	2	1	3	1	2	3
Purchase	1	3	4	2	2	4
Others	5.5	5.5	11	5	6	11
Total	**35.5**	**40.5**	**76**	**36**	**41**	**76**

X^2 = 3.71
***p* =** *>.50 with 5 degrees of freedom*

The results showed there was no statistical significance. Therefore we accept the null hypothesis that knowledge of factors considered for formulary decision-making is independent of area of practice.

Thus, all conceivable associations were tested for any significance. But none of the associations was statistically significant. Therefore we can safely say that all the pharmacists' views were independent of their demographic background and years of professional experience.

5.3 SURVEY OF PHARMACY MANAGERS

A similar survey (with some structurally similar questions) was carried out among the pharmacy managers (and other P&T Committee members belonging to the Pharmacy Departments of the individual hospitals). This was designed to understand their views on the formulary, its decision-making process and whether there was any understanding and interest in pharmacoeconomics at the institutional formulary level.

5.3.1 METHODOLOGY

The instrument used for the survey was a semi-structured questionnaire comprising primarily of closed-ended questions. However, there were some open-ended questions where deemed necessary. The questionnaire* was sent by e-mail or faxed over and no personal explanation given to any of the respondents.

Thirteen hospitals including the NUH were identified as major hospitals in Singapore of which one (National Skin Center) was left out as it was considered a Specialty Hospital. Of the remaining twelve, six are private hospitals and six public hospitals. The pharmacy

managers of the various hospitals were identified and contacted over phone to seek their cooperation in the survey by answering a particular questionnaire. The manager of one public hospital declined to participate in the survey. Eleven hospitals agreed to answer but number of respondents was identified as thirteen. This was because in two hospitals the Drug Information Service Pharmacists (members of the P&T Committees in their respective institutions) were also surveyed.

Major information areas the questions addressed were:

- ✓ the type of institution,
- ✓ number of beds,
- ✓ pharmacy budget of the respective institution,
- ✓ presence of a formulary,
- ✓ opinion about what a formulary is and what its function is,
- ✓ major factors taken into account for drug decisions,
- ✓ perceived impact of DRG on drug decisions,
- ✓ whether the formulary in their institution achieved the aims that they thought it was supposed to and
- ✓ suggestions to make the formulary achieve its designated aims.

Respondent background was known. All were 'formulary committee' members and were either DIS pharmacists or managers. Therefore no demographic or personal information was sought in the questionnaire.

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[*] See Appendix 3 – Survey Questionnaire – Pharmacy Managers

Eleven of the identified 13 respondents sent their replies and two did not. Responses came in from eight hospitals. Therefore, of a target population of 13 respondents 11 pharmacy managers responded. This could be considered to represent the views of a majority of the target population and not just the responses from a small sample of the population.

5.3.2 RESULTS*

With a response rate of 85% (11 out of 13 identified respondents), the following results were obtained.

5.3.2.1 Drug budgets

Of the respondents, 18% (n=2) had no idea about the drug budgets in their respective institutions. While 9% (n=1) mentioned a budget over 30 million dollars, 54% (n=6) claimed to have a budget of less than 20 million dollars. Another 9% (n=1) mentioned a budget of 21-30 million dollars.

5.3.2.2 Opinion about the 'formulary'

Most respondents (64%, n=7) felt that the 'formulary' is a 'list of most essential drugs' while 18% (n=2) noted it is a 'list of most used drugs'.

5.3.2.3 Functions of 'the formulary'

'The formulary' was considered by most to serve 'In controlling the hospital budget' (91%, n=10), followed by 'In promoting cost-effectiveness in drug treatment' (73%, n=8) and 'In promoting the use of the "best" drug/intervention' (64%, n=7). Only 55% (n=6) considered it as performing a role 'In restricting the use of drugs'.

5.3.2.4 Factors considered important for the formulary decision-making process

If respondents were to consider factors in order of importance for formulary decision-making, 82% (n=9) of them would consider drug effectiveness as the most important factor followed by available alternative (64%, n=7), acquisition cost (55%, n=6) and then safety (45%, n=5). The least important factors to be considered were drug/pharmacy budget (18%, n=2) followed by politics (9%, n=1) and hospital budget (9%, n=1).

72% (n=8) of the respondents felt that their approach to the formulary was 'scientific' or 'evidence-based'.

The most important results have been summarized in the following graphs.

A. 91% (n=10) respondents noted their institution has a formulary

B. A majority (91%, n=10) felt that 'aim of the formulary was to control budget'

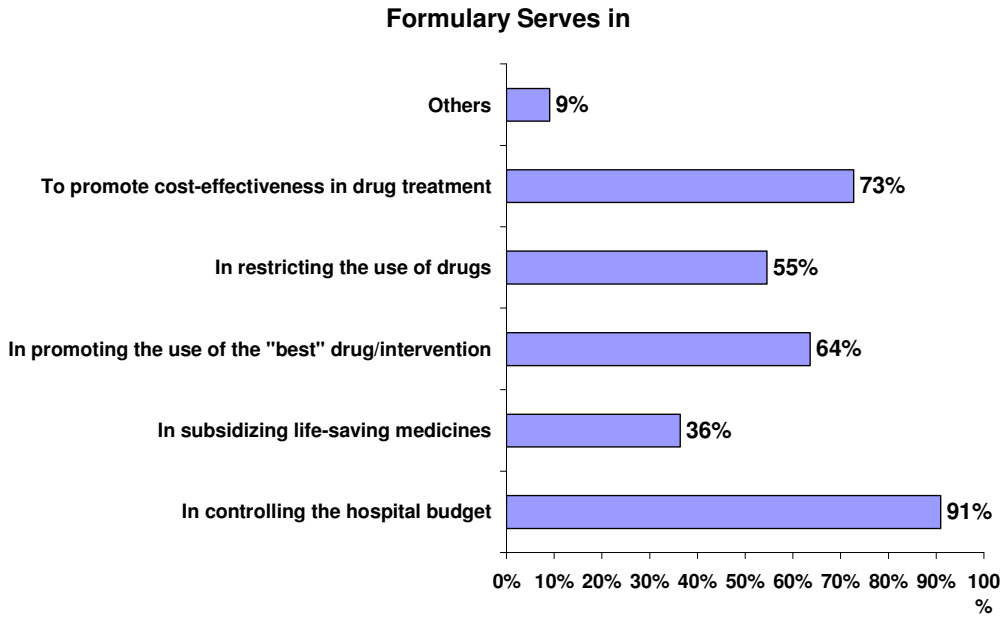

Chart 6: Pharmacy Managers' opinion on aim of a formulary

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* See Appendix 4 – Pharmacy Manager responses

C. 72% (n=8) of the respondents felt the P & T Committee was the final decision-maker with respect to inclusion or exclusion of drugs

D. More than half (82%, n=9, and 645, n=7) of the respondents opined that 'efficacy' and 'alternatives' were the two important factors taken into consideration while selecting a drug for inclusion in the formulary.

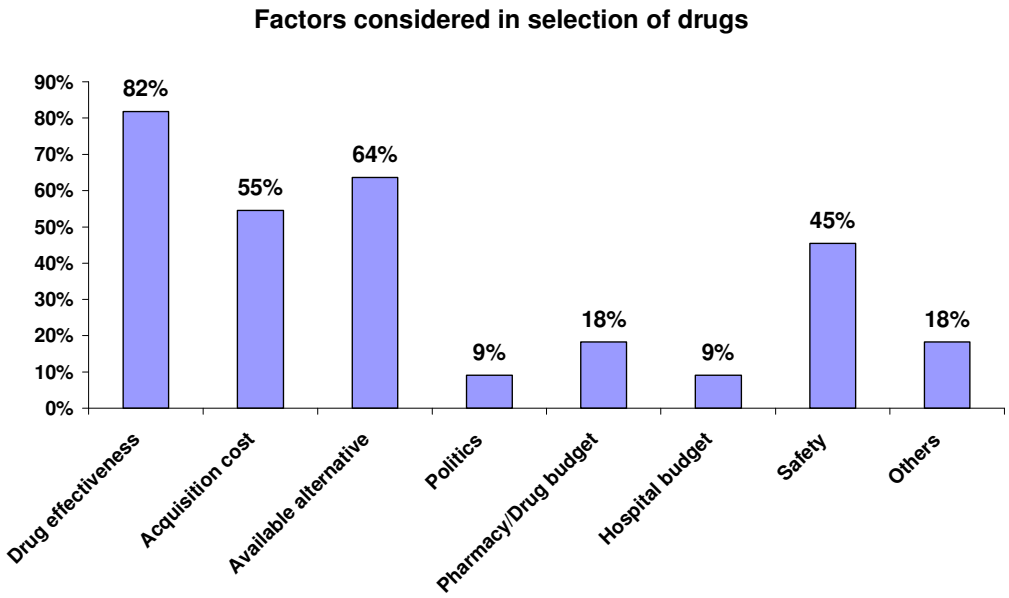


Chart 7: Pharmacy Managers' opinion factors considered in drug selection to formulary

E. Majority (64%, n=7) of respondents felt a 'Formulary' was a list of the most essential drugs

Chart 8: Pharmacy Managers' opinion of what a formulary is

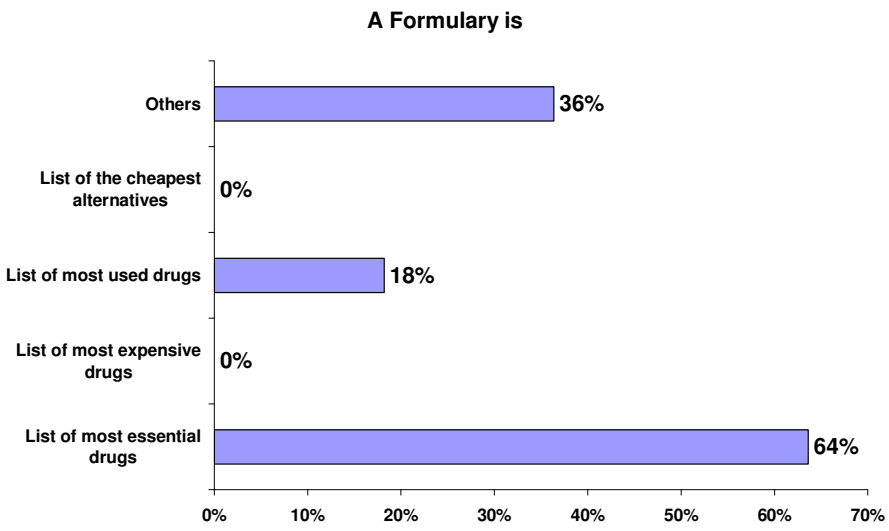


Chart 9: Pharmacy Managers' opinion on who makes formulary drug inclusion proposal

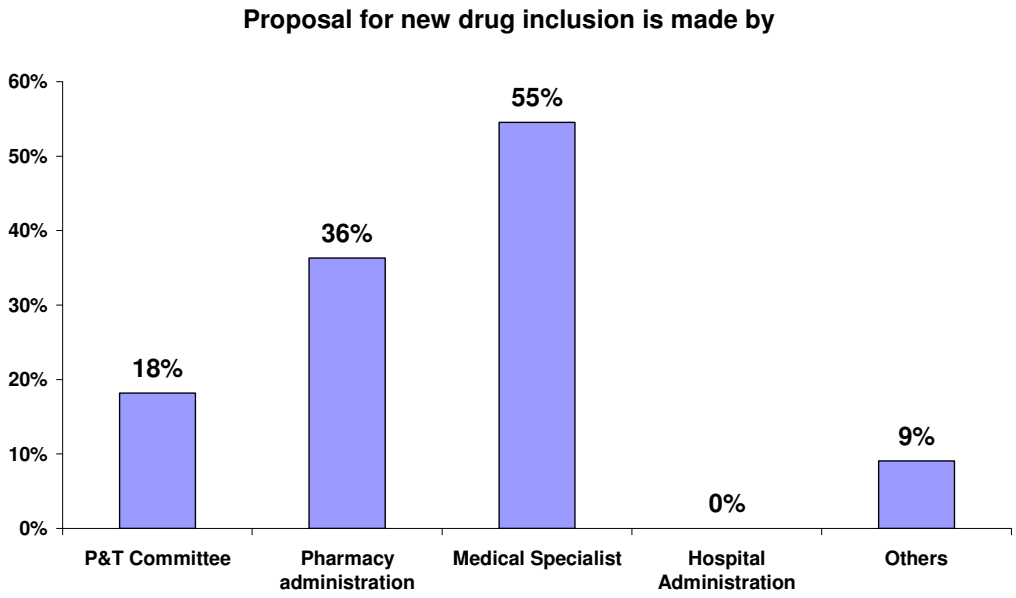


Chart 10: Pharmacy Managers' opinion on who makes final formulary drug inclusion decision

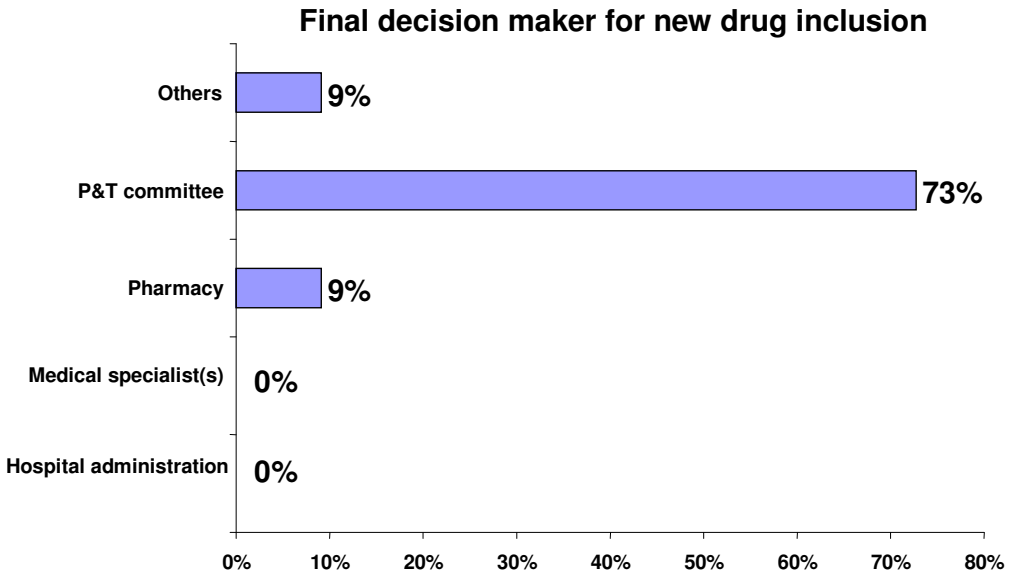
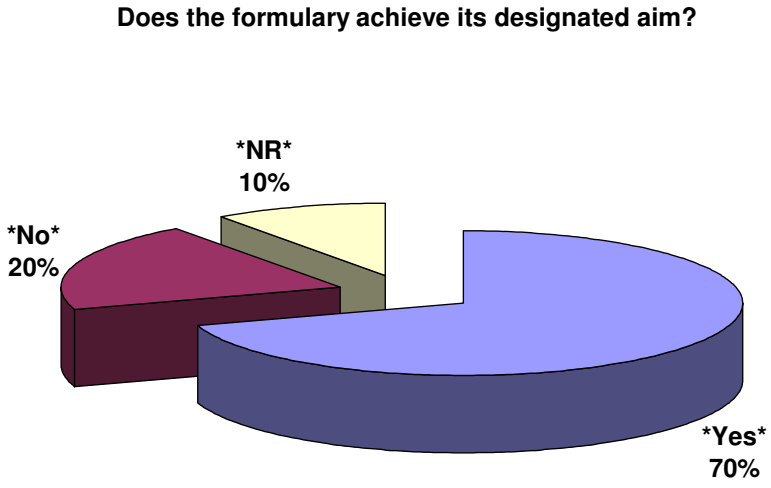


Chart 11: Pharmacy Managers' opinion on whether 'their' formulary achieves its aim



72% (n=8)of the respondents also felt that their formulary achieved the aims of a formulary as designated by each of them. 18% (n=2) of the respondents felt that it did not and among the reasons cited for why it did not, none of the respondents chose any of the statements provided in the questionnaire.

Among different additional approaches cited to help the formulary attain its aims as designated by each one of them, pharmacoeconomics and /or cost-effective featured in 3 responses. Various other institution-specific approaches were mentioned. Different reasons were cited for not being able to implement the additional approach. Most were related to the specific institutional settings. Only 18% (n=2) noted lack of expertise as one reason followed by lack of time (9%, n=1).

Important Differences between The Responses Of The Pharmacists And The Pharmacy Managers and possible causes

Both the pharmacists and the pharmacy managers agreed that a 'formulary' was a 'list of most essential drugs'. However, the major point of difference lay in their view with regard to the function of the formulary. Whereas, a majority of the pharmacy managers (91%) felt that the most important function of a formulary was to control the hospital budget, the pharmacists (71%) opined that a formulary was supposed to promote the use of the best drug or intervention. This disparity in their idea about what the formulary was supposed to do was again evident when only 35% of the pharmacists felt that their formulary satisfactorily performed its function as opposed to 70% of the managers who felt the formulary achieved its aim. Given their preoccupation with managing budgets it seems that the managers considered the formulary as another budget management tool. 'Drug effectiveness' figured topmost in the list of factors that would be considered by both general pharmacists and P&T committee members if they were to decide on the formulary. However pharmacists felt that drug effectiveness though the most important, acquisition cost was the least important factor for

consideration to them. To the pharmacy managers acquisition cost ranked third in order of importance after drug effectiveness and available alternative.

Pharmacoeconomics and Pharmacists

Promoting the health of patients is a role to which the pharmacists commit themselves when they join the profession. However, today "health" is not just considered the absence of disease or infirmity. Rather, a comprehensive approach to health is being embraced. Under this scenario, helping other healthcare professionals ensure positive outcomes has become the responsibility of the pharmacists. Good patient care lies in helping patients achieve positive outcomes that the patients and health care professionals mutually define, in the most cost-effective manner. The principal aim of pharmacoeconomics is to elaborate and analyze the outcomes that are achieved or expected to be achieved versus the costs for that care. In order for pharmacists to discharge their duties effectively and efficiently in the current therapeutic milieu, therefore, it is important that pharmacists understand pharmacoeconomics. Focusing on the patient as a whole person is a completely new orientation. In this changed scenario, pharmacists as members of the healthcare team, must be able to evaluate the relationships between process, outcomes and costs to help reproduce the best or the most cost-effective outcomes (including patient satisfaction) and thereby help improve the physical**,** mental and social well-being of the patient.

However, though pharmacoeconomics and pharmaceutical care are interrelated, the real world use of pharmacoeconomics by pharmacists seems to be confined to formulary decisions primarily. In fact, a conference held in Boston in September 1994, on applying pharmacoeconomics in patient care revealed that whatever was being used was mainly for making drug formulary decisions.[95,96,97] In several countries, formal requirements and guidelines to assist in decisions about including and subsidizing specific drugs on formularies at a national or provincial governmental level have been established. In the United States,

pharmacoeconomic studies are required on a less formal basis by P&T committees of institutions for drug inclusion on formularies.[99] Other than these, based on the literature it seems that the use of pharmacoeconomic data by pharmacists is limited.

Significant points from the survey

Based on the results of the surveys a few significant points emerged:

- The background of the respondents had no bearing on the individual's responses to questions pertaining to opinion about the formulary and its decision-making process or idea about average annual expenditure on drugs. Ideally, one would have expected some difference, more particularly, people with greater experience or at least those between 25-45 years of age (those likely to have more active interest in professional matters) to differ significantly in some views. That did not happen. Therefore, there seems to be a general lack of interest in the "formulary" and how it operates or how it is expected to operate. Moreover, there also seems to be no awareness about the problems of increasing costs. However, as is being increasingly realized, the future with an ever-increasing elderly population and increasing expectations of better quality will definitely pose challenges. If governments are to live up to these challenges 'cost-effectiveness' in health care is an important consideration. However, in Singapore, the idea of cost-effectiveness in health care is only beginning to emerge.

- Few hospitals have open formularies, with the exception of private hospitals, where patients pay in full stock all medicines.

- The final decision to stock or not stock a particular medication rests on the medical board or the P&T Committee (the chairperson of which is usually a doctor).

Thus, one can strongly argue that there is a covert need for a more complete evaluation of pharmaceuticals. Given the potential benefits of pharmacoeconomics, we would suggest that the subject has a definite role to play in formulary decision-making which would involve more comprehensive evaluation of pharmaceuticals. Therefore, it is being proposed that the feasibility of applying pharmacoeconomic principles to formulary decisions in Singapore be explored.

SECTION 6. THE METHODOLOGY OF THE PROJECT

4.1 Introduction

The project endeavours to establish that pharmacoeconomics can play a potentially useful role in formulary decision-making at the institutional level in Singapore. For this purpose, the National University Hospital (Singapore), a tertiary institution was chosen as the centre of the study.

However, if pharmacoeconomics is to contribute to a more rational allocation of health care resources at the hospital level (through a more comprehensive and scientific formulary decision-making process), P & T Committees must appreciate the potential role of that discipline in formulary decisions. This is because, in most practice settings, formularies are established and managed by this committee. At the same time, pharmacoeconomists must demonstrate that their analyses can lead to a more efficient allocation of limited resources in the purchase of drugs without compromising the quality of health care.[75, 99]

Therefore, the first steps the researcher did was to write up a proposal explaining clearly to the P&T Committee chairperson, the following points:

- Background as to why the researcher hypothesised that pharmacoeconomics could potentially be useful in formulary decisions in hospital practice settings

- Why the researcher considers it useful in the Singapore scenario (incorporating the results of a survey of hospital pharmacy managers that clearly revealed the need for such an approach)

- Time-tested benefits of incorporating pharmacoeconomics in formulary decisions by drawing on examples of countries, especially Australia. Examples of National and State level formularies were cited to demonstrate our hypothesis that similar activity at the institutional level would help improve the technical efficiency of the formulary process.

- How the researcher intended to establish the role of pharmacoeconomics in formulary decisions (the exact *modus operandii* of the project)

  Starting from the approval date, for the following 3-4 P&T Committee meetings the researcher would evaluate any one to two of the 7-8 formulary submissions in each meeting and prepare a report suggesting what impact it would have (on both clinical and economic fronts) if included in the hospital formulary. This report along with all other reports prepared by the DIS pharmacist was to be circulated one week in advance of the meeting to all the 13 members to enable them go through the reports and ready themselves for the discussion. Next, the actual review process was observed first hand by the researcher to facilitate better understanding of their standard procedure and enable the researcher to help sharpen the approach. The letter and the proposal attached together as Appendix 5.[*]

The researcher, after having obtained the hospital's consent attended four P&T Committee meetings from January 2001 through to April 2001. A total of 7 products (Basiliximab/ Daclizumab, Zanamivir/Oseltamivir, Gatifloxacin, Synercid and Linezolid) were reviewed with full and comprehensive pharmacoeconomic reports prepared for each. Each report on an average consisted of 15-18 pages and would take up to 2-3 hours to read carefully. The evaluations are all attached as appendices 6a-6e.[+] Due to the researcher's inexperience in performing evaluations, the first evaluation was substantially performed by the supervisor with some inputs from the researcher. In the interest of being truthful it was deemed more appropriate to put the supervisor's name in that evaluation when submitting for discussion with the NUH P&T Committee. Thereafter, the other evaluations were substantially performed by the researcher with inputs and corrections by the supervisor.

[*] See Appendix 5 – Letter and Proposal
[+] See Appendix 6a-6e - Evaluations

Until June 2000 the frequency of the P&T Committee meetings was once every two months. However there was no rigid rule in this regard. But, from 2000 July onward, the meetings were conducted once every month.

4.2 Process of Evaluating Formulary submissions at NUH

For the appraisal a drug "topiramate" evaluated before June 2000 and "zafirlukast" evaluated after June 2000 were chosen. Attached[σ] are the evaluations performed by the NUH DIS pharmacist and the decisions based on those evaluations. Additionally, the drug evaluations performed by the DIS pharmacist for the 7 products for which the researcher also performed evaluations were also reviewed. Following is a critical appraisal and comparison of the evaluations performed by the DIS pharmacist and later reviewed during the P&T committee meeting for decisions.

4.3 Review of Existing Evaluation Process

There seemed to be little effort at "synthesizing" findings from numerous similar and smaller trials to obtain what could be called an overall picture. The concept of meta-analysis while being understood was hardly ever performed. There was no attempt at evaluating clinical literature critically and arriving at information crucial for the decision-situation at hand. Information was derived from standard databases or journals and the conclusions reported *ad verbatim* with little attempt at finding out what the findings truly signified in the context of the NUH practice setting and formulary decisions. This may be quite understandable in view of the fact that most peer-reviewed journals are considered to produce *bona fide* information. There would seem to be little need to review clinical literature critically. No attempt at

[σ] See Appendix 7 - NUH Evaluation Process

finding out the impact on Quality of life outcomes was seen. Finally there was no reference to any economic evaluation or literature.

4.4 Process of review until June 2000

A drug company or a doctor was required to fill the request form* to incorporate a new drug in the formulary. This form was then sent to the NUH Pharmacy Department where the Drug Information Services (DIS) pharmacist evaluated the drug for its merits. The DIS pharmacist searched for relevant papers to carry out this evaluation process. Papers or studies submitted by the pharmaceutical companies were generally regarded as having a bias in favour of the company's interests. Hence, the DIS pharmacist looked for his/her own references.

The databases looked up for reference, were usually FDA web site databases and Medline. PubMed was the search engine most frequently used. Based on information available from the relevant clinical papers, the drug was compared to an alternative with respect to efficacy, side effects and cost. It was not clear, how this alternative was chosen. However, from the information available in the drug request form (which is to be filled in when a doctor requests for inclusion of a new drug), the alternatives chosen appeared to be drugs of the same class and/or drugs with the same therapeutic use in the NUH.

For *efficacy*, a direct head to head comparison was made when such studies are available. Otherwise, both the drugs were compared to a placebo.

Adverse effects included an evaluation of the drug based on the routine adverse effects. The FDA runs a very detailed account of adverse effects on its website and the DIS pharmacist made sure she got information from it. Therefore, there seemed a very strong inclination towards ensuring safety of the patients.

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* See Appendix 8 – Request Form

No references were provided for the studies based on which all the information was derived.

Cost considerations included unit cost and acquisition cost for the hospital. Cost of treatment per day as well as, total treatment cost wais only sometimes considered.

Any drug approved by the committee was considered a 'Formulary Drug'. However, if it was approved as a non-standard category drug, a 'subsidised' patient would pay in part for that drug whereas, for a standard drug the patient has to pay a subsidized rate. For a 'private full paying' patient, however, full payment for both standard and non-standard drugs is required.

Three weeks before the P & T Committee meeting, the review* along with relevant clinical papers, was sent to doctors of the relevant specialty. Expert clinical opinion of the reviewers was sought on a specified form+ after which the drug review report was finalised and then presented in the P&T committee meeting. Every round of a P&T meeting normally reviewed eight new requests.

4.5 Major changes made after June 2000

The major changes made after June 2000 were with respect to the frequency of meetings (once every month instead of once in two months) and the incorporation of references by the DIS pharmacist when doing the review. In addition, every round of meeting (because it was now more frequent than before) reviewed 5-6 requests normally instead of 8-9.

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* See Appendix 9 - Review
+ See Appendix 10 – Expert Opinion

SECTION 7. WHY WERE THE AUSTRALIAN GUIDELINES FOR THE PHARMACEUTICAL INDUSTRY ON PREPARATION OF SUBMISSIONS TO THE PBAC CHOSEN AS THE REFERENCE POINT FOR THE WHOLE PROCESS?

Starting through January 2001 to April 2001, approximately 3 weeks before each P&T Committee meeting the DIS pharmacist was approached by the researcher and asked to allocate one, or at most two, "difficult-to-evaluate" (usually due to high price and/or recent introduction into the market) product (s), to be evaluated by the researcher. Such a procedure resulted in the researcher performing the evaluation for the specified product and submitting the evaluation report approximately one week before the scheduled P&T Committee meeting.

Evaluations and recommendations made for include monoclonal antibodies like basiliximab, daclizumab, antivirals like zanamivir and oseltamivir and antibacterials like gatifloxacin, quinupristin/dalfopristin, linezolid and synercid.*

In addition to safety and efficacy, these evaluations assessed the cost-effectiveness of these high-priced drugs in the hospital setting. The above cost-effectiveness evaluations were based on a uniform method of interpretation, compilation and presentation of the 'best' evidence that could be generated from the available clinical literature. The model of "Guidelines for the Pharmaceutical Industry on Preparation of Submissions to the Pharmaceutical Benefits Advisory Committee (PBAC): including major submissions involving economic analyses" framed by the Commonwealth Department of Health and Aged Care in Australia was followed for the whole process.

These guidelines require pharmaceutical companies, seeking recommendation for national formulary listing and subsidisation, to provide a detailed economic analysis to support their case. Australia is the first country to mandate such a requirement.[100]

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* See Appendix 6 - Evaluations

Any assessment of the contribution of the Australian Guidelines as, a model for formulary committee evaluation of drug applications must note the nature and jurisdiction of the PBAC as the formulary committee. In Australia, the PBAC serves a national body responsible for recommending listing of drugs prescribed through community pharmacies. Due to the universial pharmaceutical cover provided, without such a listing, it is less likely that a drug would be marketed in Australia. The PBAC plays, therefore, a pivotal role in the entry of drugs to the Australian market. In this context, it might be expected that the PBAC would take as its principal focus, a societal perspective in the evaluation of drug applications.[101, 102]

However, while appreciating the role of the guidelines it has been cautioned that their usefulness in formulary settings at the institutional level must be reassessed before adopting them as a model because, health care institutions as drug purchasers have a different perspective compared to government regulating agencies. They are concerned with their long-term survival in a highly competitive cost and outcomes conscious environment.[101] In spite of various criticisms hurled against them, [100,102,74] the Australian guidelines may be taken as a reference point for formulary committees who wish to incorporate economic analyses as a part of their decision-making. These guidelines do stand out, because of certain distinctive features.

How Elements of the Australian Guidelines can help NUH in their formulary decision-making process

The objective of the P&T Committee at the NUH should be to rationalise the inclusion of drugs on the formulary from both clinical and economic perspective thereby ensuring judicious allocation of health care resources and ultimately facilitating the development of disease management approach to treating different health conditions. In this context, the objective of the researcher was to develop a standard procedure for evaluation of pharmaceuticals that would include -

- A sound clinical evidence
- An assessment of the economic impact of the decisions
- The financial impact of the decisions to include or withdraw drugs to / from the formulary

For developing the aforementioned standard procedure, the intent was to borrow from the various guidelines, concepts that considered most appropriate for the purposes of the research. In the opinion of the researcher certain salient features make the Australian guidelines important source for the aforementioned borrowing. These are:

- ✓ The Australian Guidelines were the first to force decision-makers to evaluate drugs by going beyond mere clinical considerations to consider in a consistent manner the impact on both economic and HRQoL outcomes of the treatment.
- ✓ Australia by following the above process has been able to keep its drug prices at a fraction of the prices in other developed countries while providing standards of care at par with those countries. In the fiscal year 1997-98, approximately 125 million prescriptions were written for a population of 18 million, at a cost of A$2.8 billion (US $1.75 billion), or about A$13 per person per month.[74] In contrast, the spending on prescription drugs by the elderly alone, in the United States was approximately US $30 billion in 1998 and was growing at an estimated 15% per year.[103]
- ✓ It is true that the guidelines have drawn criticism from some quarters for focussing too intensely on clinical implications and relying on clinical trials for pharmacoeconomic information. This could be because of two reasons: (1) because of the lack of an agreed upon methodology for deriving economic information, the use of clinical trials is preferred, (2) modelling relies too much on assumptions that may sometimes not have a basis in real life.[104, 105,106,107] Moreover, modelling could be tailor-made in a way to reach a desired or pre-selected result. Therefore, modelling is sometimes an unconvincing and unreliable approach for decision-makers. Until economists could prove to the contrary (at

least where health care is concerned), the Australian approach rooted in evidence obtained from well-designed and scientific trials, does seem to be quite acceptable.

- ✓ The Australian guidelines have been criticised for representing the traditional 'clinical paradigm' of drug-impact assessment.[108] However the role of outcomes assessment is to evaluate the anticipated impact of the proposed drug or therapy on the clinical. Outcomes can be expressed in clinical terms or in terms of a disease – specific health status measure, a HRQOL profile or preference –based instrument score. The choice of outcome measures or instrument needs to be justified and acceptable in the context of disease or therapeutic area and in terms of the usual criteria of validity and reliability. Only few instruments have been assessed within treating populations (as opposed to trial environments). [54,110] Therefore, until the time that some "pragmatic trials" or naturalised studies[110] that capture real-world effectiveness of drugs are done routinely and get accepted as well as scientifically designed randomised clinical trials, the latter will need to be used for deriving maximum information. This the researcher feels, in no way belittles the economists but rather provides them with a challenge to design 'more practically informative' studies that would also come to be accepted as well as or even better than the current 'gold standard' of the double-blind, randomized, clinical trials. Therefore, the current 'clinical paradigm' seems acceptable to the researcher.

- ✓ As a health system, it is understandable that NUH is particularly concerned with the direct cost impacts of new therapies; costs which have to be met by the health system. The hospital is primarily concerned with being able to assess the anticipated impact of introducing the product on the patterns of resource utilisation, estimated costs of treatment and the outcomes profile of patients in the therapeutic area. Such an approach to assessing interventions is very clearly explained in the Australian Guidelines.

- ✓ Moreover, the guidelines framed by different countries are largely similar to the ones in Australia. [100, 54] There are some subtle differences [54] accounted for by the difference in

purpose of the guidelines, the particular health care systems of the respective countries and the extent of government intervention in health care. [100, 101, 110]

Australia has been the only country, (other than Canada to some extent), to have rigorously and strictly enforced the guidelines (for proper conduct of pharmacoeconomic studies) at a national level.[101] The acceptance of new chemical entities on the national formulary in Australia and the ten provincial formularies in Canada depends on the results of these pharmacoeconomic studies.[111] Only those products which are proved cost-effective based on these studies are allowed entry into the market.

- ✓ The relatively lower price levels of major pharmaceutical products (multinational brands) in Australia [112] as compared to other developed countries and the overall efficiency of health care expenditure (reflected in similar standards of care achieved at a fraction of the costs of other nations) are ample testimony to the success of the guidelines.

SECTION 8. A CRITICAL APPRAISAL OF THE FORMULARY DECISION-MAKING PROCESS ON THE BASIS OF FIRST HAND OBSERVATION OF FOUR P&T COMMITTEE MEETINGS ATTENDED BY THE RESEARCHER

Traditionally, P&T committees have been responsible for overseeing the drug use process, and using formulary systems to control drug costs. By means of this method, P&T members evaluate and select from the commercially available drug products, those that are most useful for patient care and thus help in promoting rational drug therapy. In many health care systems, the P&T committee of the 1990s functions as an advisory committee and policy recommending body to the medical and administrative staff, for the purpose of promoting rational drug therapy.[113]

8.1 The P & T Committee of the National University Hospital (NUH), Singapore

The National University Hospital (NUH) is an autonomous hospital managed by its own governing body. The P & T Committee at NUH takes decisions on admission of new drugs to the hospital formulary.

Members of the P & T Committee – The membership of the committee comprises primarily of doctors from the departments of Pharmacology, Pediatrics, Medicine, Obstetrics and Gynecology, Anesthesiology, Surgery, Medical Oncology etc. The pharmacy manager is the only voting non-medical member. The DIS pharmacist is a non-voting member. There is also the finance secretary of the hospital who serves as a financial consultant.

Membership is not permanent and changes are made regularly keeping the total number of members at around ten at any time. When the project was conducted there were 13 members in the committee.

8.1.1 Roles and Responsibilities*

The primary roles of the P&T Committee are:

- To recommend policies to the medical and nursing staff and the Hospital Administration on all matters relating to the use of drugs in patients, including drugs in the treatment and prevention of disease and drugs for clinical investigation and research.

- To advice the Pharmacy Manager on the selection of drugs for specified diseases; on selection of drugs to be stocked in patient care areas; on the distribution and administration of medications, including errors in the prescribing, preparation, drawing up and administration of drugs.

- To evaluate pharmacological and clinical data from all appropriate sources on new drugs or formulations offered or requested for use in the hospital. In particular, the Committee will from time to time, conduct drug utilization reviews to measure the usage of certain drugs with regard to their safety, cost and prevention or therapeutic efficacy.

- To maintain and continually upgrade through revision a formulary of drugs accepted for use in the Hospital. The selection of items to be included in the formulary will depend on the evaluation of their efficacy, safety and cost. The Committee will attempt to minimise the duplication of similar drug types, drug entities and drug products (formulations) in order to reduce unnecessary expense.

- To monitor and review unwanted (adverse) drug reactions which occur in the hospital and relate them to similar information from other appropriate sources.

- To establish and organise appropriate educational programmes for the hospital professional staff on matters relating to drug use, including a drug information bulletin.

To advise the National Health care Group Management as to whether the standard drug list requires modification.

In the opinion of the pharmacy manager (one of the members of the P & T Committee), a 'Formulary' is "a list of the most essential drugs as these drugs must be made available for treating a variety of conditions. If drugs can be shown to be 'really needed (essential for treatment of patients)', cost is not a critical deciding factor.

8.1.2 Major approach of the P&T Committee Meeting

- With the exception of the finance secretary all members of the committee were required to attend the meeting. However, full attendance was not seen in any of the four meetings attended by the researcher. If attendance were to be considered an indicator of participant interest, then the indicator definitely showed lukewarm interest, at best.

- The members served as representatives of their individual departments and were consulted for their department's specific needs, their perception about the usefulness of the product in their respective practice settings and their estimation of the volume of actual or potential use by members of their specialty. Any other opinion relevant to the decision about the product was also welcome.

- Comments on each drug submitted for inclusion / exclusion, were invited by the chairperson. A part of this process was carried out even before the meeting was conducted, by soliciting expert opinion on certain products (usually the newer ones) from consultants considered "knowledgeable" about such and related products and who could be the most likely users of such products.

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[*] See Appendix 11 – Terms of Reference of the P&T Committee

- The “expert” opinions were usually based most often on FDA web site reports rather than what could be termed compilation of the best (or all) available evidence derived from different sources, especially reports of clinical trials published in peer reviewed literature. A major drawback with such an approach to evaluating pharmaceuticals was a conspicuous overlook of the fact that the FDA needs just enough proof of the new agent being generally safer and more efficacious than placebo to grant approval for marketing a new drug. FDA approvals are not incumbent on the comparison of the new agent with other drugs available for treating that indication. Such comparison however, is almost indispensable for making good formulary decisions.

- In an attempt to put a consensus decision approach into practice active participation with respect to expressing views was encouraged.

- Attention to numbers (volume and money value of use) was also paid and causes for over use or deviation from the normal standard of other hospitals (especially the Singapore General Hospital, comparable in size, pharmacy drug budget and volume of business) were considered.

- There seemed to be an attempt by the P&T Committee to not make the physicians feel restricted in their practice due to “cost-cutting” or “budget-control”. However, there was a general consensus that unwarranted and unbridled usage of expensive drugs had to be curtailed. Some acceptable “rules” to bring an element of accountability and responsibility when using expensive drugs were trying to be brought in. However, a system that encouraged prior approval of emergency use drugs did not seem acceptable. Doctor education (in the line of practice guidelines) was an idea being considered to facilitate more standardization in treatment practices.

- An inclination to make the decisions more rational was evident from the suggestion of members to change the format of the form (to be filled up when requesting formulary inclusions of drugs) to suit the requirements of a good evaluation. It was

agreed upon that more space for incorporating enough reasons to justify inclusion was required.

- Distinct eagerness to make the formulary selection process more transparent was evident from the suggestion that declaration of any interests in the pharmaceutical company (by the requesting doctor) be made mandatory.

- It was being felt that the evaluation process would do well to be 'a bit more scientific'. Though the term was yet to be clearly defined, the researcher felt that this could mean "more information that would facilitate better decisions". However, the members, given their tight schedules also opined that while the form should help establish proven safety and efficacy facts and quote references, it should be "concise".

- A need for differently formatting forms filled out by drug companies for requesting inclusion of their products was expressed. Simple declaration of interests, the number of company products available on the formulary and the volume of business with the NUH were suggested for inclusion in the proposed format. This may have been the result of an inclination to see if any particular company was getting unduly favoured due to vested interests of the medical specialists (who most often proposed new inclusions).

- When a consensus was difficult to arrive at, an expert in that subject was consulted. This seemed justified as not all specialties can be represented in the committee.

- A protocol requiring a check of head-to-head clinical trials or a meta-analysis of smaller trials was trying to be instituted for incorporation of expensive drugs. A definite need to check whether individual experience was borne out in well-controlled clinical trials was being expressed.

Discussion

Although during the four meetings attended by the researcher the discussion centred on the formulary, it would be inappropriate in that sense to conclude that the P&T committee in the NUH served primarily as the 'formulary committee'. Clearly, the approach of the committee had all the ingredients of a progressive decision-making body. The tactical issues involved were recognized correctly and action was being solicited. Attempts to make the information requirements more rigorous and comprehensive before acting on drug inclusion requests could be seen as a step in this direction. Mandating expert evaluations of newer (more expensive) drugs before deciding on their inclusion could definitely be interpreted as an attempt to make "more robust" decisions. Benchmarking costs and performance with other comparable hospitals could also be a case in point. Needs for more "depth" and transparency were clearly evident. For instance, doctors are usually not trained in assessing financial information. However, an attempt to evaluate financial impacts of decisions was seen. The concept of "cream off", by which excess of revenues (over a particular amount) generated in the hospital are ploughed back by the government are usually financial matters. This was also paid attention to in the meeting. Attention was drawn to the "pricing" of pharmaceuticals. For example, surprise at 50mg and 100mg tablets of a certain drug having the same price was expressed. An increasing concern about the 'true worth' or the actual value of the products being paid for was evident. Attempt to correct loopholes in the system were evident when attention to the usage of 746 vials of a particular drug for one patient was drawn. Thus, it could be said that the approach was all geared towards incorporation of pharmacoeconomics. However, a probable unfamiliarity with the subject and its use (as evident from the surveys of pharmacy managers) may have been the reason why pharmacoeconomics was not being actively used. However, as discussed subsequently, the researcher's contribution (using pharmacoeconomics for drug evaluations) was amply recognized and a definite desire to increase use of pharmacoeconomic approach to decision-making was expressed. Therefore, it was only a matter of correctly understanding and appreciating the true usefulness of the subject before it would be accepted by the committee.

SECTION 9. EVALUATION OF THE RESEARCHER'S CONTRIBUTION TO THE FORMULARY DECSION-MAKING PROCESS AT THE NUH

9.1 The researcher believes that pharmacoeconomic assessments of formulary decision would help to ensure that only those drugs or interventions, which yield the highest outcome per dollar spent, diffuse into the healthcare systems. The researcher endeavored to test this hypothesis in the setting of the university hospital through a means deemed appropriate by her. This was to evaluate one or two products for each P&T Committee meeting through 3-4 meetings and submit the evaluations for facilitating P&T Committee decision-making. An objective measure of the success of the process would be an assessment of the percentage change in the number of P&T approvals and potential cost savings to the organization as a result of pharmacoeconomic assessments. However, due to the inherent nature of the project (such information may not be forthcoming due to the time constraint of the project) it was not possible to consider them as primary outcome measures.

9.2 Ideally, economic evaluations (as proposed and demonstrated by the researcher), in addition to the primarily pharmacotherapeutic (efficacy and safety) based considerations currently taken into account by the P&T Committee at the NUH would entail a more comprehensive or in-depth evaluation of formulary actions (addition or deletion) leading to increased user satisfaction. Hence, the primary outcome measure 'user satisfaction' was measured or gauged by a questionnaire at the end of 4 P&T committee meetings.

9.3 A questionnaire[*] was prepared and circulated to 12 P&T Committee members. The questionnaire was drawn up by the researcher based on what the researcher felt would be the most useful questions to ask about the formulary decision-making process and how to improve that process. The questionnaire was drawn based on an idea of general perceptions about the process. However, this questionnaire was not pre-tested. Instead a set of questions

from the pool of questions written by the researcher was finalized by the supervisor. Of the P & T Committee members, 10 had replied and 2 in spite of repeated reminders did not. Hence, the responses represent the views of the majority of the target population i.e. (P&T Committee members of the NUH) and not just those of a very small sample of the population.

Following are the most important (relevant) responses [*] in tabular form:

Table 17. P&T Committee members' opinion of the importance of the committee

A P&T committee is	Responses		
	Yes	**No**	**Not sure**
Indispensable in every hospital	100%	0%	0%
Essential though not indispensable	0%	100%	0%
Is 'nice' to have	0%	100%	0%
Is not very important	0%	100%	0%
Is just a "show"	0%	90%	10%

The results clearly show that all members feel that a P&T Committee is 'indispensable' for every hospital and a majority (90%, n=9) of the respondents do not think that it is just a 'show'.

Table 18: P&T Committee members' opinion of the most important objectives of the committee

(n = 10)

A P&T Committee's most important objective (s) is (are)	Responses		
	Yes	**No**	**Not sure**
To control the hospital budget	40%	50%	10%

[*] See Appendix 12 – P&T Member Questionnaire
[*] See Appendix 13 – P&T Committee member responses

To facilitate efficient management of the hospital as a "health care portfolio"	80%	20%	0%
To control doctors' prescription habits	40%	50%	10%
Management of the hospital inventory	70%	30%	0%

A substantial number of members in the NUH P&T Committee feel that the most important objective (s) is (are) 'To facilitate efficient management of the hospital as a "health care portfolio" (80%, n=8), 'Management of the hospital inventory (70%, n=7)', followed by 'To control doctors' prescription habits (40%, n=4)' and 'To control the hospital budget (40%, n=4)'.

Table 19: P&T Committee members' opinion of the required constitution of the Committee (n = 10)

'Must' be members of the Pharmacy and Therapeutics Committee			
	Y	N	Not Sure
Physicians	100%	0%	0%
Pharmacists	100%	0%	0%
Financial analysts	50%	40%	10%
Hospital administrators	60%	20%	20%
Nurses	30%	50%	20%
Health economists	60%	10%	30%

All the respondents consider physicians and pharmacists as 'must be' members of the P&T Committee unanimously and without ambiguity. However, a substantial proportion (60%, n=6) feels that health economists should be considered as 'must be' members. Though 30% (n=3) have not unambiguously declared that health economists 'must be' members, they

remain unsure about the issue. Only 10% (or 1 respondent) feels that health economists should not be "must-be" members of the committee.

Table 20: P&T Committee members' opinion of value adding viewpoints (n = 10)

Viewpoints considered to add value to P&T decisions			
	Y	N	Not Sure
Financial analysis	60%	40%	0%
Health care administration	60%	40%	0%
Pharmacoeconomic analysis	90%	0%	10%

However, pharmacoeconomic analysis is considered to 'add value' to their decisions by 90% (n=9) of the respondents. Only 1 respondent (10%) though not sure about whether such an analysis adds value has also not ruled out pharmacoeconomics completely.

Table 21: P&T Committee members' opinion on desirable frequency of committee meetings

(n = 10)

Frequency of meeting to achieve a meaningful purpose			
	Y	N	Not Sure
Once every month	87%	13%	0%
Once in three months	0%	100%	0%
Once in two months	50%	33%	17%
More often	0%	75%	25%

A considerable proportion of the respondents, feels that the P&T meeting should be conducted every month to achieve a meaningful purpose. Though some (50%) would like it to be conducted every two months, 75% certainly do not want it conducted more often than once

a month. Therefore, the status quo in so far as the frequency is concerned seems very acceptable.

Table 22: P&T Committee members' opinion on decisions made by the committee (n = 10)

Kind of decisions made most often by the P&T Committee			
	Y	N	Not Sure
Patient management decisions	43%	29%	29%
Budget management decisions	43%	29%	29%
Formulary drug decisions	100%	0%	0%
Diagnostic and screening Procedures' decisions		71%	29%

This question was asked with the intention of finding out how their approach related to their work.

All the respondents feel that the P&T Committee makes formulary drug decisions. However, 43% of the respondents feel that the committee also makes patient management and budget management decisions. However, none of the respondents feels that the committee makes diagnostic and screening procedures decisions.

Table 23: P&T Committee members' opinion on ideal formulary (n = 10)

A formulary should ideally be			
	Y	N	NS
An essential drug list	89%	11%	0%

A list of life-saving drugs meant for subsidy	71%	29%	0%
A list of drugs most frequently used	63%	25%	13%
A comprehensive list of drugs avoiding generic duplication	63%	13%	25%
Others	0%	0%	0%

Opinions about what the formulary should ideally be, ranged from 'an essential drug list (89%, n=9), 'a list of life-saving drugs meant for subsidy (71%, n=7)', 'a list of drugs most frequently used (63%), to 'a comprehensive list of drugs avoiding generic duplication (63%, n=6)'. The pharmacists opined that the purpose of an ideal formulary was "to promote the use of the "best" drug/intervention.

Table 24: P&T Committee members' opinion on 'idealness' of NUH formulary (n = 10)

How close is NUH formulary to the aforesaid choice	
Not at all	0%
very slightly close	0%
somewhat close	20%
close	60%
very close	10%

A substantial proportion (60%, n=6) of the respondents think that the NUH formulary is close to their choice of 'ideal' formulary while only 20% (n=2) feels that it is 'somewhat close' to their choice. However, only 1 respondent feels it is 'very close' to the aforesaid choice.

Table 25: P&T Committee members' opinion on factors for formulary decisions (n = 10)

Factor (s) to be considered when including/ deleting drugs from a formulary				
		Y	N	NS
Cost		90%	10%	0%
Only clinico-therapeutic properties of drug and alternatives		56%	44%	0%
Institutional Budget		67%	33%	0%
Economic impact of drug on the therapeutic area		89%	11%	0%
Safety		100%	0%	0%
Cost-effectiveness		100%	0%	0%
Brand equity		11%	67%	22%
Other Quality of Life factors		89%	0%	11%

Factors cited as the ones to be considered when including/deleting drugs to and from the formulary included safety (100%, n=10), cost-effectiveness (100%, n=10), cost (90%, n=9), economic impact of the drug on the therapeutic area (89%, n=9), other quality of life factors (89%, n=9), institutional budget (67%, n=7) and brand equity (11%, n=1). An attempt was made to clarify their concepts of 'cost' and 'cost-effectiveness' in a later question.

Table 26: P&T Committee members' opinion on NUH formulary drug decision process (n = 10)

Does NUH approval process consider all factors	
Not at all	0%
only little	0%
considers partially	0%
considers	60%
considers completely	20%

A substantial proportion of the respondents felt that the NUH approval process 'considers' (60%, n=6) as opposed to 'completely considers' (20%, n=2) all the aforementioned factors in the approval process.

Table 27: P&T Committee members' opinion on 'cost' (n = 10)

Connotation of the term "cost"			
	Y	N	Not Sure
Acquisition cost	57%	43%	0%
Total cost of treatment	100%	0%	0%
Budget impact	100%	0%	0%
Cost to the patient	89%	11%	0%

The term 'cost' denoted 'total cost of treatment' and 'budget impact' to 100% (n=10) of the respondents; whereas it meant 'cost to the patient' to 89% (n=9) and 'acquisition cost' to 57% (n=6) of the respondents respectively. Therefore there seems to be some non-uniformity in their understanding of the term 'cost'.

Table 28: P&T Committee members' opinion on 'cost-effectiveness' (n = 10)

Connotation of the term "cost-effectiveness"			
	Y	N	Not Sure
Cheap	0%	86%	14%
Value for money	89%	0%	11%
Optimising the clinical efficacy, economic impact and patient quality of life	100%	0%	0%
Effective control of the institutional budget for drugs	50%	38%	13%

The term ‘cost-effectiveness’ stood for ‘optimizing the clinical efficacy, economic impact and patient quality of life’ to 100% of the respondents, followed by ‘value for money (89%, n=9)’ and ‘effective control of the institutional budget for drugs’ to 50% (n=5) of the respondents. However to none of the respondents did the term stand for ‘cheap’; though there was some ambiguity about the decision, because 14% (n=1) of the respondents were not sure if the term meant ‘cheap’.

Table 29: P&T Committee members’ opinion on prerequisites for good product review (n = 10)

The prerequisite (s) for good review of a product			
	Y	N	Not Sure
Extensive literature search	100%	0%	0%
Proper interpretation of clinical data	100%	0%	0%
Compilation of evidence most relevant to the decision	100%	0%	0%
Good presentation of available information about the product	100%	0%	0%
All of the above	89%	0%	11%

The prerequisite (s) for good review of a product were considered to be all the following by 100% of the respondents:

Extensive literature search, proper interpretation of clinical data, compilation of evidence most relevant to the decision and good presentation of available information about the product.

Table 30: P&T Committee members' opinion on comprehensiveness of medical literature (n = 10)

Extent to which literature search for review of formulary inclusions is comprehensive	
50%	20%
60%	0%
70%	20%
80%	20%
90% and more	40%

40% of the respondents felt that the literature search conducted in the hospital for evaluation purposes was comprehensive to the extent of 90% (n=9) and more, however, 20% (n=2) felt it was only 50% complete.

Table 31: P&T Committee members' opinion on decision criteria (n = 10)

Kind of evidence formulary decisions are usually based on			
	Y	N	Not Sure
Local clinical (and/or marketing) trials of the product (s) conducted for registration purposes	78%	22%	0%
Experience of senior colleagues with that product either in Singapore, or elsewhere	56%	44%	0%
International and multicenter clinical trials	100%	0%	0%
Own experience with the same product and/or a member of the same and/or similar class	67%	33%	0%
"Expert opinion" (of senior consultants) in NUH	67%	22%	11%
Review of all or/most of the available literature	100%	0%	0%

All the respondents unanimously agreed that ‘international and multicenter clinical trials’ and ‘review of all or most of the available literature’ provided the ‘evidence’ on which formulary decisions are usually based. ‘Own experience with the same product and/or a member of the same and/or similar class’ and ‘Expert opinion (of senior consultants) in NUH’ were cited as a source for evidence by 67% of the respondents. There was some ambiguity about the issue of expert opinion because 11% of the respondents were not sure whether such 'expert opinion’ was used. ‘Local clinical (and/or marketing) trials of the product (s) conducted for registration purposes’ and ‘Experience of senior colleagues with that product either in Singapore, or elsewhere’ were also mentioned as being used as evidence by 78% and 56% of the respondents respectively. Therefore there seems to be certain confusion regarding the ‘evidence’ used for evaluations in P&T committee decisions.

Table 32: P&T Committee members’ opinion drug decision ‘questions’

Questions asked before making decisions	**Response**		
	Yes	**No**	**Not sure**
completely revolutionary or other members of the same class and/or a different class for the same indication	100%	0%	0%
How new drug compares with other drugs / treatment w.r.t. safety, efficacy and cost	100%	0%	0%
Is new drug more "cost-effective" compared to others for same indication	100%	0%	0%
Does new drug radically alter quality of life experienced by patients	80%	10%	10%

Although 100% of the respondents agreed to asking about the relative efficacy, safety and cost-effectiveness of a new agent as compared to the available drugs, only 80% of the respondents agreed to asking a question about the impact of the drug on quality of life of the patient. This probably reflects the relative unfamiliarity with HRQoL as one of the outcomes in patient management.

Table 33: P&T Committee members' satisfaction with literature search

Satisfaction with literature search of evaluator	
Very satisfactory	10%
Good	80%
Okay but not good	10%
Unsatisfactory	0%

90% of the respondents felt that the literature search of the evaluator was 'good' to "very satisfactory". However, one respondent (10%) felt that it was 'okay but not good'.

Table 34: P&T Committee members' opinion on relevance of evidence presented by evaluator

Relevance of evidence presented by the evaluator	
90% relevance and above	30%
80-90% relevance	50%
less than 80% relevance	10%

While 80% (n=8) of respondents felt that relevant evidence was presented in the evaluation, one respondent felt that it had less than 80% relevance.

P&T Committee members' opinion of new approach to drug evaluation

The new approach to drug evaluation presented by the evaluator was rated 'useful', 'quite useful' and 'very useful' by 20% (n=2), 50% (n=5) and 10% (n=1) of the respondents respectively. No respondent felt that it was 'little useful'. However, one respondent (10%) rated it as 'not at all useful'.

Table 35: P&T Committee members' opinion on extensiveness of new approach (n = 10)

Whether the new method considers more comprehensive gamut of factors	
Considers completely	0%
Considers	50%
Somewhat	40%
Not at all	10%

To the question about whether the new method considers a more comprehensive gamut of factors 50% (n=5) felt it 'considers' whereas 10% (n=1) felt it 'does not consider at all'.

Table 36: P&T Committee members' satisfaction with new approach (n = 10)

The approach is	**Response**
Fully satisfactory	10%
Somewhat satisfactory	30%
Satisfactory	40%
Fairly satisfactory	10%
Not at all satisfactory	10%

The majority of the respondents (80%, n=8) rated the new approach as satisfactory to fully satisfactory.

Advantages and Disadvantages of Proposed Approach

The major advantages of the approach as perceived by the committee members are tabulated in Table 37.

Table 37: P&T Committee members' opinion on major advantages of new approach (n = 10)

Major Advantages	Response		
	Yes	No	Not Sure
Comprehensive	70%	10%	20%
Objectively attends decision at hand	80%	0%	20%
Raises pertinent issues for a wider perspective to decision	90%	10%	0%
Conducts sensitivity analysis for more robust decision	50%	20%	30%
Quantifies in economic terms the impact of a particular decision	70%	10%	20%
All of the above	80%	0%	20%

Overall, most of the committee members were very positive about the many advantages that the approach can bring to the formulary decision-making process.

As to the major disadvantages perceived with the approach used by the researcher (Table 38), 50% of the committee members felt that the current lack of technical expertise would be the major impedance in applying the approach in the current environment.

Table 38: P&T Committee members' opinion on major disadvantages of new approach

Disadvantages	Response		
	Yes	No	Not Sure
Approach is too roundabout	10%	70%	10%
The report is far too long	30%	40%	30%
Leaves no room for personal experience	30%	50%	20%
Requires special expertise that may be lacking at the moment	50%	40%	10%

Half of the respondents would recommend that the approach recommended by the researcher be followed for all drug evaluations. Of the 20% (n=2) who felt otherwise, 10% (n=1) felt that it should be reserved for 'some difficult to evaluate' products and not be used for all the

evaluations. However, 30% (n=3) of the respondents are not sure if such a process needs to be followed for all drug evaluations.

Conclusions

From the above results it may be reasonably concluded that all the members consider a P&T Committee indispensable. However, there seemed to be no unanimity regarding the most important objective of the committee. Formulary decisions appeared to be the decisions made most often by the committee but there seemed to be no agreement on what a 'formulary' meant to them. Majority of respondents however, considered it to be an "essential drug list". Pharmacoeconomic viewpoint was considered to add value to P&T Committee decisions by the majority of the members. This is congruent with the finding that a majority of the P & T Committee members at NUH felt that health economists had to be 'must be' members of the P&T Committee though there was some amount of non-surety about the idea. Three factors cited as being most important to be considered when including/deleting drugs to and from the formulary included safety, cost-effectiveness and cost. However, only one-fifth of the respondents felt that the NUH approval process considered all the factors. An attempt was made to clarify their concepts of 'cost' and 'cost-effectiveness' in a later question. There did not seem to be an agreement on what the terms should mean. Most respondents felt that each term meant more than one thing. However, everyone agreed on what the prerequisites for good review of a product should be. Generally, a majority of the respondents felt that the literature search of the evaluator was 'good' and majority opined that the evidence presented by the evaluator was of 80-90% relevance. The approach presented by the evaluator was rated from 'useful' to 'very useful' by 80% of the respondents. Again, the approach presented by the evaluator was rated from 'satisfactory' to 'fully satisfactory' by 80% of the respondents. A good majority of the respondents felt that the approach used by the evaluator offered all the advantages listed in the questionnaire. These advantages included, 'Comprehensive',

'Objectively attends decision at hand', 'Raises pertinent issues for a wider perspective to decision', 'Conducts sensitivity analysis for more robust decision', and 'Quantifies in economic terms the impact of a particular decision'. A major disadvantage perceived by half of the respondents was, that the new approach required special expertise that may be lacking at the moment. Only one respondent felt that this approach was not to be followed for drug evaluations at all. However, a majority of respondents felt that it must be followed for all or at least the 'difficult-to evaluate' drugs. The rationale in concluding that it was a "majority" was that 50% (n=5) answered in the affirmative ("yes") when asked if they would be willing to use the approach in all evaluations, 30% (n=3) not sure and only 20% (n=2) said a definitive "no"; therefore the people who wanted to recommend it were more in number. As for the support to the claim in being able to reasonably demonstrate the role of pharmacoeconomics in the formulary setting (given the constraints in time) there are other findings expressing "satisfaction" with the pharmacoeconomic analyses submitted to the committee, which corroborate the aforementioned claim. A majority of the members were satisfied with a number of facets used in the actual process of evaluations – leading to the belief that a good job was indeed done. Examples include: 90% of the respondents felt that the literature search of the evaluator was 'good' to "very satisfactory"; 80% of respondents felt that evidence presented in the evaluation was of the order 80-90% or> 90% relevance; the new approach to drug evaluation presented by the evaluator was rated 'useful', 'quite useful' and 'very useful' by 20%, 50% and 10% of the respondents respectively; the majority of the respondents (80%) rated the new approach as "satisfactory to fully satisfactory".

It seemed reasonable therefore to conclude that in totality the majority of respondents was supportive of the approach.

Comparison of the traditional role of the P&T Committee as published in the literature and the role of the P&T Committee at the NUH

Though the specific objectives of P&T Committees vary from one institution to another, the broad goals based on the literature, seem to be to ensure high-quality drug therapy for hospital patients, provide advice to the medical staff on the most safe and appropriate therapy for disease conditions treated at the hospital, provide liaison between the medical staff and the pharmacy services. To meet these responsibilities, the P&T Committee maintains a formulary of medications approved for routine patient care, reviews drug use and adverse drug reactions, and establishes procedures for prescribing, dispensing and administering drugs in the hospital. Traditionally, P&T committees have focused on drug safety, efficacy and acquisition costs when considering a request for formulary addition. In times of economic constraint, the primary objectives of a P&T Committee are usually seen to be to appropriately select medications and promote their rational use while attempting to minimize institutional expenditures.

The P&T committee at the NUH also seems to be catering to similar objectives. The formulary minimizes duplication of therapeutic agents by including selected medications that are representative and superior or equivalent to other available agents, according to the assessment of the committee members after consultation with the medical staff. Physicians are guided in their prescribing by the formulary, which, tries to include a broad but minimally duplicative list of therapeutic agents. To be responsive to the needs of the medical staff, the committee welcomes new drug additions but tries to carefully base its evidence on what it considers sound clinical reports or data from reliable sources. Since it is not the intent of the P&T Committee to prevent the use of drugs uniquely important for the care of a particular patient such drug may be obtained on a non-formulary basis. A proposed drug is not admitted to the formulary if the committee judges that meaningful therapeutic, pharmaceutical, or "cost" advantage over similar agents already available on the formulary is lacking. However, these "cost" considerations are increasingly being replaced by "economic" considerations in

an increasing number of P&T committees in major developed nations across the world. Increasingly pharmacoeconomic assessments when evaluating formulary requests are being taken into consideration. This is where the NUH P&T committee seems to lag behind. It would definitely do better to incorporate pharmacoeconomics more routinely into its formulary decisions and make more scientifically rational and defensible decisions.

SECTION 10. CONCLUSIONS

In order for getting towards an overall conclusion about the research objective to evaluate the role of pharmacoeconomics in formulary decision-making – the researcher would suggest a three-step review of the findings through the duration of the project:

10.1 The exploratory surveys conducted among pharmacists and pharmacy managers – this step served to identify and analyse the status quo perception and utility of the formulary (whether a list of cheapest drugs or otherwise) among decision-makers and other involved parties. These surveys established what the respondents felt the formulary was and whether there was any need for decision support

10.2 The attendance of the researcher at the NUH P&T Committee meetings – with the baseline practice for formulary decision-making established through the surveys, this step served to validate and further build on the survey findings with first hand observation of the process, influence, motivations, logic and strategic and tactical approach used in selection of drugs in a real hospital setting in Singapore. The researcher observed the proceedings at a few official meetings and built an understanding of the current process and further identified areas where pharmacoeconomics would significantly add value to the quality of the decision made.

10.3 Evaluation of the researcher's contribution done by the NUH P&T Committee members – building further on the findings from the two earlier steps this feedback established the degree of perceived benefits and willingness for adoption of pharmacoeconomic principles and methods, at least in the NUH.

Almost all the institutions had a 'formulary' or 'drug list' of some kind. With a clear mandate against the formulary being a list of cheapest alternatives it was evident that the formulary was perceived to be much more than a mere instrument for cost-control. The ideal formulary

was expected to promote the use of the "best" drug or 'cost-effectiveness' in treatment' while also attaining the objective of controlling the hospital budget.

Therefore, the fact that the formulary was perceived as an instrument for promoting effective drug use while also considering the issue of cost-control clearly showed that there was a need for pharmacoeconomics in formulary decisions. However, such a need was not explicitly stated. This could most possibly be attributed to the fact that P&T Committee members are probably not very familiar with this relatively new and evolving discipline. However, no study was made in this respect (i.e. familiarity of the NUH P&T Committee members with the discipline of 'pharmacoeconomics'). Formulary restriction, nevertheless, was ranked to be the most effective method for cost-control. However, in the survey of the pharmacist, no association/ correlation could be found between years and area of practice of the respondents and their knowledge about factors considered for formulary decision-making.

The researcher observed a series of P&T Committee meetings at the NUH which varied in the degree of attendance but were generally directed towards a consensus oriented systematic approach towards a significant number of issues related to health care delivery and costs at the hospital. The drug evaluation process for inclusion into or exclusion from the formulary starts with a search of relevant literature and expert views and recommendations for drugs to be used in specialist setups. However, the researcher observed that though the literature search covered most widely accepted medical databases – there is no critical review of clinical information in comparative trials and no meta-analysis of data from several smaller trials.

The researcher keenly observed the initial effort and willingness of the committee members to further strengthen the process of decision-making with more comprehensive approach balancing clinical efficacy and safety benefits with cost to the hospital or payers. The approach to the final decisions took the form of a consensus representing as far as possible the major departments of the hospital. Instead of coercing doctors to restrict usage the committee

felt it was better to educate them on that front. Formulary inclusions were trying to be rationalized from both clinical and budget impact point of view (though this was a bit crude) and requests for such inclusions also needed to be justified. The need for a more thorough evaluation of requests for formulary inclusion was clearly expressed, at least in so far as the expensive products were concerned. In fact, treatment (especially drug use) guidelines were already in place for certain conditions. Though these were rough instructions on which drugs to use in certain conditions and in what manner and were solely based on practice of experts in the respective areas, at least they signified some interest in the direction of framing appropriate clinical practice guidelines. Hence there definitely is an important role that pharmacoeconomics can play in this setup.

P & T committees in the hospitals surveyed were by far believed to be the final decision makers for drug inclusion/ exclusion in the formulary. Different questions posed to the NUH P&T Committee members revealed that a majority of respondents considers it the duty of the committee to facilitate efficient management of the hospital as an investment portfolio and not simply review the formulary at intervals. In addition, the willingness to accept pharmacoeconomic principles for a more informed and effective decision-making process was further ratified by the recommendation of a substantial majority of members that 'health economists' should be "must-be" members of the P&T Committee, together with 90% claiming that pharmacoeconomic analyses add value to their decisions.

The most important factors for drug inclusions so far as the committee members were concerned were safety and cost-effectiveness. The term cost-effectiveness to them signified either "an optimizing of clinical efficacy, economic impact and patient rated health related quality of life' or "value for money". To none of them did the term imply "cheap". The most important bases for their decisions were a review of clinical literature and expert opinion. Everyone agreed that the prerequisites to a good review were extensive literature search, proper interpretation of trial data, compilation of relevant evidence and good presentation. The researcher's approach was considered 'useful' to 'very useful' and the literature search

'satisfactory' to 'fully satisfactory'. The most important advantages of the approach followed by the researcher, in the view of the members, were that the approach raises pertinent issues for a wider perspective to the decision and objectively attends the decision at hand. However, a majority felt that such an approach required special expertise that may be lacking at the moment. In fact, most of the members felt that this approach could be followed for all or at least the difficult-to-evaluate drugs.

Based on such findings it may be reasonably inferred that the researcher was successful in adequately demonstrating to the relevant decision-makers the role of pharmacoeconomics in formulary decisions. They would even be willing to adopt such an approach but for the lack of appropriate expertise.

Therefore, it can be concluded from these findings that there exist a desire and demand, if not explicitly, but certainly covertly for the application of PE in the formulary decision process.

SECTION 11. RECOMMENDATIONS TO FURTHER STRENGTHEN THE FORMULARY DECISION-MAKING PROCESS AT THE NUH

It is increasingly important that P&T Committees base their decisions not only on the usual clinical considerations and acquisition costs but other outcome measures such as quality of life. This is because the future role of the P&T Committee may be quite different from its past and present. Future roles may include assessment of clinical outcomes information for various treatment alternatives, prospective continuous quality improvement (CQI) for current therapeutic recommendations and the establishment of policies governing the use of drugs at all levels and in all types of care.[113]

As such, the NUH P&T Committee may also have a substantially different role to perform in the future, in the context of the changing demography of the health care sector. In order that the formulary decision-making process may be more responsive to changing needs of health care delivery in general and the institutional operation in particular. Therefore, it is recommended that the NUH consider taking some necessary steps. These are:

1. Standard guidelines for effectively managing the formulary in particular should be drawn. These guidelines must look beyond efficacy by incorporating both economic and financial analyses for drug evaluation and approval.

2. Based on the above guidelines development of appropriate models to consistently evaluate cost-effectiveness of drugs or therapeutic interventions is urgently needed

3. The P&T Committee should explicitly base formulary decisions on cost-effectiveness information obtained from such models. This would ensure active usage of cost-effectiveness information.

It is quite unlikely that the NUH with its limited buying power could ever require mandatory pharmacoeconomic evaluations to be submitted by pharmaceutical manufacturers (as in

Australia) for all products submitted for formulary listing. The best the committee could do is to draw certain guidelines that would formalise information requirements for anyone making requests for formulary inclusions and set methodological standards for evaluating those formulary submissions. In particular, such guidelines should try to encourage consideration of a 'value' dimension when evaluating pharmaceutical interventions for listing. The pursuit of effectiveness alone, regardless of cost, can deprive other patients of care from which they would benefit more. Such care may be clinically effective but is inefficient and unethical.[111] Health care systems as drug purchasers should link evidence of cost-effectiveness to potential formulary inclusions. In an increasingly fiscally conscious milieu, unless such a stance is adopted, issues such as technical and economic efficiency in health care delivery cannot be addressed. A rational heath care system is one that finances expensive alternatives to existing therapeutic interventions only if such alternatives bring in additional benefits worth the extra costs. Not ensuring that such an approach is strictly followed will increase inefficiencies in the system.

The purpose should be to rationalise the inclusion of drugs on the formulary from both clinical and economic perspectives thereby ensuring judicious allocation of health care resources and ultimately facilitating the development of disease management approach to treating different health conditions. In this context, a standard procedure for evaluation of pharmaceuticals should include -

- A sound clinical evidence
- Economic impact of decisions
- The financial impact of decisions to include or withdraw drugs to / from the formulary

For developing the aforementioned standard procedure, the NUH may borrow from the various guidelines (e.g. Australian and Canadian Guidelines). In addition, the Formulary

Submission Guidelines for Blue Cross and Blue Shield of Colorado and Nevada may also be consulted.[111] These guidelines framed from the perspective of a health system concerned with its survival in an increasingly competitive environment might provide some valuable input to the framing of the NUH formulary submission evaluation procedure.

The NUH being uninitiated in the conduct and use of economic analyses, the researcher suggests that they first get used to identifying outcomes (both intermediate and final) and linking these outcomes obtained to the expenditure incurred. This process would enable an understanding of outcomes obtained for money spent (cost-effectiveness) or more appropriately incremental benefits (in the form of improved and/or more outcomes) for additional expenditure. These outcomes may be derived from reports of well-controlled randomised clinical trials or a meta-analysis of several small trials. This, the researcher recommends even while realising that randomised clinical trials do not give any idea of the effectiveness of products when used in practice but only give us a picture of efficacy (how the drug behaves under optimal conditions). This is because, reports of clinical trials are the easiest to obtain and are more readily accepted by medical professionals. Once the approach falls into place, the researcher recommends that adjustments to the clinical trial data be made in order to replicate the effect of actual practice conditions.

Comparing the drug to be evaluated with the range of comparators used normally in practice is another point worth remembering.

A point that seems noteworthy is, simply presenting cost-outcome ratios and judging cost-effectiveness not anchored to treatment targets and budget allocations within treatment areas will not be sufficient.[118] It is important to track and monitor patient outcomes. This would help the development of treatment guidelines for the optimal use of drugs and set into place procedures for the managed introduction of expensive new medicines.

A budget may be set aside to conduct institution-specific pragmatic outcome studies for certain critical drugs on a limited number of patients. These studies must aim to verify

sufficient cost-effectiveness for the new products to justify subsequent spending. Such studies can be very expensive and must be restricted to those drugs for which costs of such studies can be justified, i.e. for which costs of such studies are far less than the costs of unrestricted entry into the formulary.

Consideration of economic consequences of decisions on drug treatment would help meet the health needs of the population treated by the hospital, more efficiently and ensure good justification of the hospital pharmacy budget. This consideration would mean using of pharmacoeconomics to arrive at various treatment and service use decisions. A particularly useful step in this regard could be to set up and maintain a drug evaluation unit (employing one or more pharmacoeconomists) that would aid and augment the services of the Drug Information Services currently in operation at the hospital especially with respect to formulary decisions.

A rational health care system is one that finances expensive alternative to existing therapeutic interventions only if such alternatives bring in additional benefits commensurate with the additional expenditure and if these benefits are really 'needed'. Not ensuring that such an approach is strictly followed will increase inefficiencies in the system. In order that the NUH may successfully run as an efficient health care delivery centre, adoption of the pharmacoeconomic approach to major product and service use decisions is definitely imperative.

SECTION 12. LIMITATIONS OF THE CURRENT STUDY AND SUGGESTIONS FOR FURTHER RESEARCH

As with most other pioneering exploration, this research study also has had limitations that leave significant opportunities for further exploration in the determination and establishment of the critical role pharmacoeconomics could play in formulary decision-making.

12.1 Direct budgetary and fiscal impact: An objective measure of the success of the project would have been an assessment of the impact of the formulary decisions based on pharmacoeconomic evaluations on the potential and/or actual cost savings to the organization. However, such information being contingent on the evaluations being performed consistently for at least one fiscal year could not be gathered. Hence lack of time permitted little objective analysis of the impact on direct cost and healthcare delivery efficiency. Furthermore, trend evaluations and chronological comparisons could not be performed.

12.2 Benchmarking: Again owing primarily to the time schedule of the project, the researcher was unable to establish a nationwide perspective for the practicing hospitals with respect to the impact of pharmacoeconomics in formulary decision-making. Practice comparisons could not be made in-depth across all major healthcare providers in Singapore and hence a national picture could not be established.

12.3 Best practices in a healthcare hub: With Singapore aspiring to become a hub for the life sciences for the Asia Pacific region – the researcher believes it could have been an interesting value-add to the research findings if benchmarking information with formulary decision making practices from other similar or more developed economies could have been obtained and incorporated. Such information would likely contribute significantly in establishing best practices for Singapore for utilizing pharmacoeconomics in a better justification of use of public healthcare dollars.

12.4 Pharmacoeconomic principle based guidelines – another potential scope for research is offered by the lack of clinical guidelines for treatment (drug use) based on pharmacoeconomic principles.

12.5 Lack of awareness of the principles and the potential benefits offered by pharmacoeconomics left room for significant skepticism and hence posed as a barrier to the early start of the project and therefore to even more extensive research findings to some extent. With some convincing demonstration of the role of pharmacoeconomics to the NUH P&T Committee at least further research may take off from where this researcher left. By following the same procedure for a longer period of time, tangible impact on the budget or the number of formulary approvals in the hospital may be demonstrated. Helping make effective drug decisions and thereby pruning the formulary may achieve more efficient use of the hospital budget and better inventory control.

12.6 Standard guidelines and operating procedures for drug evaluation and approval set forth, explicit criteria for admission of new products and thereby ensure uniformity in drug selection. By requiring justification of a new product on both clinical and economic grounds by a comprehensive assessment of the therapy's benefits to patients and its costs to the health care system, the guidelines incorporate an extra 'value' dimension when considering pharmaceutical interventions for subsidization.

12.6.1. Scope for further research is offered in the area of development of such guidelines for evaluating formulary submissions at the NUH. Such guidelines apart from contributing to developing a standard procedure for evaluation of pharmaceuticals for formulary decisions at the NUH would also serve to set an example for other health care institutions in Singapore.

It is the hope of the researcher that this research would be continued further to add to and/or improve upon the findings of the current project and also that tangible action would be taken based on the available data to contribute to the efficient management of

the formulary resulting in more cost-effective treatments for patients and better management of the hospital budget. If this research could contribute to improving the formulary decision-making process at least in the institution the researcher will consider herself to have served some useful purpose.

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APPENDIX 1
Survey Questionnire-Pharmacists

Dear Sir/Madam,

Subject: Survey of pharmacists working in public hospitals in Singapore

One of my post-graduate research students Ms.Anuja Nidumolu Roy (Pharmacy) is conducting a research project to study the scope and application potential of pharmacoeconomics in hospitals in Singapore, under my guidance at the National University of Singapore.

The study methodology requires opinion of pharmacists working in different hospitals on issues addressed by the questions. The study is purely for academic purposes and has in no way any business interests associated with it. The co-operation of each of you would help in the successful completion of the research project, thereby also leading to the attainment of a higher degree by Ms.Roy. In addition, it would also provide useful background information for policy makers to decide on training of pharmacists.

It is in the aforesaid interests therefore, that I seek some of your valuable time to complete the questionnaire as soon as possible. If you need any clarification on the project, please do not hesitate to contact Ms.Roy on 8743120. All information provided by you will be treated confidentially. Any results, if published, will not reveal individual information.

Thank you.

In anticipation of your co-operation, I remain.

Sincerely yours,

Li Shu Chuen

Survey of hospital pharmacists in Singapore

Respondent particulars Code:

Institution

Name **Contact no.**
(For clarifications, if any)

Age **<25** **25-35** **35-45** **>45**

Race **Chinese** **Malay** **Indian**
other

Sex **Male €** **Female €**

No. Of years in practice **<5** **5-10** **11-20** **>20**

No. Of years since graduation **<5** **5-10** **11-20** **>20**

Areas of practice **Outpatient** **Purchase management**
Clinical specialist **Other(s), please specify**

Previous area of practice (if applicable)
Retail **Wholesale**
Other(s)

Are you a member of the P&T committee of your institution?
Yes **No**

Have you ever been a member of any P&T committee before?
Yes **No**

Questionnaire

1) **How many beds does your hospital have?**

   <100 100-199 200-499 500-999 >999 No idea

2) **How would you classify your institution?**

   Primary/Community hospital Secondary Referral Hospital

   Tertiary Hospital Specialist Hospital

3) **Do you have any idea regarding the average annual expenditure on drugs in your institution?**

   Yes No

4) **Do you think the expenditure is too high?**

   Yes No Cannot say

5) **If your answer to Qs.4 is no, what would your answer be in the light of increasing proportion of ageing population and rising drug costs?**

   Yes No Cannot say

6) **Have you heard of the following terms?**

Supply Restriction	**Yes**	**No**
Formulary Restriction	**Yes**	**No**
Reference Pricing	**Yes**	**No**
Prescription regulation/monitoring	**Yes**	**No**
	(*continued*)	
DRG	**Yes**	**No**
Fund holding	**Yes**	**No**

Capitation	**Yes**	**No**

7) Which of the following ways would you consider important in helping to control drug costs? Please rank them (if you have chosen more than one).

	Y	**N**	**Rank**
• **Formulary Restriction**	—	—	—
• **Prescription regulation/monitoring**	—	—	—
• **Reference pricing**	—	—	—
• **DRG**	—	—	—
• **Fund Holding**	—	—	—
• **Capitation**	—	—	—
• **Supply Restriction**	—	—	—
• **Any others (please specify)**	—	—	—

8) Why would you recommend the aforementioned method?

- ❑ **Forces prescribers to adhere to authority guidelines**
- ❑ **Forces prescribers to work within a limited /pre-assigned budget**
- ❑ **A scientifically determined price**
- ❑ **Confers responsibility on the fund-holder to manage funds more effectively**
- ❑ **Limits choice of drugs**
- ❑ **Any other(s), please specify**

\

9) Does your institution have a 'formulary of drugs' or a "drug list"?

Yes No Cannot say

10) In your opinion, a formulary (or a drug list) is

- **A list of the most essential drugs**
- **A list of the most expensive drugs**
- **A list of the most used drugs**
- **A list of the cheapest alternatives**
- **Any other, please specify**

11) In your opinion which of the following functions should an "ideal" formulary serve (maybe more than one)?

- **In subsidizing life-saving medicines**
- **In promoting the use of the best drug or intervention**
- **In restricting the use of drugs**
- **In controlling the hospital budget**
- **Any other, please specify**

12) Does your hospital formulary serve the aforementioned purpose(s) to your satisfaction?

Yes No Cannot say

13) What reasons would you assign to your choice of answer to Qs.12?

- **The formulary is too open**
- **It includes drugs solely on the basis of costs**
- **It does not consider the quality of drugs included in it**
- **Do not know how the decisions are made**

- **Any other(s), please specify**

14) Who makes the final decisions with respect to inclusion/exclusion of drugs in the formulary?

Hospital administration **Medical specialist(s)** **Pharmacy**

P&T committee **Other(s) please specify**

15) Do you know what factors are considered in the above approval process?

Yes **No**

16) Which of the following factors would you consider in the formulary decision-making process? Please rank them in order of importance.

	Y	N	Rank
Effectiveness of the drug	€	€	**-----**
Acquisition cost	€	€	**-----**
Available alternative	€	€	**-----**
Politics	€	€	-----
Pharmacy/Drug budget	€	€	**-----**
Hospital budget	€	€	-----
Safety	€	€	**-----**
Any other(s), please specify	€	€	**-----**

(*continued*)

17) If you were asked to use pharmacoeconomics to assist in formulary decision-making how confident are you

Not confident €

Somewhat confident €

Very confident €

Know nothing about the subject €

Thank you

APPENDIX 2
Pharmacist Responses

INSTITUTION	CGH											
No of responses	8											
Respondent code:	**CGH 1**	**CGH 2**	**CGH 3**	**CGH 4**	**CGH 5**	**CGH 6**	**CGH 7**	**CGH 8**				
Parameters												
									25	***25-35***	***35-45***	***45***
Age	25	25-35	35-45	35-45	25	35-45	25-35	25-35	25%	38%	38%	0%
									C	***O***		
Race	C	C	C		C	C	C	C	100%	0%		
									M	***F***		
Sex	F	F	M		F	F	F	F	14%	86%		
									5	***5-10***	***11-20***	***20***
No. of yrs. in practice	5	5	5-10	11-20	5	5-10	5	5	63%	25%	13%	0%
									5	***5-10***	***11-20***	***20***
No. of yrs. Since graduation	5	5-10	5-10	11-20	5	11-20	5	5	50%	25%	25%	0%
									OP	***IP***	****Cli****	****Lab****
Area of practice	OP	Aseptic dispensin	IP,OP, Purchase	OP	OP	Other	IP	IP	38%	25%	0%	0%
									*****Ret*****	***Hosp*****	*****Whole*****	***O***
Previous area of practice	NA	NA	Retail	Retail	NA	Retail	NA	NA	38%	0%	0%	0%
									Y	***N***		
Member of the P&T committee	N	N	N	N	N	N	N	N	0%	100%		
									Y	***N***		
Any previous experience in the P&T	N	N	N	N	N	N	N	N	0%	100%		
									100	***100-199***	***200-499***	***500-999***
Knowledge about no. of beds	500-999	500-999	500-999	500-999	500-999	500-999	500-999	500-999	0%	0%	0%	100%
									Primary	***Secondary***	***Tertiary***	***Specialist***
Knowledge about type of institution	Secondary	Tertiary	Secondary	Specialist	Tertiary	Secondary	Tertiary		0%	43%	43%	14%
									****Y****	****N****		
Idea of Average annual drug expenditure	N	N	N	Y	N	N	N	N	13%	88%	100%	
									Y	***N***	***Can't say***	
Whether exp. is too high	Can't say	N	Can't say	Can't say	Can't say		Y	Can't say	14%	14%	71%	100%
									Y	***N***	***Can't say***	***NA***
Idea about annual exp. (too high/not) given the facts of ageing population and rising drug costs		Can't say			Can't say		NA		0%	0%	67%	33%
Acquaintance of the following terms;												
									****Y****	****N****		
Supply restriction	Y	N	Y	Y	Y	Y		Y	86%	14%	100%	
									****Y****	****N****		
Formulary restriction	N	Y	Y	Y	Y	Y	Y	Y	88%	13%	100%	
									****Y****	****N****		
Reference pricing	N	N	Y	Y	Y	N		N	43%	57%	100%	
									****Y****	****N****		
Prescription regulation/monitoring	Y	N	Y	Y	Y	Y	Y	Y	88%	13%	100%	
									****Y****	****N****		
DRG	Y	Y	Y	Y	Y	Y	Y	Y	100%	0%	100%	
									****Y****	****N****		
Fund holding	N	N	N	Y	Y	N		N	29%	71%	100%	
									****Y****	****N****		
Capitation	N	N	N	N	Y	N	Y	N	25%	75%	100%	
Which approach cosidered important for controlling drug costs												
									1	***2***	***3***	***4***
Formulary restriction	3	1	1	1		NR	2	1	57%	14%	14%	0%
									1	***2***	***3***	***4***
Prescription regulation/monitoring	1		4	3				2	25%	25%	25%	25%
									1	***2***	***3***	***4***
Reference pricing			2	5			3		0%	33%	33%	0%
									1	***2***	***3***	***4***

INSTITUTION	KKH												
No of responses	13												
Respondent code:	**KKH 1**	**KKH 2**	**KKH 3**	**KKH 4**	**KKH 5**	**KKH 6**	**KKH 7**	**KKH8**	**KKH9**	**KKH10**	**KKH11**	**KKH12**	**KKH13**
Parameters													
Age	25-35	35-45	25-35	25-35	25-35	25-35	35-45	25-35	45	25	25-35	25-35	25
Race	C	C	C	C	C	C	C	C	C	C	C	C	C
Sex	F	F	F	M	F	F	F	F	M	F	M	F	F
No. of yrs. in practice	5	5	5	5	5-10	5	5	5	20	5	5-10	5	5
No. of yrs. Since graduation	5	5	5	5	5-10	5	11-20	5	20	5	11-20	5	5
Area of practice	Info mgmt	Cli Spe	Cli Spe	O(DIS)	OP	OP	OP	IP	Purchase	OP,IP	Cli Spe	IP	OP
Previous area of practice	O	NA	NA			NA	Retail	NA	Retail	NA	Wholesale	Retail	Retail
Member of the P&T committee	N	N	N	Y	N	N	N	N	N	N	N	N	N
Any previous experience in the P&T	Y	N	N	Y	Y	N	N	N	N	N	N	N	N
Knowledge about no. of beds	500-999	500-999	No Idea	500-999	500-999	500-999	500-999	500-999	>999	>999	500-999	500-999	No idea
Knowledge about type of institution	Specialist	Specialist	Specialist	Tertiary	Specialist	Specialist	Specialist	Specialist	Specialist	Specialist	Specialist	Specialist	Specialist
Idea of Average annual drug expenditure	Y	N	N	Y	N	N	N	N	Y	N	N	N	N
Whether exp. is too high	Can't say	Can't say	Can't say	Y	Can't say	Can't say	Y	Can't say	N	Can't say	Can't say	Can't say	Can't say
Idea about annual exp. (too high/not) given the facts of ageing population and rising drug costs		Y	Can't say	NA	Can't say	Can't say	NA	Can't say	Can't say	Can't say	Y		N
Acquaintance of the following terms;													
Supply restriction	Y	N	Y	N	N	N	N	Y	Y	N	Y	N	N
Formulary restriction	Y	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	Y
Reference pricing	Y	Y	Y	Y	N	N	N	N	N	Y	Y	N	N
Prescription regulation/monitoring	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y
DRG	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Fund holding	N	Y	N	N	N	N	N	N	N	N	Y	N	N
Capitation	Y	Y	N	N	N	N	N	N	Y	N	N	Y	Y
Which approach cosidered important for controlling drug costs													
Formulary restriction	1	2	1	3	2		1	2	1	3	2	2	3
Prescription regulation/monitoring		1	3	2	3	1	2	1	4	2		1	1
Reference pricing			4				3			4			

INSTITUTION	NUH												
No of responses	11												
Respondent code:	**NUH 1**	**NUH 2**	**NUH 3**	**NUH 4**	**NUH 5**	**NUH 6**	**NUH 7**	**NUH 8**	**NUH 9**	**NUH 10**	**NUH 11**		
Parameters													
												25	***25-35***
Age	25-35	25-35	25-35	35-45	25-35	25	25-35	25-35	35-45	25-35	25-35	9%	73%
												C	***O***
Race	C	O	C	C	C	C	C	C	C	C	C	91%	9%
												M	***F***
Sex	F	M	F	M	F	F	F	F	M	F	F	27%	73%
												5	***5-10***
No. of yrs. in practice	5	11-20	5	11-20	5	5	5	5-10	11-20	5-10	5	55%	18%
												5	***5-10***
No. of yrs. Since graduation	5	11-20	5	20	5-10	5	5	5-10	11-20	5-10	5	45%	27%
												OP	***IP***
Area of practice	IP	Cli Spe	IP	OP	CTU	OP	Cli Spe	Purchase	Cli Spe	Lab	OP	27%	18%
												*****Ret*****	***Hosp*****
Previous area of practice	NA	NA	Retail	O	O	NA	NA	Retail	Retail	Retail, IP	NA	36%	0%
												Y	***N***
Member of the P&T committee	N	N	N	N	N	N	N	N	N	N	N	0%	100%
												Y	***N***
Any previous experience in the P&T	N	Y	N	N	N	N	N	N	Y	N	N	18%	82%
												100	***100-199***
Knowledge about no. of beds	999	500-999	500-999	999	500-999	500-999	500-999	500-999	500-999	999	500-999	0%	0%
												Primary	***Secondary***
Knowledge about type of institution	Tertiary	Tertiary	Tertiary	Tertiary	Tertiary		Tertiary	Tertiary	Tertiary	Tertiary	Tertiary	0%	0%
												****Y****	****N****
Idea of Average annual drug expenditure	N	N	N	Y	N	N	N	Y	Y	N	N	27%	73%
												Y	***N***
Whether exp. is too high	NA	Y	Can't say	N	Can't say	Y		Can't say	N	Can't say	Can't say	20%	20%
												Y	***N***
Idea about annual exp. (too high/not) given the facts of ageing population and rising drug costs	Y	NA		N	NA	NA			Can't say	Y		29%	14%
Acquaintance of the following terms;													
												****Y****	****N****
Supply restriction	N	N	N	N	N	Y	Y	N	Y	N	Y	36%	64%
												****Y****	****N****
Formulary restriction	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	91%	9%
												****Y****	****N****
Reference pricing	N	Y	N	N	N	Y	N	Y	Y	N	N	36%	64%
												****Y****	****N****
Prescription regulation/monitoring	N	Y	Y	N	N	Y	N	N	Y	N	Y	45%	55%
												****Y****	****N****
DRG	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100%	0%
												****Y****	****N****
Fund holding	N	N	N	N	N	N	N	N	N	Y	N	9%	91%
												****Y****	****N****
Capitation	N	Y	N	N	N	N	N	N	Y	Y	N	27%	73%
Which approach cosidered important for controlling drug costs													
												1	***2***
Formulary restriction	NR	2	NR		1	1	2	1	4	2	4	30%	30%
												1	***2***
Prescription regulation/monitoring		1	NR			4	3		2	3	2	14%	29%
												1	***2***
Reference pricing		NR				3	1					33%	0%
												1	***2***

INSTITUTION	SGH														
No of responses	29														
Respondent code:	**SGH 1**	**SGH 2**	**SGH 3**	**SGH 4**	**SGH 5**	**SGH 6**	**SGH 7**	**SGH 8**	**SGH 9**	**SGH 10**	**SGH 11**	**SGH 12**	**SGH 13**	**SGH 14**	**SGH 15**
Parameters															
Age	25-35	35-45	25-35	35-45	35-45	25-35	25-35	25-35	25-35	45	25-35	35-45	25-35	25	25-35
Race	C	C	O	C	C	C	C	C	C	C	C	C	C	C	C
Sex	F	F	M	M	F	M	F	F	M	F	F	M	F	F	F
No. of yrs. in practice	5-10	11-20	5-10	11-20	11-20	5-10	5	5	5-10	20	5	11-20	5	5	5
No. of yrs. Since graduation	5-10	11-20	5-10	11-20	11-20	5-10	5	5	5-10	20	5-10	11-20	5	5	5
Area of practice	Lab	OP	IP	Purchase	OP	OP, Cli Spe	OP, Lab	Hosp	IP	Ret	IP	OP	OP	OP	OP
Previous area of practice	O	O	Retail	NA	Retail	NA	NA	NA	NA	Hosp pharmacy	NA	O	NA	O	O
Member of the P&T committee	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Any previous experience in the P&T	N	N	N	Y	N	N	N	N	N	Y	N	N	N	N	N
Knowledge about no. of beds	999	999	999	999		999	100-199	999	999	999	999	999	999	999	999
Knowledge about type of institution	Tertiary	Tertiary		Tertiary	Specialist	Tertiary	Tertiary	Tertiary	Tertiary	Tertiary	Tertiary	Tertiary	Tertiary	Tertiary	Tertiary
Idea of Average annual drug expenditure	N	N	N	Y	N	N	Y	N	N	N	N	N	N	N	N
Whether exp. is too high	Can't say	Y	Can't say	N	Can't say	Y	Y	Can't say	Can't say	Can't say	Can't say	N	Can't say	Can't say	Can't say
Idea about annual exp. (too high/not) given the facts of ageing population and rising drug costs	Y	NA	Can't say	Y	NA	NA	NA	Can't say	NA	Can't say	Can't say	Y	Can't say	NA	Can't say
Acquaintance of the following terms;															
Supply restriction	N	Y	N	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y
Formulary restriction	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	N	N
Reference pricing	Y	N	Y	Y	N	N	N	N	N	N	N	Y	N	N	N
Prescription regulation/monitoring	N	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	N	Y
DRG	Y	Y	N	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	N
Fund holding	N	N	N	Y	N	N	N	N	N	Y	N	Y	Y	N	N
Capitation	Y	Y	N	Y	N	N	N	N	N	N	Y	Y	Y	N	N
Which approach cosidered important for controlling drug costs															
Formulary restriction	1	1	1			3	1	1	1	NR	1	1			4
Prescription regulation/monitoring		2	3			2	3		3	NR	2		NR	3	
Reference pricing		4	2	1				3							

INSTITUTION	TTSH													
No of responses	9													
Respondent code:	**TTSH 1**	**TTSH 2**	**TTSH 3**	**TTSH 4**	**TTSH 5**	**TTSH 6**	**TTSH 7**	**TTSH 8**	**TTSH 9**					
Parameters														
										25	***25-35***	***35-45***	***45***	
Age	25-35	25	25	25	25-35	25-35	25	25-35	25-36	44%	44%	0%	0%	89%
										C	***O***			
Race	C	C	C	C	C	C	C	C	C	100%	0%			100%
										M	***F***			
Sex	F	F	F	F	F	F	F	F	F	0%	100%			100%
										5	***5-10***	***11-20***	***20***	
No. of yrs. in practice	5	5	5	5	5	5	5	5	5	100%	0%	0%	0%	100%
										5	***5-10***	***11-20***	***20***	
No. of yrs. Since graduation	5	5	5	5	5	5	5	5	5	100%	0%	0%	0%	100%
										OP	***IP***	****Cli****	****Lab****	****Pur*****
Area of practice	IP	Satellite	OP	OP	OP	OP	Satellite	Cli Spec	Satellite	44%	11%	11%	0%	0%
										*****Ret*****	***Hosp*****	*****Whole*****	***O***	***NA***
Previous area of practice	Retail	NA	Retail	NA	NA	NA	NA	NA	NA	22%	0%	0%	0%	78%
										Y	***N***			
Member of the P&T committee	N	N	N	N	N	N	N	N	N	0%	100%			
										Y	***N***			
Any previous experience in the P&T	N	N	N	N	N	N	N	N	N	0%	100%			
										100	***100-199***	***200-499***	***500-999***	***999***
Knowledge about no. of beds	999	999	500 - 999		999	999	999	999	No idea	0%	0%	0%	0%	75%
										Primary	***Secondary***	***Tertiary***	***Specialist***	
Knowledge about type of institution	Tertiary	Tertiary	Tertiary	Specialist, Secondary referral	Tertiary	Seconda ry referral	Tertiary	Tertiary	Primary	11%	0%	67%	0%	78%
										****Y****	****N****			
Idea of Average annual drug expenditure	N	N	N	Y	N	N	N	N	N	11%	89%	100%		
										Y	***N***	***Can't say***		
Whether exp. is too high	Can't say	Can't say	N	Can't say	Can't say	Can't say	Can't say	Can't say	Can't say	0%	11%	89%	100%	
										Y	***N***	***Can't say***	***NA***	
Idea about annual exp. (too high/not) given the facts of ageing population and rising drug costs	Can't say		N	Y	Can't say	Can't say	Can't say		Y	29%	14%	57%	0%	100%
Acquaintance of the following terms;														
										****Y****	****N****			
Supply restriction	Y	Y	Y	Y	Y	N	Y	Y	Y	89%	11%	100%		
										****Y****	****N****			
Formulary restriction	Y	Y	Y	Y	Y	Y	Y	Y	Y	100%	0%	100%		
										****Y****	****N****			
Reference pricing	N	N	N	N	N	N	N	N	N	0%	100%	100%		
										****Y****	****N****			
Prescription regulation/monitoring	Y	Y	N	N	N	N	N	N	N	22%	78%	100%		
										****Y****	****N****			
DRG	N	Y	Y	N	N	N	Y	Y	N	44%	56%	100%		
										****Y****	****N****			
Fund holding	N	N	N	N	N	N	N	N	N	0%	100%	100%		
										****Y****	****N****			
Capitation	N	Y	N	Y	N	N	N	N	N	22%	78%	100%		
Which approach cosidered important for controlling drug costs														
										1	***2***	***3***	***4***	***5***
Formulary restriction	1		1	1		1	2	1	1	86%	14%	0%	0%	0%
										1	***2***	***3***	***4***	***5***
Prescription regulation/monitoring	2	2		3						0%	67%	33%	0%	0%

INSTITUTION									
No of responses	70								
Respondent code:									
Parameters									
	25	***25-35***	***35-45***	***45***					
Age	17%	59%	20%	3%	99%				
	C	***O***							
Race	96%	3%			99%				
	M	***F***							
Sex	22%	78%			100%				
	5	***5-10***	***11-20***	***20***		5 = <5, 20= >20			
No. of yrs. in practice	64%	16%	17%	3%	100%				
	5	***5-10***	***11-20***	***20***		5 = <5, 20= >20			
No. of yrs. Since graduation	57%	19%	20%	4%	100%				
	OP	***IP***	****Cli****	****Lab****	****Pur*****	***Others***			
Area of practice	39%	17%	14%	4%	7%	19%	100%		
	*****Ret*****	***Hosp*****	*****Whole*****	***O***	***NA***				
Previous area of practice	29%	1%	1%	12%	56%	100%			
	Y	***N***							
Member of the P&T committee	1%	99%							
	Y	***N***							
Any previous experience in the P&T	11%	89%							
	100	***100-199***	***200-499***	***500-999***	***999***	***No idea***			
Knowledge about no. of beds	0%	2%	0%	39%	47%	8%	95%		
	Primary	***Secondary***	***Tertiary***	***Specialist***					
Knowledge about type of institution	3%	5%	68%	22%	97%				
	****Y****	****N****							
Idea of Average annual drug expenditure	16%	84%	100%						
	Y	***N***	***Can't say***						
Whether exp. is too high	15%	10%	74%	99%					
	Y	***N***	***Can't say***	***NA***					
Idea about annual exp. (too high/not) given the facts of ageing population and rising drug costs	18%	5%	44%	33%	100%				
Acquaintance of the following terms;									
	****Y****	****N****							
Supply restriction	67%	33%	100%						
	****Y****	****N****							
Formulary restriction	84%	16%	100%						
	****Y****	****N****							
Reference pricing	36%	64%	100%						
	****Y****	****N****							
Prescription regulation/monitoring	61%	39%	100%						
	****Y****	****N****							
DRG	77%	23%	100%						
	****Y****	****N****							
Fund holding	19%	81%	100%						
	****Y****	****N****							
Capitation	27%	73%	100%						
Which approach cosidered important for controlling drug costs									
	1	***2***	***3***	***4***	***5***	**6**	**7**	**NR**	
Formulary restriction	57%	19%	10%	7%	0%	0%	0%	7%	100%
	1	***2***	***3***	***4***	***5***	**6**	**7**	**NR**	
Prescription regulation/monitoring	20%	34%	27%	12%	0%	0%	0%	7%	100%
	1	***2***	***3***	***4***	***5***	**6**	**7**	**NR**	
Reference pricing	25%	10%	30%	20%	10%	0%	0%	5%	100%
	1	***2***	***3***	***4***	***5***	**6**	**7**	**NR**	
DRG	32%	41%	14%	8%	0%	0%	0%	5%	100%

APPENDIX 3
Survey Questionnaire – Pharmacy Managers

QUESTIONNAIRE

SECTION 1 :

Information about the Institution

1) **How many beds does your institution possess?**

   <100 100-199 200-499 500-999 >1000

2) **How big is the pharmacy budget of your institution?**

   <10M 10-20M 21-30M >30M

3) **How would you classify your institution?**

   Primary/community Hospital Secondary Referral Hospital

   Tertiary Referral Hospital Specialist Hospital

SECTION 2:

Information about formulary in the institution

1) **Does your institution have a formulary of drugs?**

   Yes/No

2) **If the answer to Qs.1 is yes, how long has the formulary been in existence?**

3) **If the answer to Qs. 1 is no how does your institution decide on what drugs to stock in the pharmacy?**

4) **In your opinion a formulary is:**

   a) **a list of the most essential drugs**

   b) **a list of the most expensive drugs**

   c) **a list of the most used drugs**

   d) **a list of the cheapest alternatives**

   e) **others, please specify**

5) **In your opinion a formulary can serve which of the following functions (maybe more than one)**

   a) **in controlling the hospital budget**

b) in subsidizing life-saving medicines

c) in promoting the use of the best drug or intervention

d) In restricting the use of drugs

e) To promote cost-effectiveness in drug treatment

f) Any others please specify

6) If your institution has a formulary, the proposal for inclusion of a new drug is made by:

P&T Committee Pharmacy administration Medical Specialist Hospital Administration Others please specify

7) For the above proposal, the final decision is made by

P&T Committee Pharmacy Medical Specialist Hospital Administration

Other, please specify

8) In case it is made by the P&T Committee what is the membership of this committee?

9) How often are these decisions made?

10) In making the decision, what are the major factors being taken into consideration?

Effectiveness of the drug Acquisition cost Available alternative Politics Pharmacy Budget Hospital budget Others, please specify

11) What do you think would be the impact of introduction of DRG case-mix funding on inclusion of drugs into the formulary?

12) Do you consider the approach used in formulary decision in your institution scientific or evidence-based?

Yes/No

13) Can you elaborate your reason for your choice of answer to Qs.12?

14) Do you consider that the method used for formulary decision in your institution can achieve the aims of a formulary nominated in Qs.5?
Yes/ No

15) Can you give reasons for your answer to Qs. 14?

16) If your answer is no, what additional approach do you consider necessary to achieve those aims?

17) Can you give reasons for your answer to Qs.16

18) Why is your additional approach not implemented in your formulary decision process?
Lack of time Lack of expertise Lack of support others, please specify

APPENDIX 4
Pharmacy Manager Reponses

	NUH,	TTSH,	CGH	SGH	& KKH						
No of responses	**11**					**INSTITUTION**					
Respondent code:	**P&TMBR 1**	**P&TMBR 2**	**P&TMBR 3**	**P&TMBR 4**	**P&TMBR 5**	**P&TMBR 6**	**P&TMBR 7**	**P&TMBR 8**	**P&TMBR 9**	**P&TMBR 10**	**P&TMBR 11**
Parameters											
Member of the P&T committee	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
No.of beds in institution	500-999	500-999	>1000	500-999	200-499	100-199	200-499	500-999	>1000	500-999	500-999
Type of institution	Tertiary Referral	Tertiary Referral	Tertiary Referral	Secondary referral	Specialist	Specialist	Tertiary Referral	Tertiary Referral	Tertiary Referral	Tertiary Referral	Tertiary Referral
Pharmacy budget	21-30M	No idea	>30 M	<10M	<10M	Open	<10M	10-20M	Can't say	10-20M	10-20M
Presence of formulary/drug list in institution	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y
For how long	10 years	No idea	No exact idea	All along			8 years	10 years	8 years	3 years	10 years
If no formulary how institution decides on drugs to stock	NA	NA	NA	NA	NA	On req of spec	NA		NA	NA	NA
Opinion about a formulary											
List of most essential drugs	Opinion		Opinion	Opinion	Opinion				Opinion	Opinion	Opinion
List of most expensive drugs											
List of most used drugs		Opinion			Opinion						
List of the cheapest alternatives											
Others		Part of hosp policy, for choice in prescr., docs want it				a list cov every area of trmnt	List of drugs stocked by pharmacy	Open form stocking all drugs on req by docs			
A formulary serves											
In controlling the hospital budget	Fn	Fn	Fn	Fn	Fn		Fn	Fn	Fn	Fn	Fn
In subsidizing life-saving medicines	Fn		Fn						Fn		Fn
In promoting the use of the "best" drug/intervention	Fn	Fn					Fn	Fn	Fn	Fn	Fn
In restricting the use of drugs	Fn	Fn			Fn	Fn			Fn	Fn	
To promote cost-effectiveness in drug treatment	Fn	Fn	Fn	Fn	Fn			Fn	Fn		Fn
Others				in controlling stock holding and range of drugs the hospital keeps							
Proposal for inclusion of new drugs made by											
P&T Committee		Y	Y								
											Y
Pharmacy administration	Y		Y	Y				Y			
Medical Specialist	Y		Y	Y		Y			Y	Y	
Hospital Administration											
Others							accredited docs				

Final decision-maker w.r.to drug incl/excl in the formulary											
Hospital administration											
Medical specialist(s)											
Pharmacy								Fin dec-mkr			
P&T committee	Fin dec-mkr	Fin dec-mkr	Fin dec-mkr	Fin dec-mkr		Fin dec-mkr			Fin dec-mkr	Fin dec-mkr	Fin dec-mkr
Others							accredited docs				
Membership of P&T Committee	9	Phar mgr, CFO, repr from major depts in hosp. Dis-pen-	Sr docs, pcy mgr, Sr p'cist, QM mgr	Sr docs, nurses		Pcy medical advisory board, hosp mgmt	NA	NA	nomin by HODs of major disciplines	7 phy, 2 p'cists	consultan ts fromdiffer ent iscipines - pharmaci sts
Frequency of decisions	once in two months	once in two months	once in two months	once in two months		monthly	NA	as necessary	quarterly	quarterly	quarterly
Factors considered for making the decision											
Drug effectiveness	Y	Y	Y	Y		Y		Y	Y	Y	Y
Acquisition cost	Y	Y	Y						Y	Y	Y
Available alternative	Y	Y	Y			Y		Y	Y		Y
Politics								Y			
Pharmacy/Drug budget	Y		Y								
Hospital budget			Y								
Safety		Y	Y	Y					Y	Y	
Others				cost-effectiven ess, administr a, patient complian ce, efficacy			NA				
Impact of DRG on formulary	Restrictiv e on drug use and inclusion		Rational prescr and approp and cost-effect use	will make cost-effectiven ess one imp Criterion for drug inclusion, avail. Of DUE and p'coeco studies helpful in making a decision			nothing, any item on req by doc will still be stoked	cut costs	maybe will help in imposing the formulary	so far minimal; not affected costs of drugs to hosp or pt. If there is to be impact on choice of medicatio ns, then policies and protocols have to change	NR
Whether approach used for formulary is scientific or evidence-based	Yes		Yes	Yes and no		Yes	Yes	NA	Yes	Yes	NR
Reasons for the above	Decision is based on evaln of cli papers			lit search for non-bias studies. Clinical studies by the evaluator	pharcy evaluates drug based on best evidence, Experien ce and feedback from docs final dec.		NR	NA	evalns based on clinical trials esp. RCTs	careful journal review by each member of committe e before fin dec.	NR
Does hospital formulary achieve the aims of the formulary as designated	Yes and no		Yes, to some extent	Partly		Yes	No	NA	Yes	Yes	Yes
Reasons for the aforementioned											
Formulary is too open											
Drugs included solely on cost-basis											
No consideration of drug quality											
No knowledge of the decision-making process											
Others	costs, benefits efficacy , no eco impact	forces docs to prescr. What is avail on form	Form helps manage drug budget,	const monitorin g of drug usage and feedback necessar y for measure s and policies		narrows down range of medicatio ns of equiv therap effects	NR	NA	Docs should know implica of formul if not in form it is more inconveni ent to obtain the drug, therefore impedenc e in a way	committe e members are well aware of their role	NR
If no, what additional approach	Pharmac oeconomi cs	Pharmac oeconomi cs, on readmissi on costs, DIS strengthe ned, doctor edu., commi. Rieve new ideas	if docs are more concerne d about cost to patients and use cost-effective drugs better formulary				NR	NA	NA	NA	NA
Reasons	An exp drug may reduce hosp stay or nursing time. This app not cons for curr evaln.	large scale way of these will give good results				visiting spec do not restr to formulary		NA	NA		NA
Why addl approach not implemented											
Lack of time	Y										
Lack of expertise	Y	Y									
Lack of support						Y					
Others, specify		docs on cli exp., trained ones go off to pvt settings					NR	NA	NA	NA	NA

APPENDIX 5
Letter and Proposal

To

The Chairperson,

Medical Board,

The National University Hospital,

Singapore.

Via:

Ms. Yow Kah Lai,

Pharmacy Manager,

The National University Hospital,

Singapore.

From:

Li Shu Chuen

Assistant Professor

Department of Pharmacy

The National University of Singapore.

Sub: Permission for conducting pharmacoeconomic research at the NUH

Dear Sir,

Jointly with Ms. Yow Kah Lai, Pharmacy Manager NUH, I am currently conducting a research project to study the potential role that pharmacoeconomics can play in formulary decision-making at the institution level. The study methodology requires that we attend at least 3 P&T committee meetings to observe and understand the current decision-making process. This would enable us to understand the current approach better so that we may be able to add other dimensions to enhance the aforementioned process. In this regard I would like to submit a project proposal through which I would like to convey my research plan (see attachment). I would request your kind perusal of my proposal and grant me permission to attend the meetings.

We would request your cooperation for the successful completion of the research project

In anticipation of a favorable response from your side, I remain.

Yours sincerely,

Li Shu Chuen.

PROPOSAL FOR INCLUSION OF PHARMACOECONOMIC EVALUATION IN FORMULARY DECISION-MAKING AT

THE NATIONAL UNIVERSITY HOSPITAL, SINGAPORE

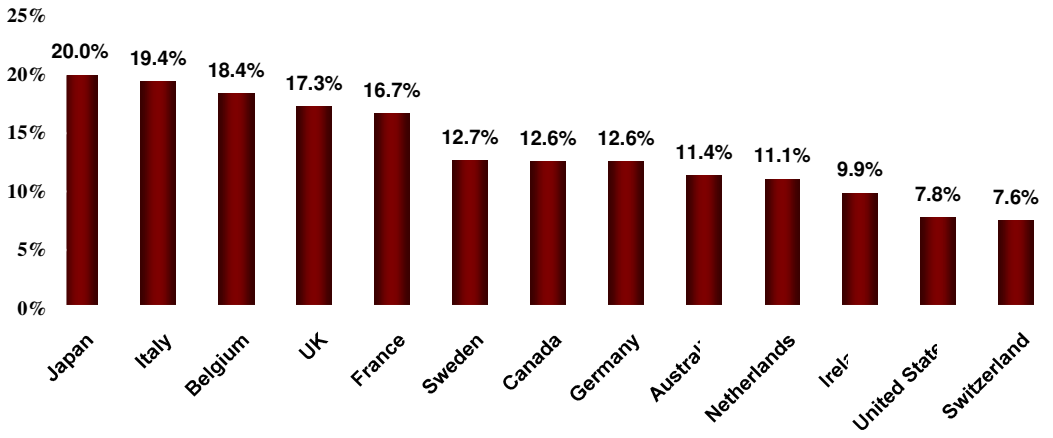
Statement of Purpose

The proposal strives to bring forth the need for Pharmacoeconomic evaluation of drugs in making Formulary decisions. This it does by drawing reference to the tested benefits of Pharmacoeconomic evaluation in other developed countries and healthcare systems and establishes the need for such considerations in Singapore.

To start with, the proposal is to include Pharmacoeconomic evaluation in the formulary decision-making process at the National University Hospital – one of the prime healthcare providers in Singapore.

Background

Today, two worldwide healthcare concerns – increasing demand for better healthcare and health-cost escalation -- have never been more pressing. Pharmaceuticals are drawing increasing public interest and attention even though they contribute not more than 20% of the total health expenditure in industrialized countries.



Pharmaceuticals' share of total health expenditure in industrial countries, 1997 (OECD Heath Data, 1998)

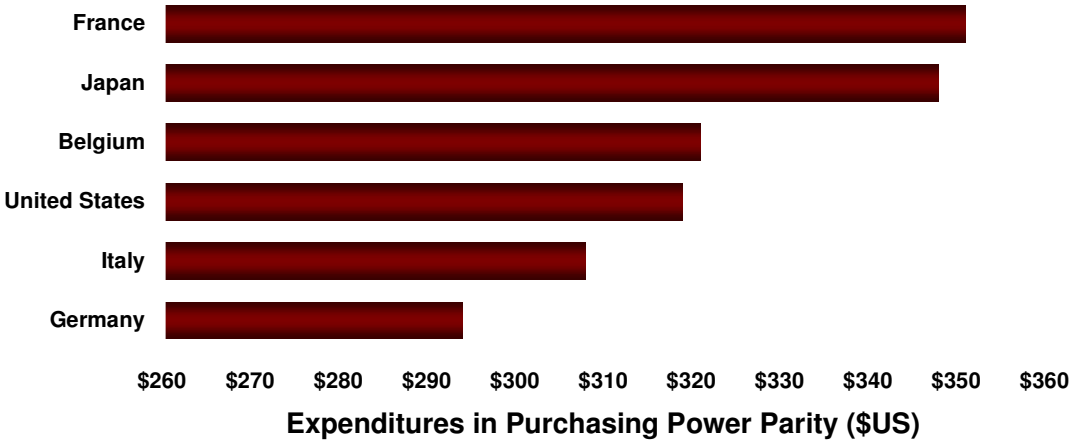
Several unique characteristics are contributing to public concerns:

- Pharmaceuticals constitute the most conspicuous part of healthcare expenditure
- Inflation rate for pharmaceuticals has sometimes outpaced the rates for other sectors as well the entire healthcare systems
- The profitability of the pharmaceutical industry has been extraordinarily high over the past few decades
- The demand for drug therapy is rapidly increasing

- New drugs and biotechnology products are entering the market at a rapid pace and at very high prices

In responding to these issues, one of the concerns is whether specific pharmaceutical products or drug therapies are cost effective. Today and in the future, it is necessary to scientifically value the costs and consequences of drug therapy.

Pharmaceutical expenditures per capita in industrialized countries, 1997 (OECD Health Data, 1998)



Two economic questions arise in this regard – how much should be spent on pharmaceuticals, a question to be addressed by politicians. The second question is – on which pharmaceuticals should this money be spent? The answer to this would be – the ones that return the maximum value for money spent. The problem of how to determine this 'value' is best solved by pharmacoeconomics.

How can Pharmacoeconomics help?

The application of economic analysis to pharmaceuticals is part of a larger global trend to maximize the value received for money spent on healthcare services, because all countries are faced with the same problem – an increasing demand for care to be paid for with stable or diminishing resources.

The term 'outcomes' is increasingly being used to describe the results and value of healthcare intervention. The clinician has traditionally been most concerned with clinical outcomes or treatments. More recently, healthcare payers and administrators have focused on the resource use or economic outcome of healthcare decisions.

Patients on the other hand are becoming increasingly knowledgeable and involved in decisions regarding their own healthcare and are seeking more information regarding the humanistic outcomes of therapy. As shown by the results of a 1998 US study by Institute for the Future and Princeton Survey Research – 45% of patients in 1998 sought information about their healthcare compared to 25% twenty-five years back.

Pharmacoeconomic research identifies, measures and compares the costs (i.e. resources consumed) and consequences (clinical, economic and humanistic) of pharmaceutical products and services.

A few questions that pharmacoeconomics may help to address are as follows –

- What drugs should be included in the hospital formulary?
- What is the best drug for a particular patient?
- What is the best drug for a particular disease?
- What are the patient outcomes for various treatment modalities?
- Will patient quality of life be improved by a particular drug therapy decision?

The key is to assure that drug therapy and related pharmacy services are not only safe and effective but also provide 'real value' in both economic and humanistic terms. **One should not expect to use Pharmacoeconomic evaluation as a means of cutting down budgets or costs. However, what it ensures is the best and most cost-effective utilization of whatever money is spent on pharmaceuticals.**

Current trends in developed Healthcare Systems

Currently, only the governments of Australia, Canada and Ontario have incorporated specific economic evaluation criteria into their pharmaceutical regulation. Australia was the first country to take this step, which makes it a model for others to examine if not to emulate.

Even in the absence of governmental regulation markets are providing incentives for economic evaluation. In the U.K recent changes in the payment methods for GPs have created an interest in pharmacoeconomic data.

In the US, healthcare providers are beginning to consider methods for using economic data in the preparation of formularies and reimbursement strategies.

Generally pharmacoeconomic data are currently being applied to three types of decisions: pricing and reimbursement and access to pharmaceutical products. The P&T committee may use the data to make formulary decisions to further or restrict access to a product.

Thus we see the emphasis on outcomes management. The direction and driving force behind these changes continues to be the recognition that consumers at all levels want 'value for money'.

Any assessment of the true "value" of pharmaceuticals, should include a complete assessment of the outcomes of healthcare procedures and treatments in three dimensions – clinical, economic and humanistic -- relevant to the therapy. Committees making decisions of whether or not to include a drug in a HMO or hospital or other formulary are gaining an appreciation of the importance of evaluating all three dimensions. Increasingly, these formulary committees and other purchasing groups are expecting pharmacoeconomic issues to be addressed in a standard fashion prior to approval or inclusion in the formulary. The clinical dimensions of safety and efficacy are evaluated during the drug development process in clinical trials. The economic and humanistic dimensions of outcomes are measured using emerging pharmacoeconomic research methodologies and data collection techniques within and alongside the traditional drug development process.

Realistically some pharmaceutical products and healthcare interventions will be in greater need of pharmacoeconomic support than others. For example, drugs that are meant for use in chronic conditions, to palliate symptoms or slow down the spread of an illness but not cure it are more likely to generate queries regarding their pharmacoeconomic benefit

than a drug that cures an acute condition. This leads to the issue of whether individual medical centers should perform their own pharmacoeconomic research.

Pharmacoeconomic Analyses in Medical Centers

Conducting pharmacoeconomic analyses in a medical center setting can be beneficial for several reasons. It can be used by decision-makers to guide drug policy decisions for the formulary system and can be incorporated into the institution's budgeting process. By generating and using pharmacoeconomic data decision-makers can be better informed about the overall impact of drug use and become less reliant on data based solely on pharmacy drug expenditure.

No longer can medical centers allow new technologies to diffuse rapidly into clinical practice without regard for evaluations of their cost-effectiveness and impact on patient quality of life. However, limitations exist for dedicating time and resources to such exercises. Therefore it would be best to prioritize and select from a variety of potential topics ones that are most important for such exercises. Highest priority should be given to products with very high acquisition costs or with high volumes of use. Newer products that offer a greater clinical benefit but cost significantly more than the competing therapy, should be evaluated to see if the positive clinical outcomes offset the higher cost of the product.

As pharmacoeconomic analyses become more sophisticated and data for drugs become more widely available the use and value of this information will undoubtedly increase. It is also likely that medical centers will need to become more involved in conducting their own clinical economic analyses for important planning and purchasing decisions. Pharmacoeconomic analyses should be seen as a powerful tool that can be used to help at least partially rationalize the selection and use of pharmaceutical agents in the medical center setting.

Pharmacoeconomics, Formulary systems and the P&T Committee

One mission of the P&T committee is to establish and maintain safe, effective, appropriate and cost-effective drug therapy in a manner that facilitates optimal patient outcomes. One way it does this is by determining which drugs should be added, deleted or restricted in the formulary based on uniformly applied criteria, evaluating and measuring drug utilization and outcomes and taking appropriate actions when opportunities for improvement are identified.

Formulary systems play a major role in facilitating appropriate drug usage, cost and quality. They are designed in part to provide savings in pharmaceutical product expenditures by facilitating the purchase of drug products at lower prices, reducing drug inventories and increasing the use of clinically similar but less expensive drugs. Successful formularies restrict access to or discourage the use of those drugs for which there are lower-cost substitutes available, thereby encouraging the use of more efficient medications.

Changing approach to the Formulary

When compiling and revising formularies, the most frequently used criteria for selecting among alternative drugs are clinical efficacy, risk of adverse effects and daily cost of drug. Too often, cost analyses focus on a search for the least costly alternative, without an explicit analysis of overall cost-effectiveness. For example if a drug is determined to be therapeutically similar to existing drugs on the formulary, then daily cost of drug therapy is weighed heavily by the P&T committee. Additional factors including QOL, patient preference and outcomes are only now beginning to be discussed as part of the formulary decision-making process. Data from pharmacoeconomic studies are increasingly entering into formulary decision-making. P&T committees are beginning to examine cost information on a broader basis taking patient outcomes into account. The goal of formulary management should not necessarily be to decrease the drug budget alone, but rather to improve the efficiency of care delivery and optimize patients' health status relative to resource constraints.

Therefore, increasing emphasis is being placed on P&T committee consideration of the non-medical economic impact of pharmaceuticals e.g. Indirect costs). To minimize variations in the quality of such studies development of standards for pharmacoeconomic evaluations is another priority.

Potential Benefits of Pharmacoeconomics in a Hospital Setting

Pharmacoeconomics:

- May be used to assess the value of pharmaceutical products and services
- May be used when choosing between competing treatment alternatives
- Can provide data necessary to make better drug use decisions
- Allows pharmacists to balance cost with quality and patient outcomes.

Contemporary medical decisions should be multidimensional (encompassing several outcomes) and the application of pharmacoeconomic principles and methods can assist in incorporating these outcomes.

Not all pharmacoeconomic data must come from a randomized clinical trial in order to be meaningful. Various strategies to aid pharmacists to put pharmacoeconomics into use, include:

- Critical evaluation, interpretation and use of the results of published studies
- Using economic modeling techniques
- Conducting institution or plan specific pharmacoeconomic studies (can be challenging in both time and monetary terms and should be reserved for medical decisions that may be significant in terms of cost and quality of care).

The Singapore Pilot-test

An initial survey was conducted among pharmacists and pharmacy managers of different hospitals in Singapore to gauge whether there was any perceived need for pharmacoeconomic evaluations. This was done by means of a questionnaire (see attached). The questionnaire was sent by e-mail or faxed over and no personal explanation given to any of the respondents. Care was thereby taken to ensure uniform administration of the questionnaire. Therefore, an unbiased understanding of the questions can be safely assumed for all respondents.

Thirteen hospitals including the NUH were identified as major hospitals in Singapore of which one (National Skin Center) was left out as it was considered a Specialty Hospital. Of the remaining twelve, six are private hospitals and six public hospitals. The pharmacy managers of the various hospitals were identified and contacted over phone to seek their cooperation in the survey by answering a particular questionnaire. Eleven hospitals agreed to answer but number of respondents were identified as thirteen. Eight of them have sent their replies, four have not and one refused. Hence, responses came in from seven hospitals. The following results emerged -

- 5/7 (71%) said they have hospital formularies.
- Aims of a formulary:
    1. 6/7 (86%) mentioned Budget control
    2. 1/7 (14%) mentioned subsidizing life-saving medicines
    3. 3/7 (43%) mentioned promoting use of the best drug or intervention
    4. 3/7 (43%) mentioned restricting use of drugs
    5. 3/7 (43%) mentioned promoting cost-effectiveness in drugs
- 4/7 (57%) said they have a proper P&T committee
- Factors taken into consideration when incorporating drugs into the formulary
    1. 4/7 (57%) mentioned efficacy
    2. 4/7 (57%) mentioned alternatives
    3. 3/7 (43%) mentioned safety
    4. 2/7 (29%) mentioned budget considerations
    5. 1/7 (17%) mentioned patient compliance (humanistic outcome consideration)
- 7/7 (100%) think their formulary is scientific or evidence-based (reason- non-bias clinical papers are referred to)
- 4/7 (57%) felt that the aims of a formulary were being only partly fulfilled
- 6/7 (86%) had no idea of what additional approach were to be taken to substantially fulfil the aims of a formulary as designated by each of them
- Impact of introduction of DRG
    1. 4/7 (57%) felt it would facilitate rational inclusion of drugs in the formulary
    2. 4/7 (57%) felt it would cut costs

3. 2/7 (29%) had no idea
4. 1/7 (17%) felt it would enable availability of drug utilization evaluation reports and pharmacoeconomic studies

Based on the results, a few significant points emerge:

- The final decision to stock or not stock a particular medication rests on the chairperson of the medical board or the P&T Committee who is usually a doctor.
- Few hospitals have open formularies. Especially, private hospitals where patients pay in full – stock all medicines. Depending on the doctor's perception of which medication is best for the patients, the doctor prescribes and the pharmacy stocks. But whether there are problems of overstocking or locked-in inventories is not clear.
- In Public hospitals, there is a clear feeling that a comprehensive evaluation of Pharmaceuticals is not done before admitting them to the formulary. However, what the exact approach to this evaluation should be – is not clear.

Thus, one can strongly argue, that there is a perceived need for a more complete evaluation of pharmaceuticals. However, only one has named Pharmacoeconomics as the solution.

Given the potential uses of Pharmacoeconomics, we would suggest that the subject has a definite role to play in Formulary decision- making. Therefore, we are proposing to evaluate the feasibility of applying pharmacoeconomic principles to formulary decisions in Singapore.

Proposed methodology:

At present, formulary submissions are evaluated taking into consideration factors like clinical efficacy, safety and cost per day of treatment. The final decisions are made by the Pharmacy and Therapeutics (P&T) committee. The researcher would like to attend the next 3-4 P&T Committee meetings with the following objectives:

- ❖ Observe and understand the decision-making process
- ❖ To try and develop a comprehensive and in-depth framework for evaluating formulary submissions by incorporating pharmacoeconomic considerations

This new framework would include guidelines for evaluating formulary submissions, which the researcher would frame taking cue from Guidelines for Formulary submissions to the PBAC for PBS listing in Australia. The researcher would also try to incorporate learning from the experiences of other countries in this area. Thereafter, the researcher would measure user satisfaction to assess the technical efficiency of the entire process. However, whether the framework is workable and can offer a more scientific and practicable alternative to the current approach, can only be gauged when it is run on a few cases. The next logical step would therefore be, to run the whole process in a few instances. An objective outcome measure would be potential cost savings to the organization measured after applying the new framework over a certain period of time.

Expected Outcomes:

Economic evaluations in addition to the current pharmacotherapeutic considerations would entail a more comprehensive or in-depth evaluation of formulary actions (addition or deletion) leading to increased user satisfaction. Pharmacoeconomic assessments of formulary actions would help to ensure that only those drugs or interventions, which yield the highest outcome per dollar spent, viz. which represent a favorable long-term cost-benefit implication diffuse into the healthcare systems.

Outcome Measures:

Primary measures : User satisfaction to be measured or gauged by a questionnaire at the end of 3 P&T committee meetings.

Secondary measures : More objective measures would be an assessment of the percentage change in the number of P&T approvals and potential cost savings to the organization as a result of pharmacoeconomic assessments; however due to the inherent nature of the project (such information may not be forthcoming and time for the project is also short) it is possible to consider them only as secondary outcome measures.

References:

1. *Principles of Pharmacoeconomics, 2nd edition; Bootman, Townsend and McGhan*
2. *The November 1995 Revised Australian Guidelines for the Economic Evaluation of Pharmaceuticals: Paul C. Langley; Pharmacoeconomics;1996 April; 9(4)341-352*

APPENDIX 6a – 6e
Evaluations

APPENDIX 6a
Basiliximab/Daclizumab

EVALUATION REPORT
ON

BASILIXIMAB INJECTION
FOR
SOLID ORGAN TRANSPLANTATION

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EXECUTIVE SUMMARY

BASILILIXIMAB INJECTION
FOR SOLID ORGAN TRANSPLANT

APPLICATION FOR INCLUSION IN NATIONAL UNIVERSITY HOSPITAL (NUH) DRUG LIST AS A NON STANDARD DRUG
SEPTEMBER 2000

Preamble: The purpose of this document is to evaluate the cost-effectiveness of basiliximab as compared to daclizumab as ant-rejection therapy in solid organ transplantation (see section on comparator).

Although the indications applied for included renal transplant as well as liver transplant, the lack of information regarding liver transplant precludes any formal evaluation to be performed. The evaluation will focus mainly on the comparative cost-effective of basiliximab and daclizumab as routine immunosuppression for renal allograft patients

Comparator(s): Daclizumab injection as per request from the NUH P & T Committee. However, in theory if the request is really an evaluation for inclusion as a non Standard Drug, then standard immunosuppressive therapy of cyclosporin and corticosteroids, with or without azathioprine would be the appropriate comparator.

Part A. For Renal Allograft

Clinical Summary: The clinical evaluation was based on four large multi-centre randomized clinical trials, two of which compared basiliximab with standard therapy, and two compared daclizumab with standard therapy (Nashan et al, 1997; Kahan et al, 1999; Vincenti, et al. 1998; Nashan et al, 1999). The trials by Nashan et al and Kahan et al compared basiliximab with standard double immunosuppressive therapy of cyclosporin and corticosteroids, while the trials by Nashan et al and Vincenti et al compared daclizumab with standard double immunosuppressive therapy of cyclosporin and corticosteroids, and triple immunosuppressive therapy that included cyclosporin and corticosteroid as well as azathioprine.

The clinically relevant outcomes used in all trials included acute rejection during the 1st 6 months after transplant, graft and patient survival at one year after transplant, safety and tolerability over 12 months.

By pooling the data, it would appear that basiliximab and daclizumab when added to standard immunosuppressive therapy produced the same trend but different magnitude in all the important outcome indicators. The results of these trials were summarized in the following table. However, the results should be interpreted with caution given the caveats associated with a common comparator approach.

Outcome Indicators	Basiliximab Group	Placebo Group	Rate Difference	Daclizumab Group	Placebo Group	Rate Difference
Biopsy-proven rejection (6 months)	32.6%	47.3%	-14.7%*	25.1%	41%	-15.9%*
Steroid resistant rejection	14.6%	26.2%	-11.6%*	7.9%	15.3%	-7.4%*
Patient survival (12 months)	96.1%	96.7%	-0.6%	98.5%	95.1%	3.4%*
Graft survival (12 months)	91.2%	89.7%	1.5%	91.4%	86.6%	4.8%
Any infection (12 months)	80.2%	79.9%	0.3%	69%	72%	-3%

Footnote: * denotes statistically significant

Costs per course of treatment: A course of basiliximab costs around S$5,922 to the hospital irrespective of patient body weight whereas the cost of daclizumab therapy would be between S$6,225 and S$9,337.50 for patient weight range from 50 –70 kg.

Economic Summary: Depending the interpretation of the clinical data, the evaluation can take the approach of either a Cost-Minimization Analysis (i.e. assuming no clinical difference between basiliximab and daclizumab) or a Cost-Effectiveness Analysis (i.e. assuming there are clinical differences between the two drugs).

CMA: A course of basiliximab for any adult would cost **S$5922**
A course of daclizumab for any adult would cost **S$9337.50** (based on a body weight of between 55-70kg)

CEA:

Outcome Indicator Used	ICER (Cost per extra outcome achieved)
Biopsy-proven rejection (6 months)	$ 284,625
Steroid-resistant rejection	Daclizumab is more costly & less effective.
Patient survival (12 months)	$83,637
Graft survival (12 months)	$103,500
Any infection (12 months)	Daclizumab is more costly & less effective.

Recommendations:

Based on the results from the CMA, basiliximab is the cheaper alternative that can achieve the same clinical outcomes as daclizumab.

If it is decided to use the results from the CEA, the use of daclizumab over basiliximab is either inferior (more costly and less effective), or gives very high ICERs in all the clinical outcome indicators. Therefore, it would appear that basiliximab is a reasonable alternative for daclizumab as an inductive immunosuppressive agent in combination with cyclosporin and corticosteroid.

Other Issues to be considered:

- Basiliximab is approved in Singapore for pediatric usage whereas daclizumab has not been approved for use in pediatric patients

- Exact role and cost-effectiveness of basiliximab and daclizumab in immunosuppressant therapy needs to be further evaluated

Part B. For Liver Transplant

Neither basiliximab, nor daclizumab, has yet been approved for use in liver transplantation in pediatrics and adults by Ministry of Health in Singapore.

Evidence used in the Evaluation

The main evidence for basiliximab was in the form of an abstract (Neuhaus et al, 1999). It was a randomized, double blind, placebo-control, multicentre study carried out in US, Canada and Europe. The results from this trial showed that patients treated with basiliximab had better clinical outcomes as measured by percentage of patients with biopsy-confirmed acute rejection at 6 months, severe rejection at 6 months, and patent and graft survival at 12 months.

Two studies were available for daclizumab in liver transplant (Eckhoff et al, 2000; Hirose et al, 2000). Hirose et al's study was a case series reporting the use of daclizumab, while Eckhoff et al's study was a retrospective evaluation of the use of daclizumab in 39 patients who had received daclizumab plus conventional immunosuppressants against 58 patients who did not receive daclizumab as case controls. The results showed that patients treated with daclizumab experienced an improved clinical outcome of reduction in the incidence of acute rejection at 6 months (18% vs. 40%, p=0.02), and similar outcomes in terms of patient survival at one, three and six months after transplant. However, the first dose of daclizumab at 2mg/kg was twice that used in renal transplant.

The evaluator did not attempt to compare the clinical efficacy of basiliximab and daclizumab through the common comparator approach as for renal transplant due to:
1. It is problematic to compare the results of randomized clinical trial with that of non-randomized trial.
2. It is meaningless to compare the efficacy of the two drugs when it is unclear whether the maximal doses of basiliximab and daclizumab were used in the studies.

Recommendation

The first consideration is that basiliximab is not yet approved for the indication of liver transplant. Coupled with the fact that very limited data on the long-term beneficial and adverse effects are available, it might not be appropriate to consider its inclusion as a non- standard drug in the formulary.

However, from the scanty data available, it would appear that there was a trend in favor of patients treated with basiliximab. Therefore, it would be advisable that the P & T Committee considers basiliximab to be used as an investigational drug for liver transplant at NUH.

BASILIXIMAB INJECTION

INCLUSION IN NATIONAL UNIVERSITY HOSPITAL FORMULARY AS A NON STANDARD DRUG SEPTEMBER 2000.

DETAILS OF DRUG AND ITS PROPOSED USE

Pharmacological class and its action

Basiliximab (Simulect) is a chimeric monoclonal antibody that binds with high affinity and specificity to the IL-2 receptor alpha chain on the surface of activated T-lymphocytes. This action competitively inhibits IL-2 mediated activation of lymphocytes, a critical pathway in the cellular immune response involved in allograft rejection.

Indications

Basiliximab is approved as part of the prophylactic immunosuppression regimen in renal transplant patients by the FDA. However, Basiliximab has not been approved for liver transplant patients. In the United States, daclizumab was introduced in December 1997 and basiliximab in May 1998.

In Singapore, basiliximab has been approved for use in renal transplant in adult and pediatric patients. Daclizumab has been approved for use in adult renal transplant patients only.

The application is for the use of basiliximab as a non-standard drug for:

(1) Prophylaxis against acute rejections in patients receiving renal transplantation when used as part of an immunosuppressive regimen that includes cyclosporin and corticosteroids, and
(2) Prophylaxis against acute rejections in liver transplant patients.

The applicants who wish Basiliximab to be incorporated in the hospital Non-standard Drug List, are, a pediatric nephrologist and a liver transplant surgeon.

Treatment Details

For Basiliximab

Adult Dosage – 1st dose of 20 mg is to be diluted to 50mL with normal saline or dextrose and administered intravenously over 20 to 30 minutes. The first dose is to be given within 2 hours prior to surgery and 2nd dose is administered on day 4 of transplantation.
Pediatric dose is 12mg/m^2, not exceeding a maximum of 20mg. The dose is to be injected twice, first within 2 hours prior to transplantation and the second on day 4 of transplantation.

For Daclizumab

Adult dosage – 1mg/kg body weight to be added to 60 mL of normal saline and administered IV over 15 minutes. The first dose should be administered within 24 hours prior to surgery and subsequent doses at 14 days intervals for a total of 5 doses. The subsequent doses should be given within a day before or after the scheduled administration.

Co-administered and substituted therapies

Basiliximab is used as part of an inductive immunosuppressive regimen that includes other immunosuppressants such as cyclosporin (calcineurin Inhibitor) and corticosteroids.

Main comparator

In theory either standard treatment without basiliximab should have been the main comparator for a formal pharmacoeconomic evaluation for inclusion into formulary.

Daclizumab is a chemical analogue of basiliximab that is recommended for the same indication. Hence, the P&T Committee feels that daclizumab and basiliximab are almost the same for all practical purposes; and therefore whichever can be substantiated to be more cost-effective for the indication(s) applied for, is the one to be incorporated in the hospital non-standard drug list.

The task at hand, therefore, is to evaluate basiliximab and daclizumab to decide which one would be a more "cost-effective" alternative given the perspective of the P&T Committee. The goal of this evaluation is limited to a comparison of daclizumab and basiliximab.

DATA FROM COMPARATIVE RANDOMISED TRIALS FOR MAIN INDICATION

Description of Search Strategies

Databases searched were MEDLINE, and CORE BIOMEDICAL COLLECTION, using the key words 'Basiliximab', 'Daclizumab', 'Immunosuppression', 'Renal transplantation', 'Monoclonal antibodies'. The bibliography sections of the literature provided by NUH were also searched for relevant articles.

Besides the literature provided by the NUH, the literature search by the evaluator retrieved a few other relevant papers. However, no head to head trials comparing basiliximab with daclizumab were found.

Listing of all References

See Appendix 1.

Part A. For Renal Allograft Transplant

Evidence used in the Evaluation

Of these articles, the primary evidence used in this evaluation was the 4 clinical trials (two trials for basiliximab - Nashan et al, 1997; Kahan et al, 1999; and two trials for daclizumab – Vincenti, et al. 1998; Nashan et al, 1999). Another article by Ekberg et al (2000) that pooled the results of the two trials for daclizumab (Vincenti, et al. 1998; Nashan et al, 1999) was also used.

Due to the lack of direct head-to-head clinical trial comparing basiliximab and daclizumab, the evaluation will adopt a common comparator approach. That is, basiliximab is compared to daclizumab via the common comparator of standard immunosuppressive therapy.

Quality of the Evidence

The primary evidence used in this evaluation was summarized in the following table.

Basiliximab Trials			
Trial	**Study Design**	**Patient randomized**	**Follow-up**
Nashan et al, 1997*	randomized, db, pc, mc	380 (placebo-187; basiliximab-193)	12 months
Kahan et al, 1999**	randomized, db, pc, mc	348 (placebo-174; basiliximab-174)	12 months
Daclizumab Trials			
Vincenti, et al 1998+	randomized, db, pc, mc	260 (placebo-134; daclizumab-126)	12 months
Nashan et al, 1999++	randomized, db, pc, mc	275 (placebo–134; Daclizumab-141)	12 months
Ekberg et al (2000)	Pooling of above 2 trials	535 (placebo-268; daclizumab-267)	12 months

Footnote: db - double-blind; pc - placebo controlled; mc – multicentre; * multinational study - Europe (including Belgium, France, Germany, Norway, Switzerland, and United Kingdom) and Canada; ** US study; + multinational study – Canada, US and Sweden; ++multinational study –Australia, Canada and Europe (Austria, Belgium, France, Germany, Italy, Sweden, and UK).

All the trials were randomized and double-blinded. The number of withdrawals and number of dropouts were all accounted for. The length of follow-up was reasonable for measuring anti-rejection therapy and the trials were large enough for the indication. The dosage regimens used for basiliximab and daclizumab were as per manufacturers' product information.

All the trials used the proportion of patients who experienced at least one acute rejection episode (biopsy confirmed) during the first 6 months after transplantation, with follow-up data for graft and patient survival at 12 months as the primary outcome variables. Safety and acute tolerability up to 12 months were also measured.

The standard therapy used in all trials except Vicenti et al (1998) was cyclosporin and cortcosteroid. The standard therapy used in the trial by Vicenti et al (1998) was cyclosporin, cortcosteroid and azathioprine. These are all acceptable standard immunosuppressive therapies.

Generally, baseline characteristics were well matched between the trial drug-treated and placebo groups. In addition, the age ranges and baseline characteristics of the patients were comparable between the basiliximab and daclizumab trials. Appropriate statistical tests were used in all the trials.

Overall, the trials used in the evaluation were all of high quality according to the hierarchy of clinical evidence.

Summary of Results of the Trials

For the **basiliximab trials**, the results of the trials by Nashan et al (1997) and Kahan et al (1999) were summarized in the following tables. All the clinical outcomes were based on ITT analysis.

Patient randomization and follow-up			
	Patient randomized	**Patients for ITT analysis**	**Patients followed for 12 months**
Nashan et al	Placebo –187 Basiliximab-193	Placebo –186 Basiliximab-190	Placebo –168 Basiliximab-165
Kahan et al	Placebo –174 Basiliximab-174	Placebo –173 Basiliximab-173	Placebo –166 Basiliximab-166

Clinical Outcomes			
Nashan et al (1997)			
Outcome Indicators	**Basiliximab Group**	**Placebo Group**	**P value**
Any rejection episode (6 months)	34.2%	52.2%	< 0.001
Biopsy-confirmed rejection (6 months)	29.8%	44%	0.012
Steroid resistant 1st rejection	10%	23.1%	<0.001
Graft survival (12 months)	86.6%	87.9%	0.591
Patient survival (12 months)	97.3%	95.3%	0.293
Infection (any type)	84.7%	86.6%	NS
Kahan et al (1999)			
Any rejection episode (6 months)	37.6%	54.9%	0.001
Biopsy-confirmed rejection (6 months)	35.3%	49.1%	0.009
Steroid resistant rejection	25.4%	41.6%	0.001
Graft survival (12 months)	94.6%	93%	NS
Patient survival (12 months)	97.1%	96%	NS
Infection (any type) 12 months	75%	73%	NS

No clinically meaningful differences in the mean daily dose of cyclosporin were observed between treatment groups throughout both trials. Hence, basiliximab addition does not reduce the dose of cyclosporin needed. There was a trend toward faster improvement in renal function in the basiliximab group.

For the **daclizumab trials**, the results of the trials by Vincenti et al (1998) and Nashan et al (1999) were summarized in the following tables. All the clinical outcomes were based on ITT analysis.

Patient randomization and follow-up			
	Patient randomized	**Patients for ITT analysis**	**Patients followed for 12 months**
Vincenti et al	Placebo –134 Daclizumab -126	Placebo –134 Daclizumab -126	Placebo –134 Daclizumab -126
Nashan et al	Placebo –134 Daclizumab -141	Placebo –133 Daclizumab -140	Placebo –133 Daclizumab -140

Clinical Outcomes						
Outcome Indicators	**Double Therapy (Nashan et al)**			**Triple Therapy (Vincenti et al)**		
	Daclizumab Group	Placebo Group	P Value	Daclizumab Group	Placebo Group	P Value
Any rejection episode (6 months)	34%	50%	0.006	25%	39%	0.04
Biopsy-proven rejection at 6month	28%	47%	0.001	22%	35%	0.03
Steroid-resistant rejection	8%	16%	0.02	8%	14%	0.09
Graft survival at 12 month	88%	83%	0.3	95%	90%	NS
Patient survival at 12 month	99%	94%	0.01	98%	96%	0.19
Infections (any type)	74%	72%	NS	No significant difference reported		

The results from pooling the data of the above-mentioned two trials of daclizumab and using the number of patients randomized were shown in the following table.

Ekberg et al (2000) Outcome Indicators	Daclizumab Group	Placebo Group	p-value
One or more biopsy-proven acute rejection at 6 months	25.1%	41%	<0.001
One or more biopsy-proven acute rejection at 1 year	27.7%	43.3%	<0.001
Steroid resistant rejection	7.9%	15.3%	0.005
1 year patient survival	98.5%	95.1%	0.022 (log-rank)
1 year graft survival	91.4%	86.6%	NS
1 year incidence of any infection	69%	72%	NA

Comparison between basiliximab and daclizumab

The objective of this evaluation is to compare the cost-effectiveness of basiliximab and daclizumab. Before any economic evaluation can be performed, it is necessary to decide on the relative clinical efficacy of the two drugs. A common comparator approach via standard therapy was used in lieu of head-to-head trial.

In order to make this comparison, the evaluator had pooled the data from the two basiliximab trials (Nashan et al, 1997; Kahan et al, 1999) to perform a meta-analysis (see Appendix 2) and the results were compared against those from Ekberg et al (2000).

Outcome Indicators	Basiliximab Group N = 363	Placebo Group N = 359	Rate Difference	Daclizumab Group N = 266	Placebo Group N =267	Rate Difference
Biopsy-proven rejection (6 months)	32.6%	47.3%	-14.7%*	25.1%	41%	-15.9%*
Steroid resistant rejection	14.6%	26.2%	-11.6%*	7.9%	15.3%	-7.4%*
Patient survival (12 months)	96.1%	96.7%	-0.6%	98.5%	95.1%	3.4%*
Graft survival (12 months)	91.2%	89.7%	1.5%	91.4%	86.6%	4.8%
Any infection (12 months)	80.2%	79.9%	0.3%	69%	72%	-3%

Footnote: * denotes statistically significant

From this comparison, it would appear that basiliximab and daclizumab when added to standard immunosuppressive therapy produced the same trend in all the important outcome indicators. In addition, the pooled results showed that daclizumab treatment had a statistically significant beneficial effect on patient survival at 12 months.

In all the other outcome indicators, the results were in favor of treatment with basiliximab or daclizumab. However, there were differences in the magnitude in these effects. In general, the magnitude of improvement in all clinical outcomes with the exception of steroid-resistant rejection appears to favor daclizumab.

Nevertheless, it must be stressed that given the caveats of inferring the difference between basiliximab and daclizumab through a common comparator, the significance of these findings need to be interpreted with caution.

Economic Evaluation

Dependent on the interpretation of the clinical data, two approaches can be adopted for the economic evaluation.

1. Taking a more conservation and cautious approach in interpretation, the evaluation can assume that there is no significant clinical difference between the two drugs. Hence, the economic evaluation would become one of **Cost-Minimization Analysis**.
2. Taking a more literal interpretation of the results as shown above, the evaluation would assume that there is some clinical difference between the two drugs and a **Cost Effectiveness Analysis** is used.

Approach 1 – Cost Minimization Analysis

The major consideration will be the cost of drug acquisition.

Cost of daclizumab per vial (25 mg/5ml)= S$622.50

Cost of basiliximab per vial (20mg/5ml)= S$2961

Hence, a course of basiliximab for any adult as per the price in Singapore would cost:

(2 x $2961.00) = S$5922

This is based on 2 doses of 20mg basiliximab for any adult patient irrespective of body weight as per manufacturer's product information.

On the other hand, the cost per course of treatment with daclizumab will be dependent on the body weight of the patient. Daclizumab is to be administered at a dose level of 1mg/kg body weight for a total of 5 doses over a 10-week period, the first dose being given within 24 hours prior to surgery and subsequent doses at intervals of 2 weeks.

Body weight	**Number of vials required per dose**	**Calculation**	**Treatment cost of daclizumab**
50 kg	2	10 x $622.50	$6225.00
55-75 kg	3	15 x $622.50	$9337.50
80-100 kg	4	20 x $622.50	$12450.00

Taking the weight of an average Asian to be in the range of 55-75 kg, the treatment cost of daclizumab will cost $9337.50.

In addition, there would be other cost, albeit small as compared to the drug cost, for visits to the outpatient clinic for further doses of the drug.

Approach 2 – Cost Effectiveness Analysis

The evaluation is based on the data from the clinical trials, the costs per course of treatment of daclizumab using a body weight of between 55 and 75 kg, and a time frame of 12 months (therefore no discounting of future costs). The incremental analysis of using daclizumab (already a non-standard drug at NUH) as compared to basiliximab will produce the following results.

Outcome Indicator Used	Calculation	ICER (Cost per extra outcome achieved)
Biopsy-proven rejection (6 months)	($9337.50 - $5922)/(0.159 – 0.147)	$ 284,625
Steroid-resistant rejection		Daclizumab is more costly & less effective.
Patient survival (12 months)	($9337.50 - $5922)/(0.034 – [-0.006])	$83,637
Graft survival (12 months)	($9337.50 - $5922)/(0.048 – 0.015)	$103,500
Any infection (12 months)		Daclizumab is more costly & less effective.

Definitely, these ICERs can vary depending on the body weight of the patient. By using a body weight of 50 kg and 80-100 kg, the following results are obtained.

Outcome Indicator Used	ICER (Cost per extra outcome achieved) based on body wt of 50kg	ICER (Cost per extra outcome achieved) based on body wt of 80-100 kg
Biopsy-proven rejection (6 months)	$25,250	$ 544,000
Steroid-resistant rejection	Daclizumab is more costly & less effective.	Daclizumab is more costly & less effective.
Patient survival (12 months)	$5,825	$163,200
Graft survival (12 months)	$9,182	$197,818
Any infection (12 months)	Daclizumab is more costly & less effective.	Daclizumab is more costly & less effective.

Definitely, the cost of treating acute rejection should also be included in the costs. However, based on the small difference between the two drugs in this clinical outcome, it is unlikely to alter the ICERs substantially except in patients whose body weight are 50 kg or less.

Recommendations

Based on the results from the CMA, basiliximab is the cheaper alternative that can achieve the same clinical outcomes.

If it is decided to use the results from the CEA, the use of daclizumab over basiliximab is either inferior (more costly and less effective), or gives very high ICERs in all the clinical outcome indicators. Therefore, it would appear that basiliximab is a reasonable alternative for daclizumab as an inductive immunosuppressive agent in combination with cyclosporin and corticosteroid.

Other issues pertinent to this evaluation

1. A significant proportion of renal transplant patients (30-50%) experiences acute rejection episodes. Indeed, it has been shown that the occurrence of an acute rejection episode correlates with a poor long-term outcome despite initial clinical evidence of therapeutic reversal. Both basiliximab and daclizumab treatments resulted in a reduction in acute rejection at 6 months as shown by the clinical trials. However, in the absence of conclusive evidence of long-term (12 months in this case) beneficial

effects on graft survival as compared to standard therapy, it is unclear how well reduction in acute rejection corresponds to prevention of chronic rejection and ultimately to graft survival.

2. If basiliximab or daclizumab are simply more potent immunosuppressants instead of being more specific, they may lead to an unacceptable increase in long-term complications like neoplasia. These agents may help in increasing choice, thereby enabling greater flexibility in prescription for the individual patient; however, the way they can be combined to obtain maximum efficacy and to keep side effects to a minimum is an issue.

Part B. For Liver Transplant

Neither basiliximab, nor daclizumab, has been approved by the FDA for use in liver transplantation in pediatrics and adults. Likewise, the indication is also not yet approved by Ministry of Health in Singapore.

Evidence used in the Evaluation

The main evidence for basiliximab was in the form of an abstract (Neuhaus et al, 1999). It was a randomized, double-blind, placebo-control, multicentre study carried out in US, Canada and Europe. The number of patients involved was large – 188 in the basiliximab treatment arm and 193 in the placebo arm. Due the fact that it was presented in the abstract form with scanty detail, it is impossible for the evaluator to comment on the quality of the study.

The results from this trial showed that patients treated with basiliximab had better clinical outcomes as measured by percentage of patients with biopsy-confirmed acute rejection at 6 months, severe rejection at 6 months, and patent and graft survival at 12 months.

Two studies were available for daclizumab in liver transplant (Eckhoff et al, 2000; Hirose et al, 2000). The study by Hirose et al (2000) was a pilot study carried out in the US that involved a total of 32 patients. In fact, the study was a case series reporting the use of daclizumab.

The study by Eckhoff et al (2000) was a retrospective evaluation of the use of daclizumab in liver transplant in a US hospital. It compared the outcomes of 39 patients who had received daclizumab plus conventional immunosuppressants against 58 patients who did not receive daclizumab as case controls. The results showed that patients treated with daclizumab experienced an improved clinical outcome of reduction in the incidence of acute rejection at 6 months (18% vs. 40%, p=0.02), and similar outcomes in terms of patient survival at one, three and six months after transplant. However, the first dose of daclizumab at 2mg/kg was twice that used in renal transplant.

In this case, the evaluator did not attempt to compare the clinical efficacy of basiliximab and daclizumab through the common comparator approach as for renal transplant. This decision was based on two factors.

Firstly, the study design of the two studies for daclizumab renders them lower in the hierarchy of evidence as they were more prone to bias as compared to randomized clinical trial. It is problematic to compare the results of randomized clinical trial with that of non-randomized trial.

Secondly, both basiliximab and daclizumab are not yet approved for the indication of liver transplant. Therefore, there are no accepted recommended doses for the two drugs for this indication. It is meaningless to compare the efficacy of the two drugs when it is unclear whether the maximal doses of basiliximab and daclizumab were used in the studies.

Recommendation

The first consideration is that basiliximab is not yet approved for the indication of liver transplant. Coupled with the fact that very limited data on the long-term beneficial and adverse effects are available, it might not be appropriate to consider its inclusion as a non- standard drug in the formulary.

However, from the scanty data available, it would appear that there was a trend in favor of patients treated with basiliximab. Therefore, it would be advisable that the P & T Committee considers basiliximab to be used as an investigational drug for liver transplant at NUH.

Appendix 1. Listing of all References

A. List of references provided by NUH

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Appendix 2. Results of Meta-analysis of the basiliximab renal transplant trials based on the random effects model (Der Simonian & Liard Method)

1. Any rejection episode (6 months)

Trial	Year	Basiliximab Obs	Basiliximab Tot	Placebo Obs	Placebo Tot	Rate Diff	95% CI Lo	95% CI Hi
Nasah et al	1997	65	190	97	186	-0.1794	-0.2779	-0.0809
Kahan et al	1999	65	173	95	173	-0.1734	-0.2769	-0.0699
Pooled Rate Difference and 95% CI						**-0.1766**	**-0.2479**	**-0.1052**

2. Biopsy-confirmed rejection episode (6 months)

Trial	Year	Basiliximab Obs	Basiliximab Tot	Placebo Obs	Placebo Tot	Rate Diff	95% CI Lo	95% CI Hi
Nasah et al	1997	51	171	73	161	-0.1415	-0.2435	-0.0395
Kahan et al	1999	61	173	85	173	-0.1387	-0.2418	-0.0357
Pooled Rate Difference and 95% CI						**-0.1401**	**-0.2126**	**-0.0676**

3. Steroid-resistant rejection episode (6 months)

Trial	Year	Basiliximab Obs	Basiliximab Tot	Placebo Obs	Placebo Tot	Rate Diff	95% CI Lo	95% CI Hi
Nasah et al	1997	19	190	43	186	-0.1312	-0.2053	-0.0571
Kahan et al	1999	34	173	51	173	-0.0983	-0.1884	-0.0081
Pooled Rate Difference and 95% CI						**-0.1179**	**-0.1751**	**-0.0607**

4. Graft Survival (12 months)

Trial	Year	Basiliximab Obs	Basiliximab Tot	Placebo Obs	Placebo Tot	Rate Diff	95% CI Lo	95% CI Hi
Nasah et al	1997	167	190	161	186	0.0134	-0.0541	0.0808
Kahan et al	1999	164	173	161	173	0.0173	-0.0329	0.0676
Pooled Rate Difference and 95% CI						**0.0159**	**-0.0244**	**0.0562**

5. Patient Survival (12 months)

Trial	Year	Basiliximab Obs	Basiliximab Tot	Placebo Obs	Placebo Tot	Rate Diff	95% CI Lo	95% CI Hi
Nasah et al	1997	181	190	181	186	-0.0205	-0.0586	0.0176
Kahan et al	1999	168	173	166	173	0.0116	-0.0270	0.0501
Pooled Rate Difference and 95% CI						**-0.0046**	**-0.0360**	**0.0268**

6. Infection

Trial	Year	Basiliximab Obs	Basiliximab Tot	Placebo Obs	Placebo Tot	Rate Diff	95% CI Lo	95% CI Hi
Nasah et al	1997	161	190	161	186	-0.0182	-0.0891	0.0526
Kahan et al	1999	130	173	126	173	0.0231	-0.0693	0.1155
Pooled Rate Difference and 95% CI						**-0.0029**	**-0.0591**	**0.0533**

APPENDIX 6b
Zanamivir/Oseltamivir

EXECUTIVE SUMMARY

ZANAMIVIR INHALATION & OSELTAMIVIR TABLET FOR TREATMENT OF INFLUENZA

APPLICATION FOR INCLUSION IN NATIONAL UNIVERSITY HOSPITAL (NUH) DRUG LIST AS A NON STANDARD DRUG

Preamble: The purpose of this document is to evaluate the cost-effectiveness of zanamivir and oseltamivir for treatment of acute, uncomplicated influenza to help the P&T Committee decide which (if any) drug is to be incorporated into the hospital Non-Standard Drug List. As there is a great deal of similarity between the two drugs, they are evaluated together whenever feasible.

Main Comparator: Zanamivir and oseltamivir are indicated for the treatment of influenza even while administering relief medications for severe or persistent infection. Therefore, standard therapy used in management of influenza is the main comparator for both drugs.

PART 1. ZANAMIVIR INHALER FOR TREATMENT OF INFLUENZA

CLINICAL SUMMARY

The primary evidence was based primarily on four well conducted randomised, double blinded, placebo control trials - NAIB 3001, NAIB 3002, NAIA 2005, and NAIB 2005. All the trials used median time to alleviation of the major symptoms as the primary outcome measure. Secondary endpoints included length of time to return to normal activities, mean symptom scores, sleep disturbance, use of relief medication, and rates of complications and associated use of antibiotics.

Time (days) to resolution of major symptoms

Trial	ITT Analysis		Difference	IP Only Analysis		Difference
	Placebo Median	Zanamivir Median		Placebo Median	Zanamivir Median	
NAIA 2005 NAIB 2005	5	5	**-0.7**	5	4	**-0.8**
NAIB 3001	6.5	5	**1.5**	6.0	4.5	**1.5**
NAIB 3002	7.5	5	**2.5**	7.5	5	**2.5**

INCIDENCE OF COMPLICATIONS (ITT ANALYSIS)

Trial	Placebo % of Patients	Zanamivir % of Patients	Difference	95% CI	p-value
NAIA 2005 NAIB 2005	12% #	8%#	4%	Not reported	-----
NAIB 3001	28%	22%	6%	-2 to 15%	0.135
NAIB 3002	34%	23%	11%	1 to 20%	0.037

Complications that necessitated the use of antibiotics

Conclusions from the Trials

1. ***The results indicated that treatment with zanamivir lead to a modest reduction in the duration and severity of influenza especially in the influenza-positive patients.***
2. ***However, the incidence of adverse effects caused by the administration of zanamivir was unclear as adverse effects caused by the drug per se was reported together adverse events that could be symptoms of the disease itself.***

PART 2. OSELTAMIVIR TABLETS FOR TREATMENT OF INFLUENZA

CLINICAL SUMMARY

The primary evidence used in the evaluation was based primarily on two well-conducted clinical trials: Trial 1 (Treanor JJ et al, 2000), and Trial 2 (Nicholson KG et al, 2000). The results are shown in the following table:

DURATION AND SEVERITY OF ILLNESS AND PROPORTION OF PARTICIPANTS RESUMING USUAL HEALTH AND ACTIVITY

Trial 1	**Influenza Infected Participants**		**All Treated Participants**	
	Placebo (n=129)	**Oseltamivir 75 mg (n=124)**	**Placebo (n=209)**	**Oseltamivir 75 mg (n=210)**
Median duration of illness (95% CI), hrs	103.3 (92.6-118.7)	71.5 (60.0-93.2)	97.0 (86.3-113.6)	76.3 (66.3-89.2)
P value	<0.001		<0.004	
Median illness severity score (range)	963 (0-4360)	597 (60-2822)	887 (0-5717)	686 (0-4604)
P value	<0.001		<0.001	
Median time to return to normal health, (95% CI), hr.	178 (156-273)	132 (123-152)	178 (156-273)	134 (128-155)
P value	<0.001		<0.001	
Median time to return to normal activity, (95% CI), hr	225 (175-226)	157 (151-198)	230 (179-277)	173 (155-203)
P value	0.02		0.01	

TRIAL 2	**Influenza Infected Participants**		**All Treated Participants**	
	Placebo (N=161)	**Oseltamivir 75 mg (N=158)**	**Placebo (N=235)**	**Oseltamivir 75 mg (N=241)**
Median duration of illness (95% CI), hr.	116.5 (101.5-137.8)	87.4 (73.3-104.7)	116.1 (99.8-129.5)	97.6 (79.1-115.3)
P value	0.02		0.05	
Median illness severity score (range)	943 (0-5408)	773.3 (0-3793)	916.6(0-5996)	851.3(0-6069)
P value	0.01		0.1 (NS)	
Median (Health AUC) scale score (range).	746 (141-1411)	809 (108-3530)	735 (105-1564)	804 (108-3530)
P value	0.003		0.002	
Median AUC (Activity) scale score (range)	703 (69-1585)	787 (0-3163)	690 (69-1595)	769 (0-3163)
P value	0.02		0.008	

Number of Influenza Infected Patients Experiencing Secondary Complications as a result of Influenza Illness and Antibiotic Use Over the Treatment Period

Trial 1	**Placebo (n=129)**	**Oseltamivir, 75-mg (n=124)**
Any secondary complication (%)	19/129 (15%)	11/124 (9%)
Antibiotic use (%)	14/129 (11%)	8/124 (6%)

TRIAL 2	**IP Patients Only**		**ITT Analysis**	
	Placebo (n=161)	**Oseltamivir 75-mg (n=158)**	**Placebo (n=235)**	**Oseltamivir, 75-mg (n=241)**
Any specified secondary illness (%)*	10 (6.2%)	9 (5.7%)	13 (5.5%)	16 (6.6%)

Antibiotic use (%)	8 (4.9%)	1 (0.6%)	10 (4.3%)	6 (2.5%)

*Specified illnesses: bronchitis, otitis, pneumonia, and sinusitis starting ≥ 48 hours after the first dose

Conclusion of the Trials

1. ***The overall conclusions were that oseltamivir did reduce the duration and severity of influenza, and also the incidence of complication arising from influenza but the effects were more pronounced in influenza-positive patients.***
2. ***At the same time, the use of oseltamivir was associated with increase incidence of adverse effects. Presumably, the adverse effects encountered in the trials were not severe as the higher incidence of adverse effect did not lead to an increased withdrawal from the trials due to adverse effects.***

ECONOMIC EVALUATION

Based on the results from the clinical trials, a cost-effectiveness analysis (CEA) is performed. Assumptions used in the evaluation include:

1. Both drug treated and placebo groups received standard symptomatic therapy.
2. The effect size difference of the various relevant outcomes used was based on those obtained from the clinical trials (as summarised in the previous section (See comparison between zanamivir and oseltamivir).
3. Zanamivir or oseltamivir will be used predominantly in the outpatient populations and hence the relevant costs to be considered include acquisition cost only. No other administration cost is involved.

Cost/course of treatment:
Zanamivir (complete kit of 20 blisters and the rota diskhaler): S$26;
Oseltamivir : $36 for 10 tablets (for a course of treatment).

SUMMARY OF ECONOMIC EVALUATION

	ICER for ZANAMIVIR	**ICER for OSELTAMIVIR**
Symptom Relief ITT ANALYSIS	$26/extra day of faster relief of major symptoms	**$**36/extra day of faster relief of major symptoms
Complications ITT ANALYSIS	S$26/5% = **S$ 520** (S$325 to S$2600) for preventing one extra patient on complications from using antibiotics. Lowest estimate: **$325** Highest estimate: **$2600**	S$36/2% = **S$1800** for preventing one extra patient on complications from using antibiotics.
IP only patients	S$26/5% = **S$520** for preventing one extra patient on complications from using antibiotics. Lowest estimate: **$289**	S$36 /5% = **S$ 720** for preventing one extra patient on complications from using antibiotics.
High-risk IP	S$26/9% =**S$289** for preventing one extra patient on complications from using antibiotics. Lowest estimate: **$123** Highest estimate: the drug is more costly and cause more patients to have complications (i.e. negative ICER value)	

KEY ISSUES PERTINENT TO DECISION MAKING

1. Efficacy vs. Effectiveness Gap

In the trials for zanamivir, the local media campaign implemented after influenza surveillance may have encouraged patients to present with symptoms early. In addition, the campaign may also have increased rate of influenza-positive patients entering the trials thus resulting in a larger proportion of IP patients in the study population than would otherwise be observed in a real-world practice situation. However, in real world setting, patients present with symptoms are to be treated with zanamivir rather than after being confirmed influenza-positive. The overall effect of zanamivir may quite likely be less than what was observed in the trials.

Likewise, the oseltamivir trials specifically screened for acute influenza patients and did not administer the study drug to patients with atypical symptoms or to those who had been ill for long. The study protocol specifically excluded individuals with medical conditions that are often associated with more severe influenza. In a real-life practice situation, it cannot however, be expected that such patients would be excluded from treatment. Hence, the beneficial effect of oseltamivir is likely to be less pronounced in real life practice settings.

2. Statistically Significance may not mean Clinically Importance.

Although both drugs significantly shorten the duration of illness when compared to placebo (0.5 to one day), the clinical significance of this effect has to be determined.

3. Timing of Treatment Initiation

To derive optimum benefit from zanamivir patients, zanamivir must be started no later than 48 hours after onset of symptoms. The effect of starting treatment after 48 hours is not clear. This is reflected in the recommendations from international regulatory bodies. **It is important to consider how likely that the patients will present for medical consultation before the symptoms occur for more than 48 hours.**

4. Importance of Reduction of Complications

Although the results from the trials show that the use of zanamivir and oseltamivir reduce the incidence of complications associated with influenza, it is important to decide on the clinical significance of this reduction in the “general” and the “at risk” populations.

5. Issue of Safety and Emergence of Resistance

The issue of how safe zanamivir is, especially in “at risk” patients should be carefullt considered given reports of respiratory problems following inhalation of zanamivir and the FDA requiring special precautionary information to be included in the package insert.

Furthermore, these drugs are not active against “latent” or “non-replicating” viruses. They only arrest viral growth. In that sense, they may be considered to be “virostatic”. Chances of the virus mutating and offering resistance with such drugs are higher.

6. Budgetary Consideration

Considering zanamivir or oseltamivir will be used predominantly only for OPD use, the number of patients treated for influenza in the outpatient setting needs to be identified to assess the budget impact of inclusion of one or both of these drugs in the non-standard drug list.

GENERAL APPROACH OF THE EVALUATION

As both Zanamivir and Oseltamivir are used for the treatment of influenza, there are many common issues relating to the decision to be made by the Pharmacy and Therapeutics Committee. Therefore, the two drugs are evaluated together.

Part A. Zanamivir Inhalation for the Treatment of Influenza

DETAILS OF THE PROPOSED DRUG AND ITS PROPOSED USE

Pharmacological class and mode of action

Zanamivir (RELENZA) is a highly selective and potent inhibitor of neuraminidase, an enzyme found on the surface of both influenza A and B viruses. Neuraminidase is involved in the release of newly synthesized virions from influenza-infected host cells. This enzyme may also help promote the movement of the virus through the respiratory tract mucus. The role of neuraminidase in viral shedding is therefore, vital in ensuring that the influenza virus is an effective pathogen. Thus Zanamivir prevents further replication and propagation of the virus.

Indications

Zanamivir was approved by the US FDA for the treatment of influenza A and B in adults and adolescents (≥ 12 years) who present with symptoms of influenza when influenza is circulating.

Treatment Details

Dosage and administration

Zanamivir is to be administered by oral inhalation only, through the Rota Diskhaler. Two blisters (2X5 mg) are to be inhaled twice daily for 5 days. No dose modification is required for the elderly or for patients with impaired renal or hepatic function. Treatment should be started as soon as possible, ideally within two days (48 hours) of the onset of symptoms.

Co-administered and substituted therapies

Co-administered therapies include relief medication in the form of anti-pyretics and cough suppressants. Since, no special anti-viral is used for influenza, zanamivir is not expected to substitute anything.

Main Comparator

Zanamivir is indicated for the treatment of influenza even while administering relief medications for severe or persistent infection. Therefore, standard therapy used in management of influenza is the main comparator.

DATA FROM COMPARATIVE RANDOMIZED TRIALS FOR MAIN INDICATION

Description of Search Strategies

Databases searched included MEDLINE (via Ovid and Pub Med), EMBASE, and CORE MEDICAL BIOMEDICAL COLLECTION using the keywords: “Zanamivir”, “Influenza”, “Clinical trial, “drug therapy” and combinations of one of more of them. The bibliography sections of the literature provided by NUH were also searched for relevant articles.

Listing of all References

Besides the literature provided by the NUH, the literature search by the evaluator retrieved a few other relevant papers. See Appendix 1.

Evidence used in the evaluation

References provided by the NUH and an independent literature search by the evaluator, revealed that for zanamivir, three phase III clinical trials (NAIB 3001, NAIA 3002 and NAIB 3002) and four phase II clinical trials (NAIA 2005, NAIB 2005, NAIB 2007, NAIA/B 2008) were conducted.

However one phase III trial (NAIA 3002) conducted in North America has been published only as an abstract with scanty information and one phase II study (NAIB 2007) conducted in Europe has not been published at all. Of the remaining phase II studies, NAIA/B 2008 (the largest involving 1256 patients) used a different dosage regimen and route of administration than the one approved by regulatory authorities for final market use. Therefore the results of these trials could not be considered for our current evaluation.

Hence, the primary evidence used in the evaluation was based primarily on the following clinical trials - NAIB 3001, NAIB 3002, NAIA 2005, and NAIB 2005. Trial NAIA 3002 was also referred to wherever relevant data was available.

Quality of the Evidence

Following is a summary in tabular form of the various clinical trials used for the evaluation.

Trial	Study Design	Patients randomised
NAIB 3001	ran, db, pc, mc	455
NAIB 3002	ran, db, pc, mc	356
NAIA/B 2005	ran, db, pc, mc	276*
NAIA 3002**	ran, db, pc, mc	777

Footnote: ran=randomized; db= double-blinded; pc=placebo-controlled; mc=multi-center; *only patients on inhaled zanamivir; *available in abstract only

All the trials used median time to alleviation of the major symptoms as the primary outcome measure. Alleviation of clinically important symptoms of influenza was usually defined as no fever (temperature < 37.8°C or 37.2°C in some patients and feverishness recorded as 'none') and headache, myalgia, cough and sore throat recorded as 'none' or 'mild' maintained for 24 hours. Though different symptoms were given in different trials all of them included the aforementioned symptoms. Patients recorded their symptom severity (as none, mild, moderate or severe), ear or oral temperature and ability to perform normal daily activities on a diary card. The frequency of this recording process varied however. In trial NAIB 3002 the patients recorded symptom scores twice daily for all 14 days and in trial NAIB 3001 the patients recorded symptom scores 4 times daily for the first 5 days and twice daily for the subsequent 9 days. In Trial NAIA/B 2005, it was mentioned that patients recorded symptoms twice daily and returned one to three days after treatment for a follow-up examination but the duration for which they recorded their symptoms is not clear. Secondary endpoints included length of time to return to normal activities, mean symptom scores, sleep disturbance, use of relief medication, and rates of complications and associated use of antibiotics.

The number of withdrawals and number of dropouts were all accounted for. The length of follow-up was reasonable for measuring anti-influenza therapy. The basis of sample size calculation was clearly mentioned in all the trials. The dosage regimens were as per the manufacturers' product information. Generally baseline characteristics were well matched between the trial drug-treated and placebo groups

in both trials. Use of paracetamol and cough mixture was stated to be similar in study NAIB 3001 but the Zanamivir group used 25% fewer tablets of paracetamol in Study NAIB 3002. Trial NAIA/B 2005 reported similar rates of use of relief medications in both the drug-treated and placebo groups. Appropriate statistical tests were used in all the trials. Overall, the trials used in the evaluation were all of reasonably high quality according to the hierarchy of evidence**.**

SUMMARY OF THE RESULTS OF THE TRIALS

MEDIAN TIME (DAYS) TO ALLEVIATION OF CLINICALLY IMPORTANT SYMPTOMS (ITT ANALYSIS)

Trial	Placebo		Zanamivir		Difference	95% CI	p-value
	n	median	n	median			
NAIA 2005 NAIB 2005	144	5	132	5	-0.7	-1.4 to 0	0.04
NAIB 3001	228	6.5	227	5	1.5	0.5 to 2.25	0.011
NAIB 3002	182	7.5	174	5	2.5	0.75 to 3.5	<0.001

MEDIAN TIME (DAYS) TO ALLEVIATION OF CLINICALLY IMPORTANT SYMPTOMS (INFLUENZA-POSITIVE (IP) PATIENTS ONLY)

Trial	Placebo		Zanamivir		Difference	95% CI	p-value
	n	median	n	median			
NAIA 2005 NAIB 2005	89	5	85	4	-0.8	-1.7 to 0	0.05
NAIB 3001	160	6.0	161	4.5	1.5	0.5 to 2.25	0.004
NAIB 3002	141	7.5	136	5	2.5	1 to 4	<0.001

INCIDENCE OF COMPLICATIONS (ITT ANALYSIS)

Trial	Placebo % of Patients	Zanamivir % of Patients	Difference	95% CI	p-value
NAIA 2005 NAIB 2005	12% #	8%#	4%	Not reported	-----
NAIB 3001	28%	22%	6%	-2 to 15%	0.135
NAIB 3002	34%	23%	11%	1 to 20%	0.037

Complications that necessitated the use of antibiotics

A subgroup analysis was also performed on the incidence of complications in high-risk patients in Trial NAIB 3001; and a subgroup analysis was performed comparing the incidence of high-risk influenza-positive patients with influenza positive patients in Trial NAIB 3002. The results of these are shown in the following Table.

INCIDENCE OF COMPLICATIONS

Trial	Patient Type	Treatment Group		Difference	95% CI	p-value
		Placebo (n)	Zanamivir (n)			
NAIB 3001	High risk patients	46% (18/39)	14% (5/37)	32%	11 to 54%	0.004
NAIB 3002	(1) High risk IP patients (2) IP patients	61% (11/18) 33% (47/141)	33% (4/12) 24% (33/136)	28% 9%	-14 to 70% -2 to 20%	0.264 0.125

In all the trials, the most significant benefit was shown by influenza – positive patients**.** In Trial NAIB 3001, symptoms were alleviated a median of 2.5 days earlier in high-risk patients on zanamivir than in placebo. However, a 95% confidence interval around the median (-1.0 to 8.0) does not show statistical difference with respect to this difference. Trials NAIA/B 2005 reported **no evidence of benefit in**

uninfected patients and no significant benefit in those without fever on enrollment, a fact confirmed in trial NAIB 3001.

In the trials, length of time to return to normal activities, mean symptom scores, sleep disturbance, use of relief medication, rates of complications and associated use of antibiotics were used as secondary end-points.

In Trial NAIB 3001, when compared with patients in placebo group, zanamivir recipients returned to normal activities significantly faster in both the ITT analysis and influenza-positive patients (IP) only analysis. In addition, sleep disturbance was less in the ITT analysis and IP only analysis, but did not reach statistical significance. When symptom scores (headache, sore throat, fever, myalgia, cough, nasal congestion, weakness, loss of appetite) during the treatment period (days 1-5) and for the entire diary card period (days 1-14) were analysed, there was no significant difference in symptom severity over days 1-5 or days 1-14 (except myalgia and weakness) in the ITT analysis between zanamivir and placebo group. However, in IP patients only analysis, zanamivir treated patients had significantly less overall symptom score on days 1-14 than those on placebo. The results are summarised in the following Table.

Trial NAIB 3001	**ITT Analysis**		**Difference**	**IP Only Analysis**		**Difference**
	Placebo	**Zanamivir**	**(95%CI)**	**Placebo**	**Zanamivir**	**(95%CI)**
Return to normal activities (days)	N =228	N=227	2.0 (0 to 4.0;p<0.001)	N =160	N =161	2.0 (0.25 - 4.0; p<0.001)
	Median	**Median**		**Median**	**Median**	
	9.0	<7.0		9.0	<7.0	
Sleep Disturbance (Day 13)	N=228	N=223	0 (-1 to 1; p=0.088)	N=160	N=159	1.0 (0 to 1.5; p=0.047)
	Median	**Median**		**Median**	**Median**	
	3	3		3	2	
Overall mean symptom scores (Days 1-5)			-1.7 (-4.8 to 1.5)			-3.6 (-7.3 to 0.1)
Overall mean symptom scores (Days 1-14)			-2.7 (-6.0 to 0.6)			-4.5 (-8.4 to-0.6)

In Trial NAIB 3002, when compared with patients in placebo group, zanamivir recipients returned to normal activities significantly faster (median 7.0 days versus 8.5 days, CI 0-4.0, p=0.025). However, it was not clear whether this difference was not specifically stated whether these results were from the ITT or IP populations. In addition, IP zanamivir-treated patients reported statistically significant reductions in the severity of headache, sore throat, feverishness, muscle and joint aches and pains, cough, weakness and loss of appetite over days 1-14.

In terms of adverse effects of the treatment, it should be noted that the trials <u>DID NOT</u> reported adverse effects caused by the tested drug per se, but reported adverse events. Adverse events reported included bronchitis, sinusitis, cough, pharyngitis, or the gastrointestinal tract like diarrhoea, nausea and vomiting. In both Trial NAIB 3001 and NAIB 3002, there were more adverse events experienced by the placebo group as compared to the zanamivir treated group (43% vs. 37%, and 35% vs. 25% for Trial NAIB 3001 and NAIB 3002 respectively). However, many of the adverse events reported in the trials could either be symptoms or complications of influenza. Considering that the researchers had already claimed the benefit hat zanamivir treatment reduces complications and accelerates symptom relief, they had not actually reported the incidence of adverse effects caused by the tested drug. Nevertheless, one can infer from the smallest difference between the adverse events experienced by placebo and zanamivir treatment groups that the incidence of adverse effects caused by zanamivir is likely to be low.

Comparison between Zanamivir and Standard therapy based on results from a published pooled efficacy analysis

A pooled study (Monto et al., 1999) was conducted incorporating all studies in which patients received zanamivir inhaled twice daily (i.e. all trials except Trial NAIA/B 2008). Statistically significant reductions of 1 day (for ITT and IP populations) and 1.5 days (for febrile IP patients), on time to alleviation of symptoms were noticed with Zanamivir. The summary of the pooled study is shown in the following Table where comparison was made with a pooled analysis performed by the evaluator using the data extracted from Trials NAIA 2005, NAIB 2005, NAIB 3001 and NAIB 3002.

	Monto et al., 1999			**Pooled Results by Evaluator**		
Population	Placebo (n)	Zanamivir(n)	Difference in days	Placebo (N)	Zanamivir (N)	Difference in days
ITT Analysis	6 (1102)	5 (1133)	1 (p <0.001)	6.4(554)	5 (533)	1.4
IP Only Analysis	6 (765)	5 (807)	1 (p <0.001)	6.3(390)	4.6(382)	1.7
Febrile IP*	6.5(595)	5(630)	1.5 (p <0.001)			
Afebrile IP	5.5 (161)	5.0 (161)	0.5 (p=0.254)			
IP Age ≥50	7.5(146)	4.5(117)	3 (p=0.003)			
IP Age <50	6.0 (619)	5.0 (690)	1 (p <0.001)			
IP Symptoms Severe**	8(222)	5(252)	3 (p <0.001)			
IP Symptoms Not Severe**	5.5 (543)	4.5 (555)	1.0 (p <0.001)			
High-risk IP	8(106)	5.5(89)	2.5 (p=0.114)			

• Baseline temperature ≥37.8C; ** Investigator's baseline global assessment of symptoms

In addition, the incidences for complications that necessitate the use of antibiotics were also pooled from the various trials. This is shown as follows.

	Placebo		Zanamivir				
Population	N	Antibiotics used	N	Antibiotics used	Difference (95% CI)	Relative risk (95% CI)	P-value
ITT	1102	196 (18%)	1133	151 (13%)	5% (1%, 8%)	0.74 (0.61, 0.90)	0.004
IP	765	139 (18%)	807	105 (13%)	5% (1%, 9%)	0.72 (0.57, 0.90)	0.006
High-risk IP	106	25 (24%)	89	13 (15%)	9% (-3%, 21%)	0.62 (0.34, 1.13)	0.161

The results indicate that in both ITT and IP only patients analyses, there are significant reduction in the incidence of complications. However, although the effect size difference is greater in the High-risk IP patients, it does not reach statistical significance probably due to the small sample size of this sub-group.

Conclusions from the Trials

3. ***The results indicated that treatment with zanamivir lead to a modest reduction in the duration and severity of influenza especially in the influenza-positive patients.***
4. ***However, the incidence of adverse effects caused by the administration of zanamivir was unclear as adverses effects caused by the drug per se was reported together adverse events that could be symptoms of the disease itself.***

Economic Evaluation

This will be performed together with oseltaminvir (see Part B).

Part B. Oseltamivir Oral Tablets for the Treatment of Influenza

DETAILS OF THE PROPOSED DRUG AND ITS PROPOSED USE

Pharmacological class and mode of action
Oseltamivir (TAMIFLU™) is a pro-drug of a potent and selective inhibitor of influenza virus neuraminidase enzymes. Neuraminidase is involved in the release of newly synthesized virions from influenza-infected host cells. This enzyme may also help promote the movement of the virus through the respiratory tract mucus. The role of neuraminidase in viral shedding is therefore, vital in ensuring that the influenza virus is an effective pathogen. Thus oseltamivir prevents further replication and propagation of the virus.

Indications

Oseltamivir is indicated for the treatment of uncomplicated acute illness due to influenza infection in adults who have been symptomatic for no more than 2 days. This indication is based on studies of naturally occurring influenza and influenza challenge studies in which the predominant infection was influenza A.

Treatment Details
Dosage and administration
Treatment should ideally begin within the first or second day of onset of symptoms of influenza. The recommended oral dose is 75mg twice daily, for 5 days. It may be taken with or without food. However, taking with food may enhance tolerability in some patients.

Co-administered and substituted therapies
Co-administered therapies include relief medication in the form of paracetamol and acetaminophen. Since, no special anti-viral is used for influenza, oseltamivir is not expected to substitute any thing.

Main Comparator
Oseltamivir is indicated for the treatment of influenza even while administering relief medications for severe or persistent infection. Therefore, standard therapy used in management of influenza is the main comparator.

DATA FROM COMPARATIVE RANDOMIZED TRIALS FOR MAIN INDICATION

Description of Search Strategies
Databases searched included MEDLINE (vis Ovid and Pub Med), EMBASE, and CORE MEDICAL BIOMEDICAL COLLECTION using the keywords “Oseltamivir”, “Influenza”, “Clinical trial”, “drug therapy” and combinations of one of more of them. The bibliography sections of the literature provided by NUH were also searched for relevant articles.

Listing of all References
See Appendix 1.

Evidence used in the evaluation

References provided by the NUH and an independent literature search by the evaluator, revealed that for oseltamivir, the following phase III clinical trials were conducted:

1. Treanor JJ et al, Efficacy and Safety of the Oral Neuraminidase Inhibitor Oseltamivir in Treating Acute Influenza – A Randomized Controlled Trial. JAMA 2000; 283:1016-24
2. Nicholson KG et al, Efficacy and Safety of Oseltamivir in Treatment of Acute Influenza: A Randomized Controlled Trial. Lancet 2000; 355:1845-1850

3. Hayden FG et al, Use of the Oral Neuraminidase Inhibitor Oseltamivir in Experimental Human Influenza: Randomised Controlled Trials for Prevention and Treatment. JAMA 1999; 283: 1240-1246
4. Hayden FG et al, Use of the Selective Oral Neuraminidase Inhibitor Oseltamivir to Prevent Influenza. NEJM 1999; 341:1336-1343

However, given the perspective of the NUH P&T Committee, the evidence used in the evaluation was restricted to trials evaluating treatment of naturally acquired influenza (i.e. Trial 1- Treanor et al, 2000 and Trial 2 -Nicholson et al, 2000) rather than challenge trial with experimental influenza (Trial 3 - Hayden et al, 1999) or trial evaluating oseltamivir for prevention of influenza (Trial 4 - Hayden et al, 1999).

Quality of the Evidence

Both Trials 1 & 2 were randomised, double-blinded, placebo controlled and multicentric. The primary outcome measure used in Trial 1 was duration (defined as time from study drug initiation to time of alleviation of symptoms) and severity of illness (assessed by an area under the curve analysis calculated as the daily symptom score times the duration of illness and expressed as "score-hours"). In Trial 2, the primary outcome measure was length of time to resolution of influenzal illness in the intention-to-treat patients. Symptom relief (as defined in both trials) was taken to occur at the start of the first 24-hour period in which all symptoms were scored as 1 or less (mild or none) and remained so for 24 hours.

The number of withdrawals and number of dropouts were all accounted for. Severity of influenza symptoms was recorded twice daily for 21 days whereas, ability to perform usual activities and health status were recorded for the dosing period (5 days). Quality-of-life measures included time to return to normal states of health and activity. Return to normal status was defined as the time (in hours) from study drug initiation to the first 24-hour period in which participants returned to their normal state and remained so for 24 hours. The length of follow-up was reasonable for measuring anti-influenza therapy. The basis of sample size calculation was clearly mentioned in all the trials. The dosage regimens used in the trials were 75mg twice daily and 150 mg twice daily. However, the approved dosage recommended in the product insert is 75 mg twice daily.

Generally baseline characteristics were well matched between the trial drug-treated and placebo groups in both trials. Appropriate statistical tests were used in the trials. Overall, the trials used in the evaluation were of reasonably high quality according to the hierarchy of evidence.

Summary of the Results of the Trials

A. Trial 1. Treanor et al, 2000)

The results of Trial 1 (are shown in the following table.

DURATION AND SEVERITY OF ILLNESS AND PROPORTION OF PARTICIPANTS RESUMING USUAL HEALTH AND ACTIVITY

Outcome measures	**Influenza Infected Participants**		**All Treated Participants**	
	Placebo (n=129)	**Oseltamivir 75 mg (n=124)**	**Placebo (n=209)**	**Oseltamivir 75 mg (n=210)**
Median duration of illness (95% CI), hrs	103.3 (92.6-118.7)	71.5 (60.0-93.2)	97.0 (86.3-113.6)	76.3 (66.3-89.2)
P value	<0.001		<0.004	
Median illness severity score (range)	963 (0-4360)	597 (60-2822)	887 (0-5717)	686 (0-4604)
P value	<0.001		<0.001	
Median time to return to normal health, (95% CI), hr.	178 (156-273)	132 (123-152)	178 (156-273)	134 (128-155)

P value	<0.001		<0.001	
Median time to return to normal activity, (95% CI), hr	225 (175-226)	157 (151-198)	230 (179-277)	173 (155-203)
P value	0.02		0.01	

Statistically significant reductions in the duration and severity of illness among those infected with influenza virus were observed. The duration of illness was reduced from **4.3 days (103.3 hours)** in the placebo group to **3.0 days (71.5 hours)** in the oseltamivir 75-mg group – a difference of 1.3 days. Similarly, treatment with oseltamivir resulted in statistically significant reduction in the symptom score AUC, reflecting both the severity and duration of illness.

In addition, individuals receiving oseltamivir reported significantly more rapid return to normal overall health and resumption of usual activities. The same trend in results was evident in both influenza-infected and all treated participants.

Individuals receiving oseltamivir 75-mg reported significantly more rapid return to normal overall health (46 hours faster) and resumption of usual activities (68 hours faster). Duration and severity of each influenza symptom (cough, myalgia, nasal obstruction, sore throat, fatigue, headache, feverishness) in infected subjects were reduced. **In particular, duration of cough was reduced from a median of 55 hours in the placebo group to 31 hours in the 75mg group.** The daily proportion of infected subjects reporting fever (oral temperature of ≥ 38°C) was reduced by treatment, and reduction in fever was evident within 24 hours of therapy and this reduction was statistically significant (95% CI, 25%-2%).

Overall incidence of physician-diagnosed secondary complications (pre-defined as pneumonia, sinusitis, bronchitis and otitis media and starting ≥ 48 hours after the first dose) and proportions of these individuals receiving antibiotics for influenza complications were significantly reduced in the oseltamivir 75-mg and 150-mg groups combined in Trial 1.

In the 75-mg group alone though less number of patients experienced secondary complications and less use of antibiotics for these complications was reported, it was not clear whether these results were statistically significant. The summary of the results for placebo and oseltamivir 75mg treatment groups is shown in the following Table.

Number of Influenza Infected Patients Experiencing Secondary Complications as a result of Influenza Illness and Antibiotic Use Over the Treatment Period

Complication	**Placebo (n=129)**	**Oseltamivir, 75-mg (n=124)**
Otitis media	1	0
Sinusitis	11	6
Bronchitis	8	5
Pneumonia	1	0
Any secondary complication (%)	19/129 (15%)	11/124 (9%)
Antibiotic use (%)	14/129 (11%)	8/124 (6%)

Upper gastrointestinal effects (nausea or nausea with vomiting) were reported more frequently in those receiving oseltamivir.

For nausea, the rates were 7.4% placebo recipients vs. 17% oseltamivir recipients (P=0.002). For vomiting, the rates were 3.4% with placebo recipients vs. 13.1% with oseltamivir recipients. The reported number of participants withdrawing from the study prematurely because of gastrointestinal events was 1 (from the group receiving oseltamivir 150-mg). In general, the number of participants withdrawing from the study was low (3% in the placebo group and 1.5% in the 75-mg group).

B. Trial 2. (Nicholson et al, 2000)

The results of Trial 2 are shown in the following table.

DURATION AND SEVERITY OF ILLNESS

TRIAL 2	Influenza Infected Participants		All Treated Participants	
	Placebo (N=161)	**Oseltamivir 75 mg (N=158)**	**Placebo (N=235)**	**Oseltamivir 75 mg (N=241)**
Median duration of illness (95% CI), hr.	116.5 (101.5-137.8)	87.4 (73.3-104.7)	116.1 (99.8-129.5)	97.6 (79.1-115.3)
P value	0.02		0.05	
Median illness severity score (range)	943 (0-5408)	773.3 (0-3793)	916.6(0-5996)	851.3(0-6069)
P value	0.01		0.1 (NS)	
Median (Health AUC) scale score (range).	746 (141-1411)	809 (108-3530)	735 (105-1564)	804 (108-3530)
P value	0.003		0.002	
Median AUC (Activity) scale score (range)	703 (69-1585)	787 (0-3163)	690 (69-1595)	769 (0-3163)
P value	0.02		0.008	

Duration of illness was significantly shorter by **29.1 hours** with oseltamivir 75-mg than with placebo **in the influenza-infected patients**.

In patients treated within 24 hours of symptom onset, symptoms were alleviated **43 hours** earlier with oseltamivir 75-mg than with placebo and this difference attained statistical significance (75-mg vs. placebo: 74.5 h (68.2-98.0) vs. 117.5 h (103.0-143.8), p=0.02).

However, in the small proportion of individuals without confirmed influenza infection **(this means ITT-IP)** (74 in the placebo group; 83 in the 75-mg oseltamivir group) median duration of illness in the 75-mg group was 126.3 h (81-151.5, p=0.93) as against 116.1 h (81.9-139) in the placebo group. Therefore, we can say that the duration of illness was significantly lower in the intention-to-treat population because of the high proportion of influenza-infected patients in this population.

In Trial 2, secondary illness occurred in 16 oseltamivir 75-mg recipients as against 13 placebo recipients in the ITT group and in 9 oseltamivir 75-mg recipients as against 10 placebo recipients in the influenza-infected group. Antibiotics to treat complications were stated to be generally less used but no statistical analysis of this variable has been done. The summary of the results is shown in the next Table.

Number of Influenza Infected Patients Experiencing Secondary Complications as a result of Influenza Illness and Antibiotic Use Over the Treatment Period

Complication	IP Patients Only		ITT Analysis	
	Placebo (n=161)	**Oseltamivir 75-mg (n=158)**	**Placebo (n=235)**	**Oseltamivir, 75-mg (n=241)**
Otitis media	0	0	1	0
Sinusitis	6	4	6	9
Bronchitis	3	5	5	7
Pneumonia	1	0	1	0
Any specified secondary illness (%)*	10 (6.2%)	9 (5.7%)	13 (5.5%)	16 (6.6%)
Antibiotic use (%)	8 (4.9%)	1 (0.6%)	10 (4.3%)	6 (2.5%)

*Specified illnesses: bronchitis, otitis, pneumonia, and sinusitis starting ≥ 48 hours after the first dose

Upper gastrointestinal effects (nausea or nausea with vomiting) were reported more frequently in those receiving oseltamivir (both 75-mg and 150-mg groups).

For nausea, the rates were 4% placebo recipients vs. 12% (2.9-12.6%) oseltamivir 75-mg recipients (p=0.002). For vomiting, the rates were 3% with placebo recipients vs. 10% (2.6-11.3%) with oseltamivir 75-mg recipients. The p-values have however, not been mentioned. 15 patients in all withdrew from the study because of adverse events of which 6 were from the placebo group and 3 from the zanamivir 75-mg group. No increase in withdrawal rate because of adverse events was reported.

Conclusion of the Trials

3. ***The overall conclusions were that oseltamivir did reduce the duration and severity of influenza, and also the incidence of complication arising from influenza but the effects were more pronounced in influenza-positive patients.***
4. ***At the same time, the use of oseltamivir was associated with increase incidence of adverse effects. Presumably, the adverse effects encountered in the trials were not severe as the higher incidence of adverse effect did not lead to an increased withdrawal from the trials due to adverse effects.***

Comparison between Zanamivir and Oseltamivir

Before any economic evaluation is performed, it is necessary to decide on the relative clinical efficacy of the two treatments that would impact on the economic evaluation. The important outcomes as reported in the trials were summarised in the following Table.

PARAMETER	ZANAMIVIR vs PLACEBO	OSELTAMIVIR vs PLACEBO
Median time to alleviation of symptoms in the ITT population	Statistically significant difference of 1 day (1133 vs.1102 patients)	Statistically significant difference of ~ 1 day - 20.7 hrs in Trial 1 (210 vs. 209 patients) - 18.5 hrs in Trial 2 (241 vs. 235 patients)
Median time to alleviation of symptoms in the I P population	Statistically significant difference of 1 day (807 vs. 765 patients)	Statistically significant difference of ~ 1 day - 31.8 hrs in Trial 1 (124 vs. 129 patients) - 29.5 hrs in Trial 2 (158 vs. 161 patients)
Median time to alleviation of symptoms in the high-risk IP population	Difference of 2.5 days (NS) (89 vs 106 patients)	No sub-group analysis for high-risk patients
Use of antibiotics to treat complications ITT IP High-risk IP	 5% difference (1 to 8%) 5% difference (1 to 9%) 9% difference (-3 to 21%)	 ~2% difference ~5% difference No subgroup analysis for high-risk patients
Incidence of adverse effects	Zanamivir recipients had slightly fewer **adverse events*** but these differences did not show statistical significance.	Overall oseltamivir treated groups showed a higher incidence of nausea and vomiting as compared to placebo and these differences were statistically significant.

* Definition of adverse events differ from normal acceptable definition of adverse effects

Therefore, in summary, it would appear that: treatment with zanamivir and oseltamivir can achieve the followings:

- ✓ Statistically significant reductions of 1 day (for ITT and IP populations) on time to alleviation of symptoms were noticed with Zanamivir. Statistically significant reduction of 20 hours (<1 day for the ITT) and 31.8 hours (Trial 1) and 29 hours (Trial 2) in the influenza-infected population in median duration of illness was noticed with oseltamivir in both the major clinical trials considered for our evaluation purpose. Therefore on an average the patient would feel better 0.5-1 day earlier when taking either zanamivir or oseltamivir in addition to standard symptomatic therapy.
- ✓ There was a reduction in complications associated with influenza in the treatment groups as compared to placebo.

However, the significance of these findings needs to be interpreted in the light of their clinical relevance. Certain key issues need to be addressed before a final decision can be made about incorporating the drug into any formulary. These issues will be discussed at the end of the section.

Economic Evaluation

Assumptions used in the evaluation include:

4. Both drug treated and placebo groups received standard symptomatic therapy.
5. The effect size difference of the various relevant outcomes used was based on those obtained from the clinical trials (as summarised in the previous section (See comparison between zanamivir and oseltamivir).
6. Zanamivir or oseltamivir will be used predominantly in the outpatient populations and hence the relevant costs to be considered include acquisition cost only. No other administration cost is involved.

According to information provided by the drug information of NUH, the acquisition cost for zanamivir (the complete kit of 20 blisters and the rota diskhaler used for oral inhalation) is S$26; and the acquisition cost of oseltamivir is S$36 for 10 tablets recommended for a course of treatment.

As there is evidence that both zanamivir and oseltamivir treatment confer a beneficial effect on the relevant clinical outcomes, a **cost-effectiveness analysis (CEA)** will be performed for each of the two drugs. The resultsof the CEA's presented as **Incremental Cost-Effectiveness Ratios (ICER)** as compared against standard treatment are summarised in the following Table.

SUMMARY OF ECONOMIC EVALUATION

	ICER for ZANAMIVIR	**ICER for OSELTAMIVIR**
Symptom Relief ITT ANALYSIS	$26/extra day of faster relief of major symptoms	**$**36/extra day of faster relief of major symptoms
Complications ITT ANALYSIS	S$26/5% = **S$ 520** (S$325 to S$2600) for preventing one extra patient on complications from using antibiotics. Lowest estimate: **$325** Highest estimate: **$2600**	S$36/2% = **S$1800** for preventing one extra patient on complications from using antibiotics.
IP only patients High-risk IP	S$26/5% = **S$520** for preventing one extra patient on complications from using antibiotics. Lowest estimate: **$289** Highest estimate: **$2600**	S$36 /5% = **S$ 720** for preventing one extra patient on complications from using antibiotics.

	S$26/9% =**S$289** for preventing one extra patient on complications from using antibiotics. Lowest estimate: **$123** Highest estimate: the drug is more costly and cause more patients to have complications (i.e. negative ICER value)	

KEY ISSUES PERTINENT TO DECISION MAKING

1. Efficacy vs. Effectiveness Gap

As mentioned in the report of the trials for zanamivir, the local media campaign implemented after influenza surveillance may have raised community awareness of the trial and encouraged patients to present with symptoms early. To derive optimum benefit from zanamivir patients, zanamivir must be started no later than 48 hours after onset of symptoms. The effect of starting treatment after 48 hours is not clear. In fact, **there is no evidence that zanamivir still produces the same effects after 48 hours.**

In addition, the campaign may also have increased rate of influenza-positive patients entering the trials thus resulting in a larger proportion of IP patients in the study population than would otherwise be observed in a real-world practice situation. Close scrutiny of most of the trials would reveal that there was generally greater benefit seen with zanamivir in IP patients**.** However, in real world setting, patients present with symptoms are to be treated with zanamivir rather than after being confirmed influenza-positive. The overall effect of zanamivir may quite likely be less in real practice than what was observed in the trials.

Likewise, the oseltamivir trials specifically screened for acute influenza patients and did not administer the study drug to patients with atypical symptoms or to those who had been ill for long. The study protocol specifically excluded individuals with medical conditions that are often associated with more severe influenza. In a real-life practice situation, it cannot however, be expected that such patients would be excluded from treatment. Hence, the beneficial effect of oseltamivir is likely to be less pronounced in real life practice settings.

2. Statistically Significance may not mean Clinically Importance.

Both zanamivir and oseltamivir significantly shorten the duration of illness when compared to placebo (0.5 to one day). However, the clinical significance of this effect has to be determined. Because, even if the claimed efficacy of zanamivir or oseltamivir in reducing the time to alleviation of major symptoms by one day may be taken to be observed in real world practice, the benefit of such reduction with respect to enhanced quality of life of the patient or in terms of economic gains (reduced resource use) is unclear. Obviously, there is probably some productivity gain in this benefit. However, this is an indirect benefit, which is to be accounted for when framing macro economic policies, but is outside the hospital's interest and the scope of the evaluation.

3. Timing of Treatment Initiation

From the results of the trials, the beneficial results were observed in patients treated within at most 48 hours of onset of symptoms**.** Therefore, to derive optimum benefit from zanamivir patients, zanamivir must be started no later than 48 hours after onset of symptoms. The effect of starting treatment after 48 hours is not clear. This is reflected in the recommendations from international regulatory bodies.

NICE recommends that zanamivir may be used to treat "at-risk" (the term being clearly defined) adults, who are able to begin their treatment within 48 hours of the start of their symptoms when flu is

circulating in the community. Similarly, FDA recommends treatment with oseltamivir in patients who have been symptomatic for no more than 2 days.

Therefore, another important point to consider is how likely that the patients will present for medical consultation before the symptoms occur for more than 48 hours.

Influenza being a self – limiting infection would it not be a better option to just undergo symptomatic treatment especially when such treatment is effective, harmless and inexpensive. The very first recommendation made by NICE is somewhat along these lines … "The NHS should not use zanamivir to treat flu in people who are otherwise healthy. These patients are advised not to visit the GP; but you are advised to stay at home and take medicines from the chemist (pharmacist) to relieve the symptoms." Report of a systematic review carried out within the Cochrane Collaboration and subsequent economic evaluation set in the context of the British Army clearly concludes that in healthy adults aged 14-60 the most cost-effective option is not to take any action.

4. Importance of Reduction of Complications

Although the results from the trials show that the use of zanamivir and oseltamivir reduce the incidence of complications associated with influenza, it is important to decide on the clinical significance of this reduction in the general population and the at risk population.

As previously mentioned, due to unique nature of clinical trial, the beneficial effect on reduction of complication associated with influenza is likely to be reduced in real life practice. Therefore, the ICER's as calculated in the economic evaluation is likely to be much higher.

In addition, any reduction in the beneficial effect will increase the number needed to treat to prevent one case of complications to a much higher number, especially in the case for the general populations. This high cost of preventing complications will be to be considered in light of the severity in otherwise healthy subjects

Even in the case of high risk populations, the effect might not be as pronounced as in the trials for the fact that these populations are normally advised to be immunised against influenza. Furthermore, in an FDA talk paper entitled "FDA Reminds Prescribers of Important Considerations Before Prescribing Flu Drugs" (dated 12, January 2000) the FDA clearly states that prescribers should also be aware that antiviral drugs have not been proven to prevent or effectively treat viral complications of influenza such as viral pneumonia.
Even the NHS advises people who are considered at-risk of complications from flu to be immunized against the flu virus (often referred to as having a 'flu-jab'). This according to the NHS should be the first line of defense against the flu for the people belonging to the "at-risk" categories and who have a higher likelihood of developing complications.

5. Issue of Safety and Emergence of Resistance

As mentioned in previous section, the way of reporting adverse effects caused by zanamivir was rather misleading in the trials. The issue how safe is zanamivir especially in at risk patients such as patients with underlying asthma or chronic obstructive pulmonary disease. FDA has received reports of respiratory problems following inhalation of zanamivir. There was also the report of one patient with underlying respiratory disease who suffered severe adverse effects after being prescribed zanamivir based on symptomatic diagnosis (Refer to NEJM 2000; 342:661-662).

The zanamivir package insert contains important precautionary information regarding risk of bronchospasm in patients with respiratory disease If a decision is made to use zanamivir in patients with airway disease, this should be done only under careful supervision and with adjunctive care including short-acting bronchodilators available.

Furthermore, with these drugs, further replication of the virus is arrested. They in no way ensure viral eradication. In that sense, they may be considered to be "virostatic". Chances of the virus mutating and offering resistance with such drugs are higher.

6. Budgetary Consideration

There are certain other hospital-specific factors that need to be considered before making a decision. It is quite unlikely that zanamivir or oseltamivir would be used for inpatients in the hospital. Considering they are meant predominantly for OPD use, the number of patients treated for influenza in the outpatient setting needs to be identified to assess the budget impact of inclusion of one or both of these drugs in the non-standard drug list.

APPENDIX 1.

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APPENDIX 6c
Gatifloxacin

EXECUTIVE SUMMARY

GATIFLOXACIN

APPLICATION FOR INCLUSION IN NATIONAL UNIVERSITY HOSPITAL (NUH) DRUG LIST AS A NON-STANDARD DRUG
JANUARY 2001

Preamble: The purpose of this document is to evaluate whether Gatifloxacin is a worthwhile addition to the hospital formulary. No specific indication has been applied for. Therefore with the broadest approach Gatifloxacin should be evaluated for all approved indications mentioned in the package insert. However, based on available literature and the company's focus -- CAP has been evaluated as the primary focus.

Comparator:
Using the Antibiotic Guidelines 2000, framed by the Department of Medicine consultants as the basis for the normal treatment pattern for CAP at the NUH
1. Penicillin G iv 2MU every 4 hourly in **young, healthy lobar pneumonia**
2. Cefuroxime iv 750mg 8-hourly or Ceftriaxone iv 1g 12-hourly for all other varieties, except suspect severe or PCP or aspiration or immuno-compromised pneumonia

Clinical Summary: The primary evidence used in the evaluation was based on two phase III head-to-head clinical trials comparing gatifloxacin with ceftriaxone IV in hospitalized patients and oral gatifloxacin with oral clarithromycin in outpatients. The results were summarized in the following table.

	Trial	Study Design	Patients randomized	Clinically evaluable	Treatment duration	Gatifloxacin	Comparator	Rate Difference	95% Confidence Interval
1	Fogarty C et al*	Pros, ran, db, mc	283	205	7-14 days	97	91 (Ceftriaxone)	6%	-2.5% to 17.6%
2	Ramirez J A **	Pros, ran, db, mc	432	372	7-14 days	95	93 (Clarithromycin)	2%	-4.2% to 9.1%

In the trial with hospitalized patients the number of days of hospitalization was also not statistically different.

No statistical difference in ADRs between the treatments in both trials.

In summary, both trials show that gatifloxacin is not statistically different (both in terms of clinical cure and in terms of bacteriologic eradication) from the other two regimens used in the trials.

Costs per day of treatment: see CMA section of economic summary

Economic Summary: Depending on the interpretation of the clinical data, the evaluation can take approach of either a Cost Minimization Analysis or a Cost-Effectiveness Analysis.

CMA: The daily cost of the individual antibiotic treatment (as shown in the following table) will be the determining factor of the choice.

Drugs	**Treatment Cost per Day**
Gatifloxacin IV (400mg once daily)	$82.19
Gatifloxacin oral (400mg once daily)	$5.40
Ceftriaxone IV (1gm 12 hourly)	$5.26
Clarithromycin oral (500mg b.d.)	$6.34

The above costs for IV drugs include acquisition and reconstitution costs only.

CEA

Hospitalized patients:

	Cost of gatifloxacin treatment	***Cost of ceftriaxone treatment***	***ICER ($ per extra patient cured)***
Scenario 1 3 days IV + 4 days oral	**$268.17**	**$47.18**	**$3,683**
Scenario 2 3 days IV + 11 days oral	**$305.97**	**$103.78**	**$3,370**
Scenario 3 7 days IV + 7 days oral	**$613.20**	**$92.82**	**$8,673**

Sensitivity Analysis: See main text

OPD patients:

	Cost of gatifloxacin treatment	***Cost of Clarithromycin treatment***	***ICER ($ per extra patient cured)***
Scenario 1 14 days	**$75.60**	**$88.76**	Gatifloxacin is dominant over clarithromycin
Scenario			Gatifloxacin is

2 11 days	**$59.40**	**$69.74**	dominant over clarithromycin
Scenario 3 7 days	**$37.80**	**$44.38**	Gatifloxacin is dominant over clarithromycin

Sensitivity Analysis: See main text

Recommendations:

1. Based on the available evidence used in this evaluation, there is no indication that Gatifloxacin offers staistically significant advantages over the other antibiotics in the treatment of either Community Acquired Pneumonia or the other indications.
2. However, the results from the economic evaluation show that oral gatifloxacin 400 mg o.d. is a cost-effective alternative to clarithromycin 500 mg b.i.d when used in the outpatient setting.
3. Because of concerns that resistance among pneumococci will rapidly emerge after widespread use of this class of antibacterial agents, it might be prudent to reserve the drug for selected patients with Community Acquired Pneumonia.

GATIFLOXACIN

INCLUSION IN NATIONAL UNIVERSITY HOSPITAL (NUH) DRUG LIST AS A NON-STANDARD DRUG JANUARY 2001

DETAILS OF THE PROPOSED DRUG AND ITS PROPOSED USE

Pharmacological class and mode of action

Gatifloxacin is a synthetic broad-spectrum 8-methoxyfluoroquinolone antibacterial agent for oral or intravenous administration. The oral form is available as 200 mg or 400 mg tablets and the intravenous form is available as 200mg/20 ml or 400-mg/40ml single-use vials intended for dilution prior to administration. The antibacterial action of gatifloxacin results from inhibition of DNA gyrase and topoisomerase IV. DNA gyrase is an essential enzyme that is involved in the replication, transcription and repair of bacterial DNA. Topoisomerase IV is an enzyme known to play a key role in the partitioning of the chromosomal DNA during bacterial cell division.

Spectrum

Gatifloxacin is an extended-spectrum fluoroquinolone with improved gram-positive and anaerobe coverage compared with older agents such as ciprofloxacin. It is slightly less active against enterobacteriaceae and pseudomonas than ciprofloxacin.

Indications

Gatifloxacin is indicated in patients greater than 18 years of age for the treatment of the following infections when caused by susceptible bacteria:
Community acquired pneumonia
Acute bacterial exacerbation of chronic bronchitis
Acute sinusitis
Uncomplicated skin and skin structure infections
Uncomplicated urinary tract infections (cystitis)
Complicated urinary tract infections
Pyelonephritis
Uncomplicated urethral gonorrhea in males
Endocervical and rectal gonorrhea in females.

Since no specific indication has been applied for gatifloxacin. Therefore with the broadest approach gatifloxacin should be evaluated for all approved indications mentioned in the package insert.

However, based on the references and the clinical literature (both comparative and non-comparative) presented by the company, a strong implication can be drawn that the gatifloxacin is intended to be promoted for use in community-acquired pneumonia. An independent literature search by the evaluator also revealed that most published trials of gatifloxacin were for community-acquired pneumonia.

In addition, according to the recommendations in the IDSA Guidelines, "newer respiratory quinolones" (of which gatifloxacin belongs) are recommended for the treatment of community-acquired pneumonia (CAP).

Based on these considerations, it would be reasonably to evaluate gatifloxacin with community-acquired pneumonia (CAP) as the main indication. Gatifloxacin will also be evaluated briefly for other indications at the end of this section.

Treatment Details

For both the oral and the intravenous routes of administration gatifloxacin is recommended once every 24 hours. When switching from IV to oral dose administration no dosage adjustment is necessary.

Co-administered and substituted therapies

Depending on the condition being treated, co-administered therapies could include other antibacterials like cephalosporins or other beta-lactams or macrolides.

Gatifloxacin is expected to substitute for the antibiotics most commonly recommended for the treatment of community-acquired pneumonia and other approved indications.

Main Comparator

The objective of this evaluation is to evaluate whether gatifloxacin is a cost-effective alternative as compared to standard practice in treating CAP at the NUH. Therefore the main comparator should be the antibiotic(s) used for treating CAP at NUH.

Using the Antibiotic Guidelines 2000, framed by the Department of Medicine consultants as the basis for the normal treatment pattern for CAP at the NUH, the following antibiotics should be the main comparators un the evaluation:

1. **Penicillin G iv 2MU every 4 hourly** In **young, healthy lobar pneumonia**
2. **Cefuroxime iv 750mg 8-hourly or Ceftriaxone iv 1g 12-hourly** for all other varieties, except suspect severe or PCP or aspiration or immuno-compromised pneumonia

With regard to OPD treatment, it is assumed that NUH being a tertiary hospital, cases of pneumonia would not be referred to the hospital unless hospitalization is needed. However, there is a clinical trial conducted for outpatients, which, has been used for outpatient treatment evaluation though very few cases are treated as outpatients at the NUH.

However, due to the unavailability of published clinical trails comparing gatifloxacin with Penicillin G or Cefuroxime in the treatment of community acquired pneumonia, the present evaluation is limited to evaluation of the cost-effectiveness of gatifloxacin with other antibiotics that are used in NUH, in this case ceftriaxone for inpatient treatment and clarithromycin for outpatient treatment (see Evidence used in the Evaluation Section).

DATA FROM COMPARATIVE RANDOMIZED TRIALS FOR MAIN INDICATION

Description of Search Strategies

Databases searched included MEDLINE (via Ovid and Pub Med), EMBASE, and CORE BIOMEDICAL COLLECTION using the keywords 'gatifloxacin' and 'clinical trial' and their combination. The bibliography sections provided by the NUH were also searched for relevant articles. Besides the literature provided by the NUH, the literature search by the evaluator retrieved a few other relevant papers (See Appendix 1). However, the evaluator could not locate any published clinical trials comparing gatifloxacin with Penicillin G or Cefuroxime.

Listing of all References

See Appendix 1.

Evidence used in the evaluation

The search revealed three direct head-to-head phase III trials one comparing Gatifloxacin to standard treatment of ceftriaxone/clarithromycin (Fogarty et al, 1999) one to oral clarithromycin (Ramirez et al, 1999), and the other to levofloxacin (Sullivan et al, 1999).

The primary evidence used in the evaluation was however, based on two clinical trials comparing gatifloxacin with ceftriaxone/clarithromycin in hospitalized patients and gatifloxacin with clarithromycin in outpatients (Fogarty et al, 1999; Ramirez et al, 1999) This is because levofloxacin is not used in NUH.

Quality of the Evidence

Both trials were randomized, double-blinded, prospective and comparative and as such would rate very high in the hierarchy of evidence.

The primary endpoint used was clinical cure rate. The term 'clinical cure' was unambiguously defined. The secondary efficacy assessment in both the studies assessed microbiologic responses in the microbiologically evaluable population. "Microbiologically evaluable" patients were clearly defined and the term 'eradicated' was precisely explained.

Adverse drug reactions were monitored in both trials as a measure of safety of the treatments.

Generally baseline characteristics were well matched between the two drug-treated groups in the trial. The most common reason for being considered clinically unevaluable was inadequate duration of therapy. Inclusion-exclusion criteria were clearly defined and stated unambiguously. However, the basis used for sample size calculation was not specified.

A summary of the two trails is listed as follows.

Trial	Study Design	Patients randomized	Clinically evaluable	Treatment duration
Fogarty C et al*	Pros, ran, db, mc,	283	205	7-14 days
Ramirez J A **	Pros, ran, db, mc	432	372	7-14 days

* 1Fogarty C et al , Treating Community-Acquired Pneumonia in Hospitalized Patients: Gatifloxacin vs. Ceftriaxone/Clarithromycin; J Respir Dis. 1999;20(11, suppl):S60-69

** 2 Ramirez JA et al, Treating Community-Acquired Pneumonia in Hospitalized Patients: Gatifloxacin vs. Ceftriaxone/Clarithromycin; J Respir Dis. 1999;20(11, suppl):S40-48

Results of the Trials

TRIAL 1 - Fogarty C et al (1999)

Treatment Details

All patients in the gatifloxacin arm received 400 mg IV +/- transition to 400 mg of gatifloxacin PO qd.

In the ceftriaxone treatment group 96 patients received 1 g IV qd and 45 received 2 g qd (NB. The regimens used is slightly different from that recommended in the Antibiotics Guidelines at NUH. The Guidelines recommend cefotriaxone to be used 1g bd). In addition, 56 ceftriaxone patients received concomitant intravenous erythromycin.

Overall 85 received step down therapy to gatifloxacin, 400 mg qd, or clarithromycin, 500 mg bid. The median duration of therapy was 3 days in both treatment groups. 22 patients (12 in the gatifloxacin group and 10 in the ceftriaxone group) received more than 14 days of therapy.

Summary of the Results of the Trial

Clinical response, clinically evaluable patients	
	Number of patients (%)

Cure rate	Gatifloxacin (n=99)	Ceftriaxone (n=106)
Total	96/99 (97%)	96/106 (91%)
Severe pneumonia	68/71 (96%)	72/80 (90%)
Mild to moderate pneumonia	28/28 (100%)	24/26 (92%)

The cure rate among clinically evaluable patients was 97% for gatifloxacin and 91% for ceftriaxone (p=NS, 95% confidence interval, -2.5% to 17.6%).

Overall bacteriologic eradication rates in microbiologically evaluable patients were 97% for gatifloxacin-treated patients and 92% for ceftriaxone-treated patients (not statistically significant).

Safety and Tolerability

The numbers of patients withdrawn from treatments due to ADRs were comparable between the two treatment arms, with 12 from ceftriaxone arm and 11 from the gatifloxacin arm.

In addition, it was reported in the article that both the severity and frequency of ADRs were substantially comparable between the two treatment arms.

TRIAL 2 (OPD) - Ramirez J A (1999)

Treatment Details

All patients in the gatifloxacin arm received 400 mg oral gatifloxacin once daily. In the other group all patients received 500 mg oral clarithromycin twice daily. The median duration of therapy was 11days in both treatment groups. However, the modal value was 14 days, which means, most patients received therapy for 14 days.

Summary of the Results of the Trial

Clinical response, clinically evaluable patients		
	Number of patients (%)	
Cure rate	Gatifloxacin (n=184)	Clarithromycin (n=188)
Total (93%)	175/184(95%)	175/188
Severe pneumonia	92%	89%

The cure rate among clinically evaluable patients was 95% for gatifloxacin and 93% for clarithromycin (p= NS, 95% confidence interval, -4.2% to 9.1%). Overall bacteriologic eradication rates in microbiologically evaluable patients were 98% for gatifloxacin-treated patients and 93% for clarithromycin-treated patients (not statistically significant).

There was no mention of any reduced incidence of hospitalization in the gatifloxacin treated group in the trial.

Safety and Tolerability

Adverse drug events and abnormal laboratory results led to discontinuation of treatment in 14 gatifloxacin treated patients and 11 clarithromycin treated patients.

Interpretation of Results from the Evidence

Thus both the trials show that gatifloxacin is not any significantly different (both in terms of clinical cure and in terms of bacteriologic eradication) from the other two regimens used in the trials. In the trial with hospitalized patients the number of days of hospitalization was also not statistically different.

[However, it should be noted that in another study of 212 patients CAP patients treated with gatifloxacin spent less time in the hospital and ICU than ceftriaxone +/- erythromycin group but not significantly so.[3] Unfortunately, this was published only in the abstract form that makes the evaluation of the data difficult.]

Economic evaluation

Dependent on the interpretation of the clinical data, two approaches can be adopted for the economic evaluation.

1. Based on the data as mentioned in the previous sections, the evaluation can assume that there is no statistically significant difference in clinical outcomes between the two drugs.

   In this case, it would be appropriate to conduct a **cost-minimization analysis** and whichever regimen would entail lesser costs, would be the better option for the NUH formulary listing.

   The duration of treatment in hospitalized patients ranges from a median of three days to a maximum duration of fourteen days for both Gatifloxacin and Ceftriaxone groups; and for OPD patients the duration of treatment ranges from a median of eleven days to a maximum of fourteen days for both Gatifloxacin and Clarithromycin groups.

   Thus there is no difference in duration of treatment between the two groups that therefore makes the Per Day Cost of Treatment more relevant -- both for hospitalized as well as OPD cases.

2. Another approach is to assume that although the analysis of the data of the clinical trials did not show statistical significant difference, there is

some clinical difference between the two drugs and a **cost-effectiveness analysis** is conducted.

Approach 1

Costs incurred for treating a typical hospitalized patient at the NUH

Condition	*Treatment used*	*Cost/day*			
		Acquisition cost	*No. of reconstitutions required*	*Reconstitution cost* (including WFI @ $0.10 for 20 ml and Syringe ~ $ 0.08)	*Total cost/day of treatment*
Young healthy lobar pneumonia	*Penicillin iv 2MU 4 hourly*	*$0.57/MU*	*6*	$0.60 + $0.08	*$10.92*
Severe pneumonia	*Cefuroxime iv 750 mg 8 hourly*	*$6/ 750 mg*	*3*	*$0.10 + $0.08*	*$18.54*
Severe pneumonia	*Ceftriaxone iv 1g 12 hourly*	*$2.45/1g*	*2*	*$0.10 + $0.08*	*$5.26*
Severe pneumonia	*Gatifloxacin iv 400mg*	*$81.31/400mg*	*1*	*$0.80 + $0.08*	*$82.19*

The above table on an average assumes that there are only reconstitution costs over normal acquisition cost. However, there is also the cost of administration with a compatible intravenous solution, especially with gatifloxacin as it cannot be given as a bolus i.v injection.

Costs incurred for treating a typical OPD patient at the NUH

Drug	*Dosage*	*Acquisition Cost*	*Cost per day of treatment*
Clarithromycin	500mg b.d.	$3.17/tablet	$6.34
Gatifloxacin	400mg o.d.	$5.40/tablet	$5.40

Approach 2

Cost Effectiveness Analysis: for treating CAP in hospitalized patients

Scenario 1: 3 days IV + 4 days oral

The evaluation is based on the data form the clinical trials, the cost per course of treatment of Gatifloxacin and Ceftriaxone using the assumption that the median duration of IV therapy is 3 days in both treatment groups followed by 4 days of oral therapy (based on total duration of therapy being between 7 – 14 days). In the Ceftriaxone group it is assumed that only Ceftriaxone is used without the addition of erythromycin.

The step-down therapies are:

- ✓ Gatifloxacin group – 400mg oral Gatifloxacin o.d.
- ✓ Ceftriaxone group – 500 mg oral Clarithromycin b.d.

Based on these assumptions, the Incremental Cost-Effectiveness Ratio of gatifloxacin as compared against ceftriaxone is calculated as follows:

($268.17 - $47.18) / 6% = $3,683/extra patient with clinical cure

However, by testing the robustness in the sensitivity analysis by using the 95%CI of the clinical cure, the ICER can be as follows:

Difference in outcome	Calculation	ICER (cost per extra outcome achieved)
-2.5 %	($268.17 - $47.18) / -2.5%	Gatifloxacin is less effective and more costly
17.6%	($268.17 - $47.18) / 17.6%	$1,255

Scenario 2: 3 days IV + 11 days oral

The evaluation is based on the data form the clinical trials the assumption that the duration of IV therapy is 3 days in both treatment groups followed by 11 days of oral therapy (based on total duration of therapy being between 7 – 14 days). The other assumptions are the same as in Scenario 1.

Based on these assumptions, the Incremental Cost-Effectiveness Ratio of gatifloxacin as compared against ceftriaxone is calculated as follows:

($305.97 - $103.78) / 6% = $3,370/extra patient with clinical cure

Again, in the sensitivity analysis, the ICERs can range as follows:

Difference in outcome	Calculation	ICER (cost per extra outcome achieved)
-2.5%	($305.97 - $103.78) / -2.5%	Gatifloxacin is less effective and more costly
17.6%	($305.97 - $103.78) / 17.6%	**$1,149**

Scenario 3: 7 days IV + 7 days oral

The evaluation is based on the assumption that the duration of IV therapy is 7 days in both treatment groups followed by 7 days of oral therapy (based on total duration of therapy being between 7 – 14 days). The other assumptions are the same as in Scenario 1.

Based on these assumptions, the Incremental Cost-Effectiveness Ratio of gatifloxacin as compared against ceftriaxone is calculated as follows:

($613.20 - $92.82) / 6% = $8,673/extra patient with clinical cure

Again, in the sensitivity analysis, the ICERs can range as follows:

Difference in outcome	Calculation	ICER (cost per extra outcome achieved)
-2.5%	($613.20 - $92.82) / -2.5%	Gatifloxacin is less effective and more costly
17.6%	($613.20 - $92.82) / 17.6%	$2,957

Cost Effectiveness Analysis: for treating CAP in outpatient

Senario 1: 14 days

The evaluation is based on the data from the clinical trials, the cost per course of treatment of Gatifloxacin and Clarithromycin using the assumption that more than 90% of the patients in both treatment arms received 7 – 14 days of therapy – median being 11 days and mode being 14 days. Therefore, most patients received treatment for 14 days.

Based on these assumptions, the Incremental Cost-Effectiveness Ratio (ICER) of gatifloxacin as compared against clarithromycin is calculated as follows:

($75.6 - $88.76) / 2%

This means that gatifloxacin is dominant over clarithromycin (less costly and more effective).

In the sensitivity analysis, the ICERs can range as follows:

Difference in outcome	Calculation	ICER (cost per extra outcome achieved)
-4.2%	($75.6 - $88.76) / -4.2%	Gatifloxacin is less effective but also less costly
9.1%	($75.6 - $88.76) / 9.1%	Gatifloxacin is dominant

Senario 2: 11 days

The evaluation is based on the assumption that more than 90% of the patients in both treatment arms received 7 – 14 days of therapy – median being 11 days and mode being 14 days. The other assumptions are the same as in Scenario 1.

Based on these assumptions, the Incremental Cost-Effectiveness Ratio (ICER) of gatifloxacin as compared against clarithromycin is calculated as follows:

($59.40 - $67.87) / 2%

Again, the ICER will show that gatifloxacin is dominant over clarithromycin.

In the sensitivity analysis, the ICERs can range as follows:

Difference in outcome	Calculation	ICER (cost per extra outcome achieved)
-4.2%	($59.40 - $69.74) / -4.2%	Gatifloxacin is less effective but also less costly
9.1%	($59.40 - $69.74) / 9.1%	Gatifloxacin is dominant

Scenario 3: 7 days

The evaluation is based on the assumption the patients the minimum duration of treatment of 7 days. The other assumptions are the same as in Scenario 1.

Based on these assumptions, the Incremental Cost-Effectiveness Ratio (ICER) of gatifloxacin as compared against clarithromycin is calculated as follows:

($37.8 - $43.19)/ 2%

Again, the ICER will show that gatifloxacin is dominant over clarithromycin.

In the sensitivity analysis, the ICERs can range as follows:

Difference in outcome	Calculation	ICER (cost per extra outcome achieved)
-4.2%	($37.8 - $44.38) / -4.2%	Gatifloxacin is less effective but also less costly
9.1%	($37.8 - $44.38) / 9.1%	Gatifloxacin is dominant

Issues pertinent to current evaluation

The recommendation by the company to use gatifloxacin is based on the premise that resistance in respiratory pathogens to commonly used antimicrobial agents (specifically pneumococcal resistance to penicillin) is on the rise.

However, the evaluator believes that the decision-makers should consider the following issues before making any decision.

1. **Importance of ascertaining how significant this resistance is with respect to the clinical condition**

   It is well established that antimicrobial resistance is strongly correlated to the pattern of antibiotic usage and the particular geographical location. For instance, important differences exist between the susceptibility patterns of some respiratory tract pathogens to commonly used antimicrobial agents between the US and Canada with the Canadian strains being more susceptible to currently available agents.[4] There is data

to suggest that most pneumonia caused by isolates defined as not fully susceptible to penicillin should respond well to treatment with a beta-lactam antibiotic using optimal dosing, although treatment failures may occur at higher levels of resistance. In addition, resistance to penicillin in otitis media may not mean resistance in CAP. Therefore to know what susceptibility pattern exists in the hospital is very important to rationalize the use of antibiotics better.

2. Interpretation of the IDSA Guidelines

The company seems to be also trying to 'sell' the mention of fluoroquinolones in the IDSA Guidelines. It is true that the IDSA Guidelines recommend fluoroquinolones for empiric therapy of CAP but with the clear messages that where indicated, etiologic pathogen directed therapy is preferable and a narrow spectrum over a broad spectrum is better when the etiology is understood. Amongst reasons assigned for the need to establish etiologic diagnosis prevention of antibiotic abuse and reduction of antibiotic expense have explicit mention. In the event of etiologic diagnosis having been established or strongly suspected pathogen-specific treatment is recommended. If it is available later then changing to the antimicrobial agent that is most cost-effective, least toxic and **most narrow in spectrum** is encouraged.

3. Issue of safety

A few quinolones have either been withdrawn from the markets or their licenses suspended in view of the drug related adverse effects [7]. Therefore it would be advisable to proceed slowly when adopting another new member of the same class.

4. The concern of increasing the chances of resistance and unnecessarily pushing up the hospital drug costs

In the absence of a real 'clinical necessity' or situation demanding the use of this particular drug if gatifloxacin is approved without restriction to either indication or specialty then chances are, it would be used even for indications where say, ciprofloxacin would suffice. The IDSAGuidelines clearly state that resistance patterns of S. pneumoniae (the most commonly implicated etiologic agent) should be just one of a gamut of factors guiding empirical antibiotic selection. There is also a clear mention of recent reports indicating increasing resistance to fluoroquinolones in selective locations correlating with excessive fluoroquinolone use (Hong Kong, England, Ireland, Canada).

Other indications

Acute exacerbations of chronic bronchitis

An analysis of data from a subset of 211 North American patients who had participated in a randomized, double-blind, multicenter trial showed 89% (76/85) patients achieved clinical cure with gatifloxacin 400 mg/d as against 77% (62/81) patients receiving cefuroxime axetil 250 mg bd (p=0.01). Treatment was administered 7-10 days. When the entire study population was taken clinical cure rates were 86% and 83% in the gatifloxacin and cefuroxime groups.[8,9] It is unclear from the article whether this difference is statistically significant and what was the population size in the trial.

Acute sinusitis

A randomized, double blind, multicenter trial of adults with acute infection of the maxillary sinuses, compared the safety and efficacy of gatifloxacin (400 mg once a day for 10 days) to clarithromycin (500 mg twice daily for 14 days).[10] Inclusion exclusion criteria were clearly specified and the terms 'clinical success' or failures were defined. Blinding and method of randomization were described. Follow-up for reporting of adverse events was done for 30 days post-treatment. The basis of sample size calculation was mentioned clearly. Of a total of 421 patients 133 from the gatifloxacin group and 144 from the clarithromycin group were clinically evaluable. At the test-of-cure assessment, 93% (124 of 133) of patients treated with gatifloxacin and 90% (129 of 144) of the patients treated with clarithromycin had a response defined as clinical success. Therefore a 10-day course of gatifloxacin 400 mg once daily was as effective as a 14-day course of clarithromycin 500 mg twice daily, in outpatients with acute, uncomplicated maxillary sinusitis. This would mean that one which works out to be cheaper for the course of therapy should be the drug of choice.

An open-label multicenter non-comparative study to evaluate the safety and efficacy of gatifloxacin in acute sinusitis revealed an overall clinical efficacy of 95%.[11] However the unblind and non-comparative nature of the study make conclusive comparison with other antibiotic treatments difficult .

Urinary tract infection

Pooled analysis of data from two double blind trials that enrolled 728 patients with complicated urinary tract infections (85%) and pyelonephritis (15%) showed positive clinical responses occurring in 93% of patients treated with gatifloxacin 400 mg, vs. 91% of those treated with ciprofloxacin 500 mg twice daily (each given for 7-10 days), respective bacterial eradication rates were 88 and 83% (not statistically significant). [12]

Uncomplicated Gonococcal Infections

The efficacy of single doses of gatifloxacin (400 or 600 mg) or ofloxacin 400 mg in 728 patients with uncomplicated gonococcal infections was investigated in a randomized, double blind trial. [13] Bacterial eradication rates in men with urethral gonorrhoea were 99, 100 and 100% with gatifloxacin 400mg, gatifloxacin 600mg and ofloxacin 400mg respectively; in women with endocervical gonorrhoea, bacterial eradication rates were 99, 99 and 100%(not statistically significant).

Skin and soft tissue infections

Gatifloxacin 400 mg/day for 7 to 10 days showed clinical and bacteriological efficacy similar to that of 7 to 10 days' treatment with levofloxacin 500 mg/day in 407 patients with uncomplicated skin and soft tissue infections in a randomized, double blind trial. [14]
Clinical cure rates were 91% in the gatifloxacin group and 84% in the levofloxacin group (not statistically significant).

It should be emphasized that most of the trials were reported only as abstracts. Therefore limited details of these trials are available as evidence at present and may be considered low in the hierarchy of evidence.

Recommendations:

1. Based on the available evidence used in this evaluation, there is no indication that Gatifloxacin offers staistically significant advantages over the other antibiotics in the treatment of either Community Acquired Pneumonia or the other indications.
2. However, the results from the economic evaluation show that oral gatifloxacin is a cost-effective alternative to clarithromycin in the outpatient setting.
3. Because of concerns that resistance among pneumococci will rapidly emerge after widespread use of this class of antibacterial agents, it might be prudent to reserve the drug for selected patients with Community Acquired Pneumonia.

Appendix 1

Listing of all references used in the current evaluation

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2. Grossman RF, The role of fluoroquinolones in respiratory tract infections; Journal of Antimicrobial Chemotherapy 1997; 40 suppl. A, 59-62

3. Blondeau JM, A review of the comparative in-vitro activities of 12 antimicrobial agents, with a focus on five new 'respiratory quinolones'; Journal of Antimicrobial Chemotherapy 1999; 43 suppl. B, 1-11

4. Piddock LJV et al, Activities of New Fluoroquinolones against Fluoroquinolone-Resistant Pathogens of the Lower Respiratory Tract; Antimicrobial Agents and Chemotherapy, Nov. 1998, 42 (11): 2956-2960

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APPENDIX 6d
Synercid

SYNERCID FOR THE TREATMENT OFNOSOCOMIAL PNEUMONIA, SKIN AND SKIN STRUCTURE AND VREF INFECTIONS FOR INCLUSION IN NATIONAL UNIVERSITY HOSPITAL (NUH) DRUG LIST AS A NON-STANDARD DRUG
MARCH 2001
EXECUTIVE SUMMARY

Part A. Nosocomial pneumonia

Comparator: The appropriate would be Ceftriaxone. The comparator of vancomycin used in the trial submitted by the applicant would not be considered appropriate.

Clinical Summary:
The main evidence for the evaluation of this indication is an article by Fagon et al (2000). Analysis of clinical and bacteriologic responses demonstrated that quinupristin/dalfopristin produced a success rate equivalent to that of vancomycin.

CLINICAL AND BY-PATIENT BACTERIOLOGIC SUCCESS IN THE BACTERIOLOGICALLY EVALUABLE AND THE ALL-TREATED POPULATIONS

Treatment groups			
Outcome	Synercid	Vancomycin	Difference (95% CI)
Bacteriologically evaluable population (n)	87	84	
▪ Clinical success, (%)	49 (56.3)	49 (58.3)	-2.0% (-16.8 to 12.8)
▪ By-patient bacteriologic success, n (%)	51 (58.6)	54 (64.3)	-5.7% (-20.2 to 8.9)
All-treated population, n	150	148	
▪ Clinical success, n (%)	65 (43.3)	67 (45.3)	-1.9% (-13.2 to 9.3)
All-treated population with a baseline pathogen, n	112	107	
▪ By-patient bacteriologic success, n (%)	59 (52.7)	59 (55.1)	-2.4 % (-15.7 to 10.7)

In subgroup analysis of the efficacy of synercid in eradicating S. aureus isolated from the patient, Synercid does not seem to be particularly effective against MRSA. All the rates though not statistically different from the vancomycin group were nevertheless always less than the vancomycin-treated group.

Costs per day of treatment: $218.61

Economic Summary
Approach 1 - Cost-minimisation Analysis

The assumption used in this evaluation is that there is no statistical difference between the mean duration of two treatments. Therefore, the daily cost of treatment for the two treatments becomes the major consideration in the analysis. The daily treatment cost of the various antibiotics is listed in the following table.

Antibiotics	*Cost/day*			
	Acquisition cost	*No. of reconstitutions required*	*Reconstitution cost* (including WFI @ $0.10 for 20 ml and Syringe ~ $ 0.08)	*Total cost/day of treatment*
Ceftriaxone	$1.98/1 g	2	(0.10+0.08) 2=0.36	$4.34
Vancomycin	**$2.05 / 500mg**	**2**	**0.72**	**$8.92**
Tobramycin	$15.00 / 80mg	No recons reqd	-	$45.00
Aztreonam	$28.50	3	0.54	$86.04
Synercid	**$81.00/ 500mg vial**	**3**	**0.54**	**$218.61**

Approach 2- Cost Effectiveness Analysis

This approach assumes that although the data of the clinical trials did not show statistically significant difference, there is some clinical difference between the two drugs. The ICER for the CEA is calculated based on the effect size difference as shown in the trial and the per course treatment cost estimated from the CMA (as shown above).

Clinical cured - All-treated population	
Base case	**Synercid is more costly and less effective**
Sensitivity analysis	
1. **Best case** - Synercid has 9.3% more clinical success. Duration of treatment is taken as the least (6.1 days) for synercid and the duration of treatment for Vancomycin is taken as 13.6 days. 2. **Worst case**	($1333.52 – $121.31)/ 9.3% = **$ 13034.51/extra patient clinically cured** **Synercid is more costly and less effective**
Bacteriologic cured – evaluable patients	
Base case	**Synercid is more costly and less effective**
1. **Best case** - Synercid has 8.9% more bacteriological success. Duration of treatment as per clinical cured. 2. **Worst case**	($1333.52 – $121.31)/ 8.9% **= $13620.33/extra patient bacteriologically cured** **Synercid is more costly and less effective**

Conclusions: Synercid is not a very cost-effective drug when compared with vancomycin regardless of which approach is adopted.

Part B. Skin and skin structure infections

Comparator: The appropriate comparator should be cloxacillin, the comparator used in the evidence supplied by the applicant of oxacillin or cefozolin plus vancomycin might not be the most appropriate comparators.

Evidence used in the evaluation

One study by Nichols RL et al (1999) is used in the evaluation of the cost-effectiveness of synercid in the treatment of skin and skin structure infections. The published paper combined the results from two randomized, direct head-to-head, open-label phase III clinical trials of virtually identical design were conducted across 10 countries around the world

Results of the Trial

The clinical success rate among clinically evaluable patients was 68.2% for synercid and 70.7% for comparators (p=NS, 95% confidence interval, -10.1% to 5.1%).

Number (%) of pathogens eradicated or presumed eradicated in the Bacteriologically evaluable population		
	Synercid (190 patients)	Comparator (161 patients)
Total pathogens	215/323 (66.6%)	188/242 (77.7%) [a]
S. aureus [b]	70/109 (64.2%)	75/100 (75.0%)
S. pyogenes	25/30 (83.3%)	10/13 (76.9%)

[a] P =0.004, [b] P=0.091

Number of pathogens eradicated, presumed eradicated		
Methicillin resistance marker	Synercid	Comparator
S.aureus • *Methicillin resistant* • *Methicillin sensitive* • *Methicillin test not done*	70/109 7/9 (77.8%) 45/70 (64.3%) 18	75/100 3/6 (50.0%) 49/64 (76.6%) 23

Thus the trial shows that Synercid is not significantly better in terms of clinical success from comparator regimens for the treatment of skin and skin structure infections.

Economic evaluation
Based on the data from the clinical trials, the cost per course of treatment of Synercid and vancomycin and cefazolin, the following results are obtained.

Clinical cured - All-treated population	
Base case	**Synercid is more costly and less effective**
Sensitivity analysis	
1. **Best case** - Synercid has 5.1% more clinical success when compared to the comparator. Duration of treatment is taken as the lesser one reported in the two trials i.e. 7 days. Duration of treatment using the comparator is taken as the greater one reported in the two trials i.e. 8.7 days.	($1530.27 – $77.60)/ 5.1% **= $ 28483.73/extra patient clinically cured**
2. **Worst case**	**Synercid is more costly and less effective**

Part C. Infections caused by vancomycin-resistant Enterococcus faecium

Evidence used in the evaluation
A published artcile by Mollering et al (1999) was used as the main evidence to evaluate the effectiveness of synercid in the treatment of VREF infection. The study was a non-comparative one and patients were recruited on a need-basis.

Clinical, bacteriological and overall success rates by population

	Number of patients (%)		
Outcome parameter	All-Treated (N=396)	Clinically evaluable (n=193)	Bacteriologically evaluable (N=156)
Clinical success (%; 95% CI)	219 (55.3%; 50.4 - 60.2%)	142 (73.6%; 67.4-79.8%)	110 (70.5%; 63.4- 77.7%)
Bacteriological success (%; 95%CI)	241 (60.9%; 56.1- 65.7%)	ND	110 (70.5%; 63.4- 77.7%)
Overall success (%; 95% CI)	204 (51.5%; 46.6 - 56.4%)	ND	102 (65.4%; 57.9 - 72.9%)

ND: Not done

The results demonstrated that synercid do possess a degree of clinical efficacy in treating VREF infections.

Economic evaluation
No economic evaluation can be performed for this indication because:
(1) The unavailability of a comparator (no drug is approved at NUH for the treatment of VREF)
(2) The nature of the evidence (single arm study)

Although one might argue that synercid can be compared against placebo, this is theoretically correct, as currently there is no other antibiotic stocked at NUH for the treatment of VREF infections. However VREF infections can be potentially fatal, it would not be ethical to use placebo as a comparator. Linezolid might be considered for use in case VREF infection emerges, but at the present moment, it is not stocked at NUH.

Issues pertinent to current evaluation

1. Clinical Efficacy and Safety Consideration

Although the comparators used by the applicant to support the use of synercid for the treatment of nosocomial pneumonia and tskin structure infections cannot be considered the antibiotics of first choice for the treatment of those indications, the results from the trials could not demonstrate any statistically significant clinical advantages for synercid. Similarly, adverse effects profiles are not established to be any better than the comparators. On the contrary, there is a trend that synercid are doing worse than the comparators in both aspects.

2. Consideration for the treatment of MRSA infections

In Singapore, the approved Product Information for synercid clearly stated that pending susceptibility results, any MRSA should be treated with an eight-hourly dosing of synercid because of the high-likelihood of macrolide resistance. However, in-vitro studies have indicated that the activity of Synercid against S. aureus that are constitutively resistant to macrolides, lincosamides and type B streptogramins (MLS_BC resistance) is reduced compared with that against isolates which do not possess this mechanism of resistance. The majority of MRSA possess MLS_B C. Furthermore, the trial as furnished by the applicant as evidence to support the use did not show Synercid to be any more advantageous than vancomycin.

3. Concern of increasing the chances of microbial resistance and unnecessarily pushing up the hospital drug costs

Besides the lack of demonstrated clinical advantages, definitely, the economic evaluation for synercid in the treatment of nosocomial pneumonia and skin and skin structure infections do not show good cost effectiveness as shown by ICER against the comparators.

Recommendations

1. There is no evidence to support that the use of synercid offer any advantages over existing antibiotics in the treatment of nosocomial pneumonia, and skin and skin structure infections.
2. In the lack at the moment for an antibiotic for the treatment of VREF infections, there is a rationale to restrict the use of synercid for proven VREF infections only.

DETAILS OF THE PROPOSED DRUG AND ITS PROPOSED USE

Pharmacological class and mode of action

Synercid™ is an injectable streptogramin antibiotic consisting of a 30:70 mixture (w/w) of two chemically distinct water-soluble semi-synthetic derivatives of pristinamycin: quinupristin/dalfopristin. Quinupristin and dalfopristin act synergistically by binding to distinct sites of the 50S sub-unit of the bacterial ribosome, dalfopristin causes a conformational change in the ribosome which in turn increases the affinity of the ribosome for quinupristin.

Spectrum of antibacterial action

Synercid has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections:

Aerobic gram-positive microorganisms

- *Enterococcus faecium*
- *Staphylococcus aureus*
- *Streptococcus pyogenes*

NOTE: Synercid is **not active** against *Enterococcus faecalis*. Differentiation of enterococcal species is important to avoid misidentification of *Enterococcus fae*calis as *Enterococcus faecium*.

Synercid also exhibits in vitro MIC of ≤1.0 µg/mL against most isolates (≥90%) of the following aerobic gram-positive microorganisms: Corynebacterium jeikeium, Staphylococcus aureus (methicillin-resistant strains), Staphylococcus epidermidis (including methicillin-resistant strains) and Streptococcus agalactiae. However, the safety and effectiveness of Synercid in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Therapeutic indications

Synercid is indicated for the treatment of the following infections when **known or suspected** to be caused by **susceptible gram-positive organisms**, when **intravenous therapy is appropriate**, and when there are **no other antibacterial agents** active against the organisms that are **suitable** for treatment of the infection in the individual patient:

- Nosocomial pneumonia
- Skin and soft tissue infections
- Clinically significant infections due to Enterococcus faecium

Treatment Details

For VREF infections and nosocomial pneumonia therapy with 7.5 mg/kg per day every 8 hours for duration of 10 days is suggested.
However, for skin and skin structure infections, a 12-hourly regimen of 7.5mg/kg for 7 days is recommended except when the infection is suspected to be macrolide resistant S. aureus or MRSA when an 8-hourly dosing is recommended.

Co-administered and substituted therapies

Depending on the condition being treated, co-administered therapies could include other antibacterials like aztreonam, imipenem (for aztreonam-resistant cases) or tobramycin (where *P. aeruginosa* is indicated).

Synercid is expected to substitute for the antibiotics most commonly recommended for the treatment of nosocomial pneumonia, skin and skin structure infections and clinically significant Enterococcus faecium infections in the NUH. These are ceftriaxone and cloxacillin for nosocomial pneumonia and skin and soft tissues infections respectively.

EVALUATION OF SYNERCID FOR THE TREATMENT OF DIFFERENT INDICATIONS

Main Comparator
The appropriate standard management practice for treating those indications at the NUH should be taken as the comparator in each of those indications.
There are no updated antibiotics guidelines per se, the existing guideline was published in 1990. However, there is a leaflet recommending on the use of antibiotics used in the Department of Medicine at NUH. Based on this information, the following antibiotics should be the main comparators in the evaluation:

1. Ceftriaxone for nosocomial pneumonia (however, most of the treatment is pathogen based)
2. Cloxacillin for skin and skin structure infections
3. At the NUH they are yet to treat a case of VREF. Linezolid might be considered for use in case VREF infection emerges, but at the present moment, it is not stocked at NUH.

However, due to the unavailability of published clinical trails comparing Synercid with ceftriaxone or cloxacillin in the treatment of nosocomial pneumonia and skin and soft tissue infection respectively, the evidence provided by the applicant uses vancomycin +/- azreonam/imipenem with or without additional tobramycin as comparator for treatment of nosocomial pneumonia, and oxacillin or cefazolin plus vancomycin as comparator for skin and skin structure infections.

Nevertheless, it is highly unlikely that vancomycin will be used as the antibiotic of first choice in the treatment of nosocomial pneumonia. Therefore, the choice of comparator in this case is inappropriate. On the other hand, the antimicrobial spectrum of cloxacillin is fairly similar to that of oxacillin and cefazolin (especially oxacillin). Hence the choice of these two antibiotics as comparators would be acceptable. **However, the inclusion of vancomycin as part of the comparator treatment regimen would also render the choice of comparator inappropriate.**

Data from comparative randomized trials for main indication

Description of Search Strategies

A literature search was done primarily to locate clinical trials conducted for Synercid for the indications applied for, namely, nosocomial pneumonia, skin and skin structure infections and clinically significant enterococcus infections. The search revealed only no additional published articles besides those supplied by the applicant.

Listing of all References

See Appendix 1.

PART A. NOSOCOMIAL PNEUMONIA

Evidence used in the evaluation

The main evidence for the evaluation of this indication is an article by Fagon JY et al (2000). **However, it must be noted that vancomycin would not be an appropriate comparator for the treatment of nosocomial pneumonia.**

Quality of the Evidence

The study by Fagon et al (2000) is a prospective, randomized, open-label, international, multicenter direct head-to-head phase III trial comparing Synercid to treatment with vancomycin +/- aztreonam and tobramycin in nosocomial pneumonia.

A summary of the trial is as follows.

Patients randomized	**Bacteriologically evaluable**	**Treatment duration**
298 (Synercid 150; Vancomycin 149)	171	5-14 days Mean duration Synercid: 10.1 $\pm$ 4.0 days Vancomycin: 9.5 $\pm$ 4.1 days

The primary endpoint used was the test-of-cure assessment in the bacteriologically evaluable population that consisted of clinically evaluable patients with documented causative gram-positive baseline pathogens. Clinical response was based on subjective measures like signs and symptoms and an objective measure the chest radiograph (between the seventh and the thirteenth day after the end of treatment). The duration of adverse event monitoring was satisfactory and so was the recording of patient survival.

Inclusion-exclusion criteria were clearly defined and stated unambiguously and there was sufficient measures taken to minimize bias, considering that it was an unblinded study. Treatment assignment was stratified on intubation status. The method of randomization used was also specified.

Generally baseline characteristics were well matched between the two drug-treated groups. The distribution of the most frequently isolated baseline pathogens was similar for both the Synercid and vancomycin groups. However, the frequency of bacteremic pneumonia at enrollment was significantly greater in the vancomycin group than in the Synercid group, in both the all-treated populations intubated at baseline and in the bacteriologically evaluable population. Bilateral pneumonia was significantly more frequent in the Synercid group than in the vancomycin group in the all-treated population intubated at baseline.

Treatment duration was between 5 to 14 days. The distribution of treatments with aztreonam, imipenem, and tobramycin was comparable for both treatment groups.

Although due to the study design, this trial would rate as average in the hierarchy of evidence. Nevertheless, the study going by the report was conducted well.

Summary of the Results of the Trial

Analysis of clinical and bacteriologic responses in the bacteriologically evaluable population and the all-treated population demonstrated that quinupristin/dalfopristin produced a success rate equivalent to that of vancomycin.

CLINICAL AND BY-PATIENT BACTERIOLOGIC SUCCESS IN THE BACTERIOLOGICALLY EVALUABLE AND THE ALL-TREATED POPULATIONS

Treatment groups			
Outcome	Q/D	Vancomycin	Difference (95% CI)
Bacteriologically evaluable population (n)	87	84	
▪ Clinical success, (%)	49 (56.3)	49 (58.3)	-2.0% (-16.8 to 12.8)
▪ By-patient bacteriologic success, n (%)	51 (58.6)	54 (64.3)	-5.7% (-20.2 to 8.9)
All-treated population, n	150	148	
▪ Clinical success, n (%)	65 (43.3)	67 (45.3)	-1.9% (-13.2 to 9.3)
All-treated population with a baseline pathogen, n	112	107	
▪ By-patient bacteriologic success, n (%)	59 (52.7)	59 (55.1)	-2.4 % (-15.7 to 10.7)

Comparability of clinical response between treatment groups was also observed in different subsets of patients based on demographic variables, presenting severe conditions considered as prognostic and risk factors. For instance, clinical success rates in patients presenting with multi-lobar pneumonia were similar between the Synercid (20/43 or 47.0%) and vancomycin groups (25/45 or 56%) (p=NS). Similarly, clinical success rates in patients presenting with bacteremic pneumonia were similar between the Synercid (4/7 or 57.0%) and vancomycin groups (3/17 or 18%) (p=NS), although in this case, the chance of statistical error is high due to the number of patients involved (7 and 17).

CLINICAL SUCCESS RATES BY METHICILLIN RESISTANCE MARKERS FOR Staphylococcus aureus IN THE BACTERIOLOGICALLY EVALUABLE POPULATION AND THE ALL-TREATED POPULATION WITH BASELINE PATHOGEN

Number of pathogens eradicated, presumed eradicated, or satisfactorily reduced			
BACTERIOLOGICALLY EVALUABLE POPULATION			
Methicillin resistance marker	Synercid	Vancomycin	Difference (95% CI)
S.aureus, n (%)	27/52 (51.9)	28/55 (50.9)	1% (-17.9 to 20.0)
▪ *Methicillin resistant,n (%)*	6/20 (30.9)	8/18 (44.4)	-14.4% (-44.9 to 16.1)
▪ *Methicillin sensitive, n (%)*	18/27 (66.7)	18/31 (58.1)	8.6% (-16.3 to 33.5)
▪ *Methicillin test not done, n (%)*	2/5 (40.0)	2/6 (33.3)	6.7%(-50.5 to 63.8)

ALL-TREATED POPULATION WITH A BASELINE PATHOGEN			
S.aureus, n (%)	27/68 (39.7)	28/69 (40.6)	-0.87% (-17.3 to 15.5)
▪ *Methicillin resistant, n (%)*	6/31 (19.4)	8/20 (40.0)	-20.7% (-46.2 to 4.9)
▪ *Methicillin sensitive, n (%)*	19/31 (61.3)	18/39 (46.2)	15.14% (-8.1 to 38.3)
▪ *Methicillin test not done, n (%)*	2/6 (33.3)	2/10 (20.0)	13.3% (-31.8 to 58.5)

Synercid does not seem to be particularly effective against MRSA. All the rates though not statistically different from the vancomycin group were nevertheless always less than the vancomycin-treated group.

Safety and Tolerability

Number (%) patients		
	Synercid Group(N=150)	Vancomycin Group (N=148)
Adverse Clinical Events		
• Non-venous	145 (96.7%)	138 (93.2%)
• Venous	36 (24.0%)	29 (19.6%)
Related Adverse Clinical Events*		
• Non-venous	39 (26.0%)	9 (6.1%)
• Venous	28 (18.7%)	16 (10.8%)
Discontinuation due to Adverse Clinical Events	23 (15.3%)	14 (9.5%)
Discontinuation due to Adverse Laboratory Events	2 (1.3%)	0 (0.0%)

* Probable or possible relationship according to investigator assessment

Of note is the fact that none of the aforesaid differences showed any statistical significance. The numbers of patients withdrawn from treatments due to adverse clinical events were comparable between the two treatment arms, with 23 from Synercid arm and 14 from the vancomycin arm. However, the frequency of related adverse clinical events was substantially higher in the Synercid arm though this difference was not statistically significant.

In an abstract of the same trial attached as part of product monograph it has been reported that 32% (48/150) of Synercid and 27% (40/148) of vancomycin patients discontinued therapy prematurely. These results were not reported in the published paper but only in the monograph. Adverse clinical events and drug ineffectiveness were the most frequent reasons for the discontinuations (12.0 % and 8.8% versus 7.3% and 7.4% respectively, for the Synercid and vancomycin groups).

Interpretation of Results from the Evidence

Thus the trial shows that treatment with Synercid is not any significantly different in terms of clinical success and bacteriologic eradication from vancomycin statistically, but there is a general trend of better outcomes with the vancomycin treatment group. Similar trend again not statistically significant is observed with adverse events. Even in the sub-group analysis with MRSA, similar trend is still evident.

Economic evaluation

(NB. The following economic evaluation compares synercid with vancomycin for the treatment of nosocomial pneumonia, but vancomycin would not be considered the first line antibiotic for treatment of this indication.)

Dependent on the interpretation of the clinical data, two approaches can be adopted for the economic evaluation.

3. A more conservative approach of a cost-minimization analysis based on the data as mentioned in the previous sections, assuming that there is no statistically significant difference in clinical outcomes and adverse effect profiles between the two drugs. In this case, whichever regimen would entail lesser costs would be the preferred option.

4. Another approach is performing a cost-effectiveness analysis based on the treatment cost obtained from the hospital and the effect size differences of clinical outcomes to calculate an ICER for synercid. This assumes that there is some clinical difference between the two drugs in spite of no statistically significant difference.

Approach 1 - Cost-minimisation Analysis

The assumption used in this evaluation is that there is no statistical difference between the mean duration of two treatments. Therefore, the daily cost of treatment for the two d treatment becomes the major consideration in the analysis. The daily treatment cost of the various antibiotics used in the trial and ceftriaxone (which is the drug of first choice for treatment of nosocomial pneumonia) is listed in the following table.

Costs incurred for treating a typical hospitalized patient at the NUH

Antibiotics	*Cost/day*			
	Acquisition cost	*No. of reconstitutions required*	*Reconstitution cost* (including WFI @ $0.10 for 20 ml and Syringe ~ $ 0.08)	*Total cost/day of treatment*
Ceftriaxone	$1.98/1 g	2	(0.10+0.08) 2=0.36	$2.34
Vancomycin	**$2.05 / 500mg**	**2**	**0.36**	**$2.41**
Tobramycin	$15.00 / 80mg	No recons reqd	-	$15.00
Aztreonam	$28.50	3	0.54	$29.04
Synercid	**$81.00/ 500mg vial**	**3**	**0.54**	**$81.54**

Based on the observation from the trial, there existed no difference in the proportions of patients and the pattern of use of additional antibacterials between the two treatment groups. Therefore only the daily treatment costs of Synercid and vancomycin are taken for calculating the cost of treatments per course by multiplying the daily cost of treatment with the average duration (see following table).

Treatment	*Dosage*	*Administration Cost*	*Cost per day of treatment*	*Total cost of treatment (Range)*
Vancomycin group	1 g every twelve hourly	$2.41/500 mg	$9.64	$91.58 ($52.06 – $131.10)
Synercid group	7.5 mg/kg every 8-hourly	$81.54/500 mg	$220.15 (assuming average patient weight of 60 kgs and 1350mg of Synercid consumed)	$2223.51 ($1342.91–$ 3104.10)

Approach 2- Cost Effectiveness Analysis

The ICER for the CEA is calculated based on the effect size difference as shown in the trial and the per course treatment cost estimated from the CMA (as shown above).

Clinical cured - All-treated population	
Base case	**Synercid is more costly and less effective**
Sensitivity analysis	
1. **Best case** - Synercid has 9.3% more clinical success. Duration of treatment is taken as the least (6.1 days) for synercid and the duration of treatment for Vancomycin is taken as 13.6 days. 2. **Worst case**	($1342.91 – $131.10)/ 9.3% = **$ 13030.22/extra patient clinically cured** **Synercid is more costly and less effective**
Bacteriologic cured – evaluable patients	
Base case	**Synercid is more costly and less effective**
1. **Best case** - Synercid has 8.9% more bacteriological success. Duration of treatment as per clinical cured. 2. **Worst case**	($1342.91 – $131.10)/ 8.9% **= $13615.84/extra patient bacteriologically cured** **Synercid is more costly and less effective**

Conclusions: Synercid is not a very cost-effective drug when compared with vancomycin regardless of which approach is adopted.

PART B. Skin and skin structure infections

Evidence used in the evaluation

One study by Nichols RL et al (1999) is used in the evaluation of the cost-effectiveness of synercid in the treatment of skin and skin structure infections.

Quality of the Evidence

The published paper combined the results from two randomized, direct head-to-head, open-label phase III clinical trials comparing Synercid with oxacillin and vancomycin (in the USA Trial) or with cefazolin and vancomycin (in the International Trial) for treating skin and skin structure infections. The two trials of virtually identical design were conducted across 10 countries around the world. A summary of the trial is as follows.

Patients randomized	Clinically evaluable	Bacteriologically evaluable	Treatment duration
893 (Synercid : 450; Comparator: 443)	562 (Synercid : 289; Comparator: 273)	351 (Synercid : 190; Comparator: 161)	3-14 days

The primary endpoint used was clinical response at the Test-of-cure visit (or at End-of-treatment, if the patient was discontinued from the study prematurely) in the clinically evaluable population. The terms "clinically evaluable" and "clinical success" were unambiguously defined. Measures taken to minimize bias (considering that it was an open-label study) were clearly described.

Generally baseline characteristics were well matched between the two drug-treated groups in the trial. Inclusion-exclusion criteria were clearly defined and stated unambiguously. The method of randomization used was specified. The following reasons for not conducting the studies in a blinded fashion were given and were justifiable.

Overall the studies could be rated as well designed and properly conducted; however because of their open-label nature they would rank only moderately high in the hierarchy of evidence.

Results of the Trial

In general, the duration of treatment was longer in the comparator group (see table below).

	Synercid (N=289)	Vancomycin (N=273)	p-value
USA Trial	7.0± 3.20	8.4 ± 3.4	<0.001
International Trial	7.7± 3.5	8.7± 3.3	=0.005

The clinical success rate among clinically evaluable patients was 68.2% for synercid and 70.7% for comparators (p=NS, 95% confidence interval, -10.1% to 5.1%). However, there was a lower rate of clinical success in the Synercid group (57.1%) compared with the comparator regimens (78.2%) in the setting of polymicrobial infections (p=0.012).

Overall incidence of baseline pathogens and bacteriologic eradication rates by resistance markers for *S. aureus* in bacteriologically evaluable patients were as follows.

Number (%) of pathogens eradicated or presumed eradicated in the Bacteriologically evaluable population

	Synercid (190 patients)	Comparator (161 patients)
Total pathogens	215/323 (66.6%)	188/242 (77.7%) [a]
S. aureus [b]	70/109 (64.2%)	75/100 (75.0%)
S. pyogenes	25/30 (83.3%)	10/13 (76.9%)

[a] P =0.004, [b] P=0.091

Number of pathogens eradicated, presumed eradicated		
Methicillin resistance marker	Synercid	Comparator
S.aureus	70/109	75/100
• *Methicillin resistant*	7/9 (77.8%)	3/6 (50.0%)
• *Methicillin sensitive*	45/70 (64.3%)	49/64 (76.6%)
• *Methicillin test not done*	18	23

The by-pathogen bacteriological eradication rate for all pathogens was lower in the Synercid group (66.6%) than in the comparator group (77.7%; P=0.004). A total of 120 of 190 (63.2%) patients in the Synercid group and 108 of 161 in the comparator group experienced clinical success with the eradication or presumed eradication of their pre-therapy pathogen (s). 58 Synercid and 48 comparator patients were both a clinical and bacteriological failure.

In addition, a total of 22 patients in the bacteriologically evaluable population had a pathogen isolated from superinfection (17 of these patients belonged to the Synercid group while 5 patients belonged to the comparator group). In addition 4 patients in the Synercid group and 5 patients in the comparator group, for whom a pre-therapy pathogen was not found, experienced a subsequent superinfection. This indicated that there were more treatment complications in the synercid treated groups compared to the comparator group.

Safety and Tolerability

308 patients (172 from the Synercid group and 136 from the comparator group) prematurely discontinued. The most common reasons for discontinuation were: **adverse clinical events in the** Synercid **group** accounting for **86/172 (50%)** of discontinuations and **treatment failures in the comparator group** accounting for **51/136 (37.5%)** of discontinuations.

283 of 450 (62.8%) Synercid-treated and 239 of 443 (54.0%) comparator-treated patients reported at least one adverse clinical event. The percentage of patients reporting a drug-related adverse venous event at least once during treatment was higher in the Synercid group (66.2%) than in the comparator group (28.4%).

Most frequently reported drug-related adverse events*

Number of patients (%)		
	Synercid Group (N=450)	Comparator Group (N=443)
Patients with adverse clinical events**	113 (25.1)	58 (13.1)
Nausea	114(6.2)	59 (2.0)
Vomiting	115 (3.8)	60 (0.9)
Rash	116 (3.1)	6 (1.4)
Pain	117 (3.1)	1 (0.2)
Pruritus	12 (2.7)	10 (2.3)
Patients with adverse venous events	298 (66.2)	126 (28.4)
Discontinuation due to Adverse Clinical Events	86 (19.1%)	21 (4.7%)
Discontinuation due to therapeutic failure	25 (5.5%)	51 (11.5%)

* Probable or possible drug related events, which occurred in ≥ 2% of either treatment group.

** Excludes venous adverse events

Interpretation of Results from the Evidence

Thus the trial shows that Synercid is not significantly better in terms of clinical success from comparator regimens for the treatment of skin and skin structure infections. The clinical success rate was higher in comparator-treated patients in both trials with polymicrobial infection. Furthermore, it was mentioned that when clinical success in the bacteriologically evaluable population was analyzed in a logistic regression model Synercid patients with polymicrobial infection were less likely than all other patients to be cured or improved (odds ratio = 0.23). That would mean synercid may not be effective in polymicrobial infections.

Economic evaluation

The evaluation is based on the data from the clinical trials, the cost per course of treatment of Synercid and vancomycin and cefazolin using drug administration costs only. Oxacillin is not stocked at NUH and hence not used in the evaluation. However, it should be noted that cefazolin plus vancomycin as a combination may not be the most appropriate comparator for the treatment of skin and skin structure infections.

Clinical cured - All-treated population	
Base case	**Synercid is more costly and less effective**
Sensitivity analysis	
1. **Best case** - Synercid has 5.1% more clinical success when compared to the comparator. Duration of treatment is taken as the lesser one reported in the two trials i.e. 7 days. Duration of treatment using the comparator is taken as the greater one reported in the two trials i.e. 8.7 days. 2. **Worst case**	($1541.05 – $83.87)/ 5.1% **= $ 28572.15/extra patient clinically cured** **Synercid is more costly and less effective**

PART C. Infections caused by vancomycin-resistant Enterococcus faecium

Evidence used in the evaluation

A published artcile by Mollering et al (1999) was used as the main evidence to evaluate the effectiveness of synercid in the treatment of VREF infection.

Quality of the Evidence

The two prospective emergency-use studies of virtually identical design were conducted both in the USA and the world. One study (USA study) enrolled only patients with VREF infection at pre-selected investigative sites in the USA with a documented high prevalence of VREF; the second study, which permitted inclusion of patients with infection caused by both VREF and other gram-positive bacterial pathogens, was conducted worldwide to allow availability of Q/D on an urgent basis to eligible patients. Data from the two trials was integrated and published as a journal article, from which information for the current evaluation was derived.

The study was a non-comparative one and patients were recruited on a need-basis that was clearly elaborated. The primary endpoints used were clinical, bacteriological and overall success rates in the all-treated, clinically evaluable and bacteriologically evaluable patients. A summary of the study is as follows.

Patients enrolled	**No. with VREF**	**Clinically evaluable**	**Bacteriologically evaluable**	**Treatment duration**
467	396	193	156	1-108 days

Inclusion-exclusion criteria were clearly defined and stated unambiguously. Overall the studies could be rated as well designed and properly conducted; however because of their open-label and non-comparative nature they would rate only moderately high in the hierarchy of evidence.

Results of the Trial

The clinical success rate among clinically evaluable patients was 73.6% (confidence interval 67.4% to 79.8%). However, there was a lower rate of clinical success in the all-treated group (55.3%) and the bacteriologically evaluable group (70.5%).

Clinical, bacteriological and overall success rates by population

Number of patients (%)			
Outcome parameter	All-Treated (N=396)	Clinically evaluable (n=193)	Bacteriologically evaluable (N=156)
Clinical success (%; 95% CI)	219 (55.3%; 50.4 - 60.2%)	142 (73.6%; 67.4-79.8%)	110 (70.5%; 63.4- 77.7%)
Bacteriological success (%; 95%CI)	241 (60.9%; 56.1- 65.7%)	ND	110 (70.5%; 63.4- 77.7%)
Overall success (%; 95% CI)	204 (51.5%; 46.6 - 56.4%)	ND	102 (65.4%; 57.9 - 72.9%)

ND: Not done

Overall success rates by population by indication

Number of patients (%)			
Indication	All-Treated (N=396)	Clinically evaluable (n=193)	Bacteriologically evaluable (N=156)
Intra-abdominal infection	53/135 (39.3)	44/68 (64.7)	33/56 (58.9)
Bacteremia of unknown origin	58/113 (51.3)	22/36 (61.1)	14/27 (51.9)
UTI	24/35 (68.6)	19/23 (82.6)	16/18 (88.9)
Central catheter-related bacteremia	23/32 (71.9)	12/14 (85.7)	10/12 (83.3)
Skin and skin structure infection	19/31 (61.3)	16/21 (76.2)	13/18 (72.2)
Bone and joint infection	7/13 (53.8)	5/6 (83.3)	5/6 (83.3)
Endocarditis	4/9 (44.4)	1/5 (20.00	1/4(25.0)
Respiratory tract infection	4/9 (44.4)	3/4(75.0)	1/2(50.0)
Deep wound infection	4/4 (100.0)	3/3 (100)	3/3 (100)
Intravascular infection (not endocarditis)	1/3 (33.3)	1/3 (33.3)	1/3 (33.3)
Other infection	10/16 (62.5)	8/11 (72.7)	6/8 (75.0)

Safety

33 patients prematurely discontinued treatment due to adverse events judged possibly or probably related to study drug. Related laboratory adverse events leading to study discontinuation occurred in five patients (1.3%).

Related[a] adverse events (all-treated population)

Number of patients (%) patients		
Adverse events related to study drug[a]	Most frequent (>1.0%) N=396	Leading to treatment discontinuation N=396
Arthralgia	36 (9.1)	13 (3.3)
Myalgia	26 (6.6)	11 (2.8)
Nausea	13 (3.3)	4 (1.9)
Pain	10 (2.5)	1 (0.4)
Asthenia	6 (1.5)	1 (0.4)
Rash	6 (1.5)	1 (0.4)
Vomitting	6 (1.5)	2 (1.1)
Diarrhoea	5 (1.3)	0 (0.0)
Pruritus	5 (1.3)	0 (0.0)

a Related adverse events are tose judged possibly or probably related to study drug

Interpretation of Results from the Evidence

The overall success rate varied by indication, with somewhat lower rates observed in the intra-abdominal (58.9%) and bacteremia of unknown origin (51.9%) indications and higher rates in UTI (88.9%), central catheter-related bacteremia (83.3%) and skin and skin structure infection (72.2%) indications. Furthermore, it was mentioned that one of the statistically significant explanatory factors associated with clinical failure was presence of VREF bacteremia at study entry (odds ratio = 0.20; p=0.0001). This means that patients having VREF bacteremia at entry would be less likely to be cured than those without bacteremia at entry.

Economic evaluation

No economic evaluation can be performed for this indication because:

(3) The unavailability of a comparator (no drug is approved at NUH for the treatment of VREF)
(4) The nature of the evidence (single arm study)

Although one might argue that synercid can be compared against placebo, this is theoretically correct, as currently there is no other antibiotic stocked at NUH for the treatment of VREF infections. However VREF infections can be potentially fatal, it would not be ethical to use placebo as a comparator.

Linezolid might be considered for use in case VREF infection emerges, but at the present moment, it is not stocked at NUH.

Issues pertinent to current evaluation

1. Clinical Efficacy and Safety Consideration

The comparators used by the applicant to support the use of synercid for the treatment of nosocomial pneumonia and skin and skin structure infections cannot be considered the antibiotics of first choice for the treatment of those indications. For these indications, the first choice of antibiotics would be ceftriaxone and cloxacillin respectively.

Normally, the choice of antibiotics for treatment of any indications is dependent on the prevailing susceptibility pattern of the pathogens, and the safety of the antibiotics. Therefore the comparators used as evidence by the applicant would not represent the best option or most effective treatments for those indications. However, even using these comparators, the results from the trials could not demonstrate any statistically significant clinical advantages for synercid. Similarly, adverse effects profiles are not established to be any better than the comparators. On the contrary, there is a trend that synercid are doing worse than the comparators in both aspects. A particular drawback with Synercid has been the high incidence of adverse clinical events and subsequent discontinuation of therapy. This has been seen generally in all comparative trials and in the non-caomparative clinical trials patients experienced severe arthralgias and myalgias.

2. Consideration for the treatment of MRSA infections

The recommendation by the company to use synercid is based on the premise that resistance in gram-positive pathogens to commonly used antimicrobial agents (specifically staphylococcal resistance to methicillin, and enterococcal resistance to vancomycin) is on the rise.

In Singapore, the approved Product Information for synercid clearly stated that pending susceptibility results, any MRSA should be treated with an eight-hourly dosing of synercid because of the high-likelihood of macrolide resistance. However, in-vitro studies have indicated that the activity of Synercid against S. aureus that are constitutively resistant to macrolides, lincosamides and type B streptogramins

(MLS_BC resistance) is reduced compared with that against isolates which do not possess this mechanism of resistance. The majority of MRSA possess MLS_B C.

Furthermore, the trial as furnished by the applicant as evidence to support the use did not show Synercid to be any more advantageous than vancomycin.

3. Concern of increasing the chances of microbial resistance and unnecessarily pushing up the hospital drug costs

Added to all the above considerations there is always a concern when incorporating an antibiotic that of encouraging unnecessary and irrelevant or inappropriate usage thereby impacting both resistance and hospital budgets unfavorably.

Besides the lack of demonstrated clinical advantages, definitely, the economic evaluation for synercid in the treatment of nosocomial pneumonia and skin and skin structure infections do not show good cost effectiveness as shown by ICER against the comparators.

Recommendations

1. There is no evidence to support that the use of synercid offer any advantages over existing antibiotics in the treatment of nosocomial pneumonia, and skin and skin structure infections.
2. In the lack at the moment for an antibiotic for the treatment of VREF infections, there is a rationale to restrict the use of synercid for proven VREF infections only.

Appendix 1

Listing of all references used in the current evaluation

1. JY Fagon et al, Treatment of Gram-positive Nosocomial Pneumonia Prospective randomized, comparison of Quinupristin/Dalfopristin versus Vancomycin. American Journal of Respiratory Critical Care Medicine 2000; 161: 753-762

2. Nichols RL et al; Treatment of hospitalized patients with complicated gram-positive skin and skin structure infections: two randomized, multicenter studies of quinupristin/dalfopristin versus cefazolin, oxacillin or vancomycin. Journal of Antimicrobial Chemotherapy 1999, 44, 263-273.

3. Moellering RC et al; The efficacy and safety of quinupristin/dalfopristin for the treatment of infections cased by vancomycin-resistant Enterococcus faecium. Journal of Antimicrobial Chemotherapy 1999, 44, 251-261.

4. Winston DJ et al, Quinupristin/Dalfopristin Therapy for Infections Due to Vancomycin-Resistant *Enterococcus faecium.* Clinical Infectious Diseases 2000; 30: 790-97.

5. Drew RH et al, Treatment of methicillin-resistant *Staphylococcus aureus* infections with quinupristin-dalfopristin in patients intolerant of or failing prior therapy. Journal of Antimicrobial Chemotherapy 2000; 46: 775-784.

6. Pechere JC et al, Current and future management of infections due to methicillin-resistant staphylococci infections; the role of quinupristin/dalfopristin. Journal of Antimicrobial Chemotherapy 1999; 44: *Topic A,* 11-18.

7. Nichols RL, optimal treatment of complicated skin and skin structure infections. Journal of Antimicrobial Chemotherapy 1999; 44: *Topic A,* 19-23.

8. Rubinstein E et al, Safety and tolerability of quinupristin/dalfopristin: administration guidelines. Journal of Antimicrobial Chemotherapy 1999; 44: *Topic A,* 37-46.

9. Linden PK, Quinupristin/Dalfopristin: A New Therapeutic Alternative for the Treatment of Vancomycin-Resistant Enterococcus faecium and Other Serious Gram-Positive Infections. Today's Therapeutic Trends 1997; 15(2): 137-153.

APPENDIX 6e
Linezolid

LINEZOLID FOR THE TREATMENT OF COMMUNITY-ACQUIRED PNEUMONIA, NOSOCOMIAL PNEUMONIA, SKIN AND SKIN STRUCTURE AND VREF INFECTIONS FOR INCLUSION IN NATIONAL UNIVERSITY HOSPITAL (NUH) DRUG LIST AS A NON-STANDARD DRUG
APRIL 2001

DETAILS OF THE PROPOSED DRUG AND ITS PROPOSED USE

Pharmacological class and mode of action

Linezolid is a synthetic antibacterial agent which, is the first of a new class of compounds, the oxazolidinones. Linezolid binds to a site on the bacterial 23S ribosomal RNA of the 50S sub-unit and prevents the formation of a functional 70S initiation complex which is an essential component of the translation process. Its activity is bacteriostatic against some species (eg enterococci) and bactericidal against others (eg pneumococci).

Spectrum of antibacterial action

Linezolid has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections:

Aerobic and facultative gram-positive microorganisms

- *Enterococcus faecium (vancomycin-resistant strains only)*
- *Staphylococcus aureus (including methicillin-resistant strains)*
- *Streptococcus agalactiae*
- *Streptococcus pneumoniae (penicillin-susceptible strains only)*
- *Streptococcus pyogenes*

The following in-vitro data are available, but their clinical significance is unknown. At least 90% of the following organisms exhibit an in-vitro minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for linezolid. However, the safety and efficacy of linezolid in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic and facultative gram-positive microorganisms

- *Enterococcus faecalis (including vancomycin-resistant strains)*
- *Enterococcus faecium (including vancomycin-susceptible strains)*
- *Staphylococcus epidermidis (including methicillin-resistant strains)*
- *Staphylococcus hemolyticus*
- *Streptococcus pneumoniae (including penicillin-resistant strains)*
- *Viridans group streptococci*

Aerobic and facultative gram-negative microorganisms

Pasteurella multocida

Therapeutic indications

Linezolid is indicated for the treatment of the adult patients with the following infections caused by the susceptible strains of the designated microorganisms:

- Community –acquired pneumonia caused by Streptococcus pneumoniae (penicillin sensitive strains only), including cases with concurrent bacteraemia, or Staphylococcus aureus (methicillin-sensitive strains only)

- Nosocomial pneumonia caused by Staphylococcus aureus (methicillin-sensitive and methicillin-resistant strains) or *Streptococcus pneumoniae (penicillin-sensitive strains only)*. Combination therapy may be clinically indicated if the documented or presumptive pathogens include gram-negative organisms.

- Uncomplicated skin and skin structure infections caused by *Staphylococcus aureus (imethicillin-sensitive strains only)* or *Streptococcus pyogenes.*

- Complicated skin and skin structure infections caused by *Staphylococcus aureus (imethicillin-sensitive and methicillin-resistant strains), Streptococcus pyogenes* or *Streptococcus agalactiae*. Combination therapy may be clinically indicated if the documented or presumptive pathogens include gram-negative organisms.

- Vancomycin-resistant *Enterococcus faecium* including cases with concurrent bacteraemia.

Treatment Details

Linezolid is available as intravenous injection, film-coated tablets or oral suspension. No dosage adjustment is required when switching from intravenous to oral therapy as oral bioavailability is approximately 100%. The injection should be administered over a period of 30-120 minutes. The oral forms may be taken with or without food. Both forms are recommended to be administered twice daily.

Recommended dosage and duration for adults

Infections (including those associated with concurrent bacteraemia)	Twice daily dosage and route of administration	Duration of treatment
Community –acquired pneumonia	600 mg IV or orally	10-14 days
Nosocomial pneumonia		
Uncomplicated skin and skin structure infections	400 mg orally	10-14 days
Complicated skin and skin structure infections	600 mg IV or orally	10-14 days
Enterococcal infections	600 mg IV or orally	14-28 days

Co-administered and substituted therapies

Depending on the condition being treated, co-administered therapies could include other antibacterials active against gram-negative aerobes (e.g. aztreonam).

Linezolid is expected to substitute for the antibiotics most commonly recommended for the treatment of nosocomial and community-acquired pneumonia, skin and skin structure infections and vancomycin-resistant Enterococcus faecium infections in the NUH. These are ceftriaxone and cloxacillin for nosocomial pneumonia and skin and soft tissue infections respectively.

EVALUATION OF SYNERCID FOR THE TREATMENT OF DIFFERENT INDICATIONS

Main Comparator

The appropriate standard management practice for treating those indications at the NUH should be taken as the comparator in each of those indications.
Based on information provided by one of the consultants at the Department of Medicine and a leaflet (Antibiotic Guidelines 2000) recommending on the use of antibiotics used in the Department of Medicine at NUH, the following antibiotics should be the main comparators in the evaluation:

3. Ceftriaxone for nosocomial pneumonia (however, most of the treatment is pathogen based)
4. Penicillin G in young, healthy lobar pneumonia, cefuroxime or ceftriaxone for all other varieties, except suspect severe or PCP or aspiration or immunocompromised pneumonia
5. Cloxacillin for skin and skin structure infections
6. At the NUH they are yet to treat a case of VREF. There is no recommendation for the treatment of VRE at NUH.

The antimicrobial spectrum of cloxacillin is fairly similar to that of oxacillin. Hence the choice of this antibiotic as a comparator would be acceptable in skin and soft tissue infections.

Data from comparative randomized trials for main indication

Description of Search Strategies

A literature search was done primarily to locate clinical trials conducted for Linezolid for the indications applied for and also for any other articles that may be relevant to the decision at hand. The search revealed a few additional published articles besides those supplied by the applicant. The search included a MEDLINE search (via PubMed) and the bibliography sections of the articles available were also looked into for additional papers.

Listing of all References

See Appendix 1.

PART A. COMMUNITY ACQUIRED PNEUMONIA

Evidence used in the evaluation

The trial conducted for Community-acquired pneumonia in outpatients is yet to be published as a journal article. From the available literature it seems that it was presented as an abstract in a scientific proceeding (Program and abstracts of the American Thoracic Society International Conference (Toronto). New York: American Thoracic Society, 2000: 654). However, the evaluator could not retrieve this abstract. The best the evaluator could do was to read about this trial from different articles published about Linezolid and report from one article [R]. This article contained fairly more information about the trial as compared to other articles. An abstract entitled “Linezolid Eradicates common pathogens in community-acquired pneumonia: summary of three studies” by Cammarata SK et al and presented at the European Conference on Clinical Microbiology and Infectious Diseasesin 2000 was provided by the company. This abstract was also referred to and any additional information was also incorporated.

Quality of the evidence

The study was a randomized, single-blind study that included **>540 adult outpatients with community-acquired pneumonia.** Linezolid (600 mg orally twice daily) was compared with cefpodoxime (200 mg orally twice daily). Treatment continued for 7-14 days, with follow-up at 15-21 days after the end of therapy. Approximately 22% of patients had multilobar pneumonia and ~9% had pleural effusion at baseline (Pharmacia, unpublished data). Nothing else could be known about this trial. Hence the quality of evidence used here would be considered to be very poor.

Summary of the results

Of 201 clinically evaluable patients who received Linezolid treatment, 180 (~90%) had clinical cure; similarly, 187 (~91%) of 206 patients who received cefpodoxime treatment had clinical cure (P=0.68).

Clinical efficacy in evaluable patients

Agent	Number of patients with clinical cure/total no. treated	% clinically cured
Linezolid	180/201	90%
Cefpodoxime	187/206	91%

Among 49 microbiologically evaluable patients who received linezolid treatment, the microbiological success rate was 88% (43); among 47 microbiologically evaluable patients, who received cefpodoxime treatment, the microbiological success rate was 89% (42).

Microbiological efficacy in evaluable patients

Agent	Number of patients with microbiological cure/total no. evaluable	% clinically cured
Linezolid	43/49	88%
Cefpodoxime	42/47	89%

Rates of eradication of pathogens

Agent	*S. pneumoniae*	*S. aureus*	*H.influenzae*
Linezolid	24 of 27 (88.9%)	11 of 12 (91.7%)	10 of 12 (83.3%)
Cefpodoxime	19 of 21 (90.5%)	11 of 12 (91.7%)	13 of 15 (86.7%)

It is unclear from the above table whether the eradication rates for pathogens were number of pathogens eradicated by total number of pathogens isolated.

Safety and Tolerability

The most common treatment-related adverse events were diarrhoea, nausea and headache; these events were generally mild to moderate in intensity and similar between treatment groups. There were two deaths described in the linezolid treatment group and none in the cefpodoxime treatment group. Although both deaths occurred early during the course of treatment, neither was considered treatment related (Pharmacia, unpublished data).

Interpretation of results

The results clearly show that linezolid is at bet equivalent to the comparator and in no way better than it.

Economic evaluation

The evaluator opines that performing an economic evaluation based on such scanty evidence would do justice neither to the time of the evaluator nor the reader and would not be a fair evaluation on which to base decisions.

Evidence used in the evaluation

The trial conducted for **community-acquired pneumonia in hospitalized patients** is yet to be published as a journal article. From the available literature it seems that it was presented as an abstract in a scientific proceeding (Program and abstracts of the 9th International Congress on Infectious Diseases (Buenos Aires). Boston: International Society of Infectious Diseases, 2000). However, the evaluator could not retrieve this abstract. However, the following evidence is derived from the same article that was used in CAP for outpatients.

Quality of the evidence

The trial was a multinational,randomized, open-label trial that evaluated linezolid as treatment of >700 patients with CAP who required hospitalization. Patients received either linezolid (600 mg iv twice daily) or ceftriaxone (1 g twice daily), which was switched to oral linezolid (600 mg twice daily) or oral cefpodoxime (200 mg twice daily), respectively at the investigator's discretion. Follow-up occurred 15-21 days after the end of treatment. In both clinically evaluable treatment groups at baseline, ~15% of patients had pleural effusion, and around 34% of patients presented with multilobar pneumonia (Pharmacia, unpublished data). Nothing else could be known about this trial. Hence the quality of evidence used here would be considered to be very poor.

Summary of the results

Among 272 clinically evaluable patients in the linezolid treatment group, the clinical cure rate was 91% (247); among 254 patients in the ceftriaxone/cefpodoxime treatment group, the clinical cure rate was 89% (225) (P=0.40).

Clinical efficacy in evaluable patients

Agent	Number of patients with clinical cure/total no. treated	% clinically cured	P-value
Linezolid	247/272	91%	0.40
Ceftriaxone	225/254	89%	

For a subset of 53 patients for whom blood cultures were positive for S. pneumonia, there was a clinical cure rate of 93% among the 30 patients who received linezolid treatment, compared with 70% among the 23 patients who received ceftriaxone/cefpodoxome treatment (P=0.02). No demographic or baseline history explains the fact that the clinical cure rate achieved with linezolid treatment was higher than that achieved with cephalosporin treatment for patients with S. pneumonia community-acquired pneumonia and bacteraemia.

Safety and Tolerability

Diarrhoea and nausea were the most common adverse events described in both treatment groups. Although there were slightly more deaths in the ceftriaxone/cefpodoxime treatment group than in the linezolid group (19 vs 15), none of the deaths in either group was attributable to study medication, and most occurred during the posttreatment period (Pharmacia, unpublished data).

Rates of eradication of pathogens

Agent	*S. pneumoniae*	*S. aureus*	P-value

Linezolid	63 of 71 (89%)	18 of 20 (90%)	>0.2
Ceftriaxone	62 of 69 (90%)	13 of 17 (77%)	

Interpretation of results

The results clearly show that linezolid is equivalent to the comparator and in no way better than it.

Economic evaluation

The evaluator opines that performing an economic evaluation based on such scanty evidence would do justice neither to the time of the evaluator nor the reader and would not be a fair evaluation on which to base decisions.

PART B. NOSOCOMIAL PNEUMONIA

Evidence used in the evaluation

The main evidence for the evaluation of this indication is an article by Rubinstein E et al (2001). However, it must be noted that vancomycin may not be an appropriate comparator for the treatment of nosocomial pneumonia.

Quality of the Evidence

The study by Rubinstein et al (2001) is a prospective, randomized, double-blind, international, multicenter, head-to-head phase III trial comparing Linezolid +/- aztreonam with vancomycin +/- aztreonam in empirical treatment of nosocomial pneumonia.

A summary of the trial is as follows:

Patients included for ITT	Clinically evaluable	Microbiologically evaluable	Treatment duration (ITT)	Treatment duration (clinically evaluable)
396 (Linezolid 203; Vancomycin 193)	204 (Linezolid 108; Vancomycin 96)	94 (Linezolid 54; Vancomycin 40)	7-21 days Mean duration Linezolid: 9.6 ± 4.4 days Vancomycin: 8.9 ± 4.4 days	Mean duration Linezolid: 11.6 ± 3.4 days Vancomycin: 10.6 ± 3.1 days

The primary endpoint used was the clinical outcome at the test-of-cure assessment (conducted at the follow-up visit 12-28 days after the end of therapy) in the clinically evaluable population and microbiological outcome at the microbiologically evaluable population (clinically evaluable patients with a confirmed baseline pathogen from respiratory specimens or blood cultures that was not resistant to either study medications).
Clinical response was based on subjective measures like signs and symptoms and an objective measure the chest radiograph (between the twelfth and twenty-eighth day after the end of treatment).
Inclusion-exclusion criteria were clearly defined and stated unambiguously. Generally baseline characteristics were well matched between the two drug-treated groups. The distribution of baseline pathogens was similar for both the Linezolid and vancomycin groups.
Treatment duration was between 7 and 21 days. This trial would rate high in the hierarchy of evidence.

Nevertheless, the study report definitely leaves room for improvement. Neither the method of randomization was specified nor was there mention of measures taken to minimize bias, considering

that vancomycin's dose adjustment was done by unblinded personnel, not involved in assessment of either efficacy or safety. Nothing was mentioned about the duration of adverse event monitoring.

Summary of the Results of the Trial

Analysis of the primary efficacy variables demonstrated that linezolid produced a success rate equivalent to that of vancomycin.

Assessment of efficacy in clinically evaluable and microbiologically evaluable populations

Test of Cure Assessment	Linezolid	Vancomycin	P-value	Difference (95% CI)
Clinical outcome [a]	107	91	0.79	-14.9 to 11.3
▪ Cure	71 (66.4%)	62 (68.1%)		
▪ Failure	36 (33.6%)	29 (31.9%)		
▪ Indeterminate	1	5		
Microbiological outcome [b]	53	39	0.69	-22.8 to 15.0
▪ Success	36 (67.9%)	28 (71.8%)		
▪ Failure	17 (32.1%)	11 (28.2%)		
▪ Indeterminate	1	1		

Note. Percentages are based on number of assessed patients excluding missing and indeterminate patients. [a] Among clinically evaluable patients. [b] Among microbiologically evaluable patients

Clinical success rates and microbiological success rates were similar between the Linezolid and vancomycin groups.

Eradication rates at follow-up by pathogen among microbiologically evaluable patients

Pathogen	Linezolid recipients	Vancomycin recipients
Staphylococcus aureus	25/41 (61.0)	15/23 (65.2)
▪ Documented	3/41 (7.3)	5/23 (21.7)
▪ Presumed	22/41 (53.7)	10/23 (43.5)
MRSA	15/23 (65.2)	7/9 (77.8)
▪ Documented	1/23 (4.3)	2/9 (22.2)
▪ Presumed	14/23 (60.9)	5/9 (55.6)
Streptococcus pneumonia	9/9 (100)	9/9 (100)
▪ Documented	3/9 (33.3)	6/9 (66.7)
▪ Presumed	6/9 (66.7)	3/9 (33.3)

NOTE. Data are number of patients with eradication/total (%).

Linezolid does not seem to be particularly "better" against any of the pathogens. All the rates though not statistically different from the vancomycin group were nevertheless always less than the vancomycin-treated group. In addition, in the linezolid group, the "documented eradication rate" was always less than the "presumed eradication rate".

It would also do well to look at the baseline pathogen distribution to obtain a better understanding of linezolid's efficacy with respect to microbiological eradication.

Baseline pathogen distribution in the two treatment groups

Parameter	Linezolid recipients (n=203)	Vancomycin recipients (n=193)
No baseline pathogen	79 (38.9%)	89 (46.1%)
Gram-negative pathogens only	30 (14.8%)	21 (10.9%)
Target pathogens only	73 (36.0%)	67 (34.7%)
Mixed pathogens	21 (10.3%)	16 (8.3%)

Safety and Tolerability

Safety assessments were done for the ITT population.

Important adverse events and laboratory evaluations

	Linezolid Group (N=203)	Vancomycin Group (N=193)
Adverse Clinical Event		
▪ At last 1 event	143 (70.4%)	143 (74.1%)
▪ Most common adverse event - Diarrhoea	19 (9.4%)	15 (7.8%)
Drug related Adverse Clinical Events occurring in >1% patients		
▪ Diarrhoea	9 (4.4%)	5 (2.6%)
▪ Abnormal liver function tests	2 (1.0%)	3 (1.6%)
▪ Rash	0 (0%)	3 (1.6%)
Discontinuation due to Adverse Clinical Events	13 (6.4%)	20 (10.4%)

Of note is the fact that there were 36 deaths (17.7%) in the linezolid group as compared to 49 (25.4%) in the vancomycin group. Though none of the deaths in either study medications were attributed to study medications, 30 of 36 (83.3%) and 36 of 49 (73.4%) deaths in the linezolid and vancomycin groups respectively were due to concomitant underlying diseases. Thus reduction in mortality was not a statistically significant advantage of Linezolid when compared to vancomycin.

Interpretation of Results from the Evidence

Thus the trial shows that treatment with Linezolid does not demonstrate statistically significant differentce in terms of clinical success and bacteriologic eradication from vancomycin, but there is a general trend of better outcomes with the vancomycin treatment group. In terms of adverse events, again not statistically significant, Linezolid is slightly better than vancomycin, though the numbers in this case are far too small to conclude anything with certainty.

Economic evaluation

(NB. The following economic evaluation compares linezolid with vancomycin for the treatment of nosocomial pneumonia, but vancomycin would not be considered the first line antibiotic for treatment of this indication.)

Dependent on the interpretation of the clinical data, two approaches can be adopted for the economic evaluation.

5. A more conservative approach of a cost-minimization analysis based on the data as mentioned in the previous sections, assuming that there is no statistically significant difference in clinical outcomes and adverse effect profiles between the two drugs. In this case, whichever regimen would entail lesser costs would be the preferred option.
6. Another approach is performing a cost-effectiveness analysis based on the treatment cost obtained from the hospital and the effect size differences of clinical outcomes to calculate an ICER for linezolid. This assumes that there is some clinical difference between the two drugs in spite of no statistically significant difference.

Approach 1 - Cost-minimisation Analysis

The assumption used in this evaluation is that there is no statistical difference between the mean duration of the two treatments. Therefore, the daily cost of treatment for the two drug treatments becomes the major consideration in the analysis. The daily treatment cost of the various antibiotics used in the trial and ceftriaxone (which is the drug of first choice for treatment of nosocomial pneumonia) is listed in the following table.

Costs incurred for treating a typical hospitalized patient at the NUH

Antibiotics	*Cost/day*			
	Acquisition cost	*No. of reconstitutions required*	*Reconstitution cost* (including WFI @ $0.10 for 20 ml and Syringe ~ $ 0.08)	*Total cost/day of treatment*
Ceftriaxone	$1.98/1 g	2	(0.10+0.08) 2=0.36	$2.34
Vancomycin	**$2.05 / 500mg**	**2**	**0.36**	**$2.41**
Linezolid	**$82.00/ 600mg vial**	**-**	**-**	**$164.00**

Based on the observation from the trial, there existed no difference in the proportions of patients and the pattern of use of additional antibacterials between the two treatment groups. Therefore, only the daily treatment costs of linezolid and vancomycin are taken for calculating the cost of treatments per course by multiplying the daily cost of treatment with the average duration (see following table).

Treatment	*Dosage*	*Administration Cost*	*Cost per day of treatment (Including reconstitution costs)*	*Total cost of treatment (Range)*
Vancomycin group	1 g bd	$2.41/500 mg	$9.64	$102.18 ($72.30 – $132.07)
Linezolid group	600 mg bd	$ 82/600 mg	$164.0 (assuming bd dosage)	$1902.40 ($1344.80–$2460.0)

Approach 2- Cost Effectiveness Analysis

The ICER for the CEA is calculated based on the effect size difference as shown in the trial and the per course treatment cost estimated from the CMA (as shown above).

Clinical cured – Clinically evaluable population	
Base case	**Linezolid is more costly and less effective**
Sensitivity analysis	
1. **Best case –** Linezolid has 11.3% more clinical success. Duration of treatment is taken as the least (8.2 days) for linezolid and the duration of treatment for Vancomycin is taken as 13.7 days. 2. **Worst case**	($1344.80 – $132.07)/ 11.3% = **$ 10732.12/ extra patient clinically cured** **Linezolid is more costly and less effective**
Microbiologically evaluable patients	
Base case	**Linezolid is more costly and less effective**
1. **Best case** - Linezolid has 15.0% more bacteriological success. Duration of treatment as per clinical cured. 2. **Worst case**	($1344.80 – $132.07)/ 15.0% **= $8084.87/extra patient bacteriologically cured** **Linezolid is more costly and less effective**

Conclusions: Linezolid is not a very cost-effective drug when compared with vancomycin regardless of which approach is adopted.

PART C. UNCOMPLICATED SKIN AND SKIN STRUCTURE INFECTIONS

The trial conducted for uncomplicated skin and skin structure infections is yet to be published as a journal article. From the available literature it seems that it was presented as an abstract in some scientific proceeding. However, the evaluator could not retrieve this abstract. The best the evaluator could do was to read about this trial from different articles published about Linezolid and reporting in one article that seemed to be quite comprehensive is repeated here.

Quality of the evidence

The study was a multinational, randomized, double-blind study, linezolid (400 mg twice daily) was compared with clarithromycin (250 mg twice daily) as treatment of 332 adult patients with uncomplicated skin and skin structure infections. Treatment continued for 7-14 days, with follow-up at 7-21 days after the end of treatment. The most common diagnoses in both treatment groups at baseline were cellulitis, skin abscesses, and furuncle. However, nothing else could be known about the design of the trial and as such it can be said to be poor evidence.

Summary of the results

Of 124 clinically evaluable patients who received linezolid treatment 113 (91%) had clinical cure compared with 114 (93%) of 123 patients who received clarithromycin treatment.

Clinical efficacy in evaluable patients

Agent	Number of patients with clinical cure/total no. treated	% clinically cured
Linezolid	113/124	91%
Clarithromycin	114/123	93%

Among microbiologically evaluable patients who received linezolid treatment, the microbiological success rate was 98%; among microbiologically evaluable patients, who received clarithromycin treatment, the microbiological success rate was 97% (P=0.67) (Pharmacia, unpublished data).

Rates of eradication of pathogens

Agent	*S. aureus*	*P-value*
Linezolid	38 of 39 (97%)	0.75
Cefpodoxime	51 of 53 (96%)	

(Pharmacia, unpublished data)
It is unclear from the above table whether the eradication rates for pathogens were number of pathogens eradicated by total number of pathogens isolated.

Safety and tolerability

Adverse events were generally mild to moderate in intensity; nausea and diarrhea were the most common treatment related adverse events in both treatment groups (Pharmacia, unpublished data). There were no deaths described in either treatment group during the study (Pharmacia, unpublished data).

PART D. COMPLICATED SKIN AND SKIN STRUCTURE INFECTIONS

Evidence used in the evaluation

One phase III, double-blind, comparative study by Stevens DL et al is used primarily in the evaluation of the cost-effectiveness of linezolid in the treatment of skin and skin structure infections. This study was published as a journal article. The other studies that are mainly open-label phase II studies are available only as abstracts.

Quality of the Evidence

The published paper described a randomized, direct head-to-head, double-blind, double-dummy phase III multicenter clinical trial comparing Linezolid with oxacillin –dicloxacillin for treating skin and skin

structure infections. The trial of was conducted across 133 centres from November 1998 to June 1999. A summary of the trial is as follows.

Treatment	Patients randomized	Patients included for ITT analysis	Clinically evaluable	Microbiologically evaluable	Treatment duration (days, (mean ± s.d.)	IV treatment duration (days, mean ± s.d.)
Linezolid	403	400	298 (74.5%)	143 (35.8%)	13.4 ± 5.4 days	4.7 ± 3.3 days
Oxacillin Dicloxacillin	423	419	302 (72.1%)	151 (36.0%)	13.4 ± 6.0 days	4.7 ± 3.1 days

The primary endpoints used were clinical cure rates in both the intent-to-treat (ITT) population and the clinically evaluable (CE) population and the microbiological success rate in microbiologically evaluable (ME) patients. The terms "clinically evaluable", "clinical success", "microbiologically evaluable" and "microbiological success" were unambiguously defined.

Generally baseline characteristics were fairly well matched between the two drug-treated groups in the trial. However, the mean duration of infection in the Linezolid group at baseline was, 5.6±7.8 days as compared to 6.2±15.1 days in the oxacillin-dicloxacillin group.
Inclusion-exclusion criteria were clearly defined and stated unambiguously. The method of randomization used was, however, not specified. Measures taken to ensure blinding and minimize bias were clearly described. The number of discontinuations (dropouts and withdrawals) was also clearly enumerated with reasons. Overall the study could be rated as well designed and properly conducted.

Results of the Trial

In the ITT population clinical cure rates were comparable between the two treatment groups. 279 of 400 (69.8%) of linezolid-treated patients and 272 of 419 (64.9%) oxacillin-dicloxacillin-treated patients achieved clinical cure (p=0.141; 95% CI, -1.58 to 11.25). The clinical success rate among clinically evaluable patients was 88.6% (264 of 298) for linezolid and 259 of 302 (85.8%) for oxacillin-dicloxacillin-treated group (p=0.300, 95% confidence interval, -2.5% to 8.2%).

Clinical cure rates in the ITT and clinically evaluable patients

Patient group	Linezolid	Oxacillin-dicloxacillin	*95% CI*	*P value*
ITT	279/400 (69.8%)	272/419 (64.9%)	*-1.58, 11.25*	*0.141*
Clinically evaluable	264/298 (88.6%)	259/302 (85.8%)	*-2.5, 8.2*	*0.300*

In the microbiologically evaluable patients, the microbiological success rate was 88.1% in the linezolid group versus 86.1% in the oxacillin-dicloxacillin group (p=0.606; 95% CI, -5.6 to 9.7).

Microbiological cure rates in the microbiologically evaluable patients

Linezolid	Oxacillin-dicloxacillin	*P value*	*95% CI*
126/143 (88.1%)	130/151 (86.1%)	*0.606*	*-5.6, 9.7*

The by-pathogen bacteriological eradication rate for the clinically important pathogens was similar between the treatment groups. However, for S. aureus, the eradication rate in the linezolid-treated group was better (91.4%) as compared to comparator-treated group (84.5%) though not statistically significant (p=0.139). A small discrepancy however, was noted in the reporting of this eradication. This was reported differently in the body and differently in the table. The table defined eradication as number of eradicated pathogens divided by the total number of pathogens whereas, the text defined it as number of patients free of infection divided by the total number of patients.

Eradication rates of selected baseline pathogens in microbiologically evaluable patients

Pathogen	Eradication rate (%)			
	linezolid	Oxacillin-dicloxacillin	P	95% CI
S. aureus	85/93 (91.4%)	87/103 (84.5%)	0.139	-2.1, 16.0

S. pyogenes	23/29 (79.3%)	27/32 (84.4%)	0.607	-24.4, 14.3
S. agalactiae	7/7 (100%)	4/6 (66.7%)	0.608	-4.4, 71.1

There was no mention of any reduction in the duration of hospital stay using linezolid. The total durations of treatment both intravenous and per oral were stated to be similar in both treatment groups.

Safety and Tolerability

189 of 400 patients (47.3%) in the linezolid-treated group and 173 of 419 (41.3%) comparator-treated patients reported at least one adverse clinical event. The percentages of patients with at least one adverse considered drug-related were similar between the linezolid (67/400 or 16.8%) and oxacillin-dicloxacillin (72/419 or 17.2%) groups. Nausea was the most common drug related adverse event reported in both linezolid (14/400 or 3.5%) and comparator (12/419 or 2.9%) groups. Serious adverse events were reported in 5.5% of the linezolid group and 4.5% of the comparator group.
Hypertension was reported in 12 of 400 (3.0%) of linezolid-treated patients and 1 of 419 (0.2%) of oxacillin-dicloxacillin treated patients. However, whether this difference reached statistical significance is not clear. Anyway, since linezolid is a mild inhibitor of monoamine oxidase (MAO) the likelihood of this happening due to linezolid cannot be ruled out. However, in this case it has been clearly stated that this was not due to MAO inhibiting or interacting properties as 11 of these 12 patients were not on any concomitant medications.

Most frequently reported adverse events in ≥ 2% of either treatment group

Number of patients (%)		
	Linezolid Group (N=400)	Oxacillin-dicloxacillin Group (N=419)
Patients with adverse clinical events	189 (47.3%)	173 (41.3%)
Nausea	23 (5.8%)	24 (5.7%)
Headache	22 (5.5%)	16 (3.8%)
Vomiting	13 (3.3%)	8 (1.9%)
Hypertension	12 (3.0%)	1 (0.2%)
Diarrhoea	11 (2.8%)	12 (2.9%)
Localised Pain	11 (2.8%)	3 (0.7%)
Dyspepsia	10(2.5%)	7 (1.7%)
Insomnia	10(2.5%)	9 (2.1%)
Dizziness	9 (2.3%)	3 (0.7%)
Abdominal pain (localized)	8 (2.0%)	5 (1.2%)
Constipation	7 (1.8%)	13 (3.1%)
Pruritus (non-application site)	6 (1.5%)	9 (2.1%)
Fever	5 (1.3%)	11 (2.6%)
Discontinuation due to Adverse Clinical Events	12 (3.0%)	23 (5.5%)
Discontinuation due to therapeutic failure	9 (2.3%)	15 (3.6%)

An important point noteworthy however, is that significantly more patients in the oxacillin-dicloxacillin group withdrew due to adverse events judged to be drug-related than did patients in the linezolid group (3.6% versus 1.0%, p=0.014)

Interpretation of Results from the Evidence

Thus the trial shows that linezolid is as effective as (but not significantly better than) the comparator regimen in terms of clinical success for the treatment of skin and skin structure infections. The clinical success rate although was higher in the linezolid-treated patients in both the clinically evaluable and intention-to-treat patients, did not reach statistical significance.

The adverse event profile was also comparable to oxacillin-dicloxacillin treatment. However, there was more discontinuation due to AE in the oxacillin/dicloxacillin treated group. Special caution may be

required in patients with concomitant administration of adrenergic agents due to the potential for interaction with linezolid, a mild inhibitor of monoamine oxidase.

Economic evaluation

The evaluation based on the data from the clinical trial, the cost per course of treatment of linezolid and oxacillin-dicloxacillin using drug administration costs only, could not be done in this case because both oxacillin and dicloxacillin are not available in Singapore. However, cloxacillin which has a fairly similar spectrum a compared to oxacillin is available in both intravenous and oral forms. And, taking the prices of cloxacillin dosage forms and assuming them to have the same activity as the oxacillin-dicloxacillin regimen in the trial the following results would be obtained.

Costs incurred for treating a typical hospitalized patient at the NUH

Antibiotics	*Cost/day*			
	Acquisition cost	*No. of reconstitutions required*	*Reconstitution cost* (including WFI @ $0.10 for 20 ml and Syringe ~ $ 0.08)	*Total cost/day of treatment*
Cloxacillin	$0.50/500 mg	8	(0.10+0.08) 8= 1.44	$5.44
Linezolid	**$82.00/ 600mg vial**	**-**	**-**	**$164.00**

Switch to the respective oral forms would mean:

Linezolid 600 mg twice daily which works out to ($73× 2) =$146 a day and
Cloxacillin 500 mg four times a day which works out to ($0.08 × 4) = $ 0.32 a day.

The situation based on mean and total durations of intravenous therapy in both the drug treated groups and the resultant clinical and microbiological cures in the ITT populations and the microbiologically evaluable populations may be summarized as follows:

Clinical cured - All-treated population	
Base case - Linezolid has 4.9% more clinical success when compared to the comparator. Duration of treatment is taken as 13.4 days (4.7 days i.v. and 8.7 days oral). Duration of treatment using the comparator is taken as reported in the trial i.e. 13.4 days (4.7 days i.v. and 8.7 days oral).	($2041 - $28.35)/4.9% **= $41074.49** / extra patient clinically cured assuming average treatment durations with both drugs as reported in the trial.
Sensitivity analysis	
1. **Best case** - Linezolid has 11.25% more clinical success when compared to the comparator. Duration of treatment is taken as the lesser one reported in trial i.e. 8 days total (1.4 days i.v. and 6.6 days oral). Duration of treatment using the comparator is taken as the greater one reported i.e. 19.4 days total (7.8 days i.v. and 11.6 days oral). 2. **Worst case**	($1193.2 – $46.14)/11.25% **= $ 10,196.09 /extra patient clinically cured** **Linezolid is more costly and less effective**

The evaluator would conclude that Linezolid would involve very high ICER s for modest benefits, which have not been demonstrated to be statistically significant.

PART E. INFECTIONS CAUSED BY VANCOMYCIN-RESISTANT ENTEROCOCCUS FAECIUM

Evidence used in the evaluation

A published artcile by Chien et al (2000) was used as the main evidence to evaluate the effectiveness of linezolid in the treatment of VREF infection.

Quality of the Evidence

The study was a case series report of 17 patients with infections (15 patients with VRE and 2 patients with methicillin-resistant *Staphylococcus* species) treated prospectively for serious multi-drug resistant gram-positive bacterial. The study was conducted in one center in the USA. Patient selection was done according to a compassionate-use protocol that was adequately described.
The primary endpoints used were microbiological cure and clinical cure and these terms were clearly defined. A summary of the study is as follows.

Overall the study though well designed and properly conducted at best can be qualified as an "experience" with Linezolid in VRE infections and cannot be taken as "strong evidence". This is due to reasons that will be discussed shortly.

Results of the Trial

Clinical Response

A total of 15 patients were involved in the study. The mean duration of hospitalization prior to VRE infection was 19.4 $\pm$ 3.1 days. VRE was routinely isolated from multiple sites. The mean number of infected sites per patient was 2.6 $\pm$ 0.2. Pre-existing medical conditions included dialysis-dependant renal failure (6), orthotopic liver transplantation (5), abdominal or thoracic surgery (6), malignancy (3), bacterial endocarditis (2), HIV infection (1) and 13 of 15 patients were undergoing treatment in the ICU.
The mean duration of therapy was 20.5 $\pm$ 3.5 days (range 5-42 days) with the longest duration of IV therapy of 42 days for VRE endocarditis. In addition 10 patients (73.3%) underwent either surgical drainage or debridement of the infection or removal of an infected prosthetic device. Three patients (20%) required a second course of therapy because the VRE infection recurred.

Ten patients (66.7%) were alive at the end of the intended treatment period. Microbiological cure was achieved in all of these patients. Eight patients (53.3%) were alive at short-term follow-up (7-10 days after completion of therapy), all were determined to be clinically cured at that time. Seven patients (46.6%) were alive at long–term follow-up (15-30 days after completion of therapy), and all were still considered clinically cured.
Overall 8 patients died before long-term follow-up. Five of these patients died before completing the intended course of therapy. None of these deaths was attributable to VRE infection. Overall clearance of the original VRE infection was demonstrated for all but one of the patients who died before long-term follow-up.

Safety

Two patients developed probable adverse reactions to therapy. These were leukopenia and nausea.

Interpretation of Results from the Evidence

Though the study seems to have been conducted as per a well-defined protocol, without a comparator or control group it cannot be definitively determined if the clinical outcome was a result of linezolid therapy. Since, abscess drainage and prosthetic device removal were also done concurrently with linezolid therapy, it cannot be said for sure that the favourable clinical outcome was the sole result of linezolid therapy. The follow-up was a maximum of 30 days that does not seem to be adequate to measure relapse for some of the indications. In addition, the high-mortality rate observed in the study (53.3%) casts some doubts on the claim that Linezolid being considered "highly effective".

Economic evaluation

No economic evaluation can be performed for this indication because:

1. The unavailability of a comparator (no drug is approved at NUH for the treatment of VREF)
2. The nature of the evidence (single arm study)

Although one might argue that linezolid can be compared against placebo, this is theoretically correct, as currently there is no other antibiotic stocked at NUH for the treatment of VREF infections. However VREF infections can be potentially fatal, it would not be ethical to use placebo as a comparator.

In a journal article [A] discussing Linezolid it was mentioned that clinical and microbiological success rates in patients receiving intravenous linezolid were studied in VRE infections. The efficacy of 7 to 28 days' twice daily linezolid 200 mg and 600 mg was

Linezolid at twice-daily dosages of 200 or 600 mg affected clinical cure in 73.7% and 86.6% of patients with vancomycin-resistant enterococcal infections (positive cultures of urine, wound, abscess, respiratory secretions, or peritoneal or pleural fluid) respectively. The higher dosage was significantly (p=0.015) more effective in producing microbiological cure (85.7% 58.6%). However, this data was obtained from the parent company and nothing more about this study could be understood.

Issues pertinent to current evaluation

1. Clinical Efficacy and Safety Consideration

The comparators used by the applicant to support the use of linezolid for the treatment of nosocomial pneumonia and skin and skin structure infections cannot be considered the antibiotics of first choice for the treatment of those indications. For these indications, the first choice antibiotics would be ceftriaxone and cloxacillin respectively.

Normally, the choice of antibiotics for treatment of any indications is dependent on the prevailing susceptibility pattern of the pathogens, and the safety of the antibiotics. Therefore the comparators used as evidence by the applicant would not represent the best option or most effective treatments for those indications. However, even using these comparators, the results from the trials could not demonstrate any statistically significant clinical advantages for linezolid. Similarly, adverse effects profiles are not established to be any better than the comparators.

2. Consideration for the treatment of VRE infections

The recommendation by the company to use linezolid is based on the premise that resistance in gram-positive pathogens to commonly used antimicrobial agents (specifically staphylococcal resistance to methicillin, and enterococcal resistance to vancomycin) is on the rise. However, the evidence for such indications in well-controlled clinical trials (especially for VRE infections) is scanty at best.

3. Concern of increasing the chances of microbial resistance and unnecessarily pushing up the hospital drug costs

Added to all the above considerations there is always a concern when incorporating an antibiotic that of encouraging unnecessary and irrelevant or inappropriate usage thereby impacting both resistance and hospital budgets unfavorably.

Besides the lack of demonstrated clinical advantages, definitely, the economic evaluations for linezolid in the treatment of nosocomial pneumonia and skin and skin structure infections do not show good cost effectiveness as shown by ICER against the comparators.

Recommendations

3. There is no evidence to support that the use of linezolid offer any advantages over existing antibiotics in the treatment of nosocomial pneumonia, and skin and skin structure infections.
4. In the lack at the moment for an antibiotic for the treatment of VREF infections, there is a rationale to restrict the use of linezolid for proven VREF infections only.

Appendix 1

Listing of all references used in the current evaluation

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APPENDIX 7
NUH Evaluation Process

Title: (generic name – brand name – strength – dosage form)

1) Centralize text
2) Use bold font
3) Use capital letter
4) Underline text

E.g. **OFLOXACIN (TARIVID®) 200 MG/100ML**

Introduction

Include - chemical class of the drug
- spectrum of activity (when necessary)
- indications

Product information

- tabulate information whenever possible

Alternative drug available in NUH

Pharmacokinetics

Include – ADME (whenever possible)
- if the drug is compared to another of the same class, tabulate information

Pharmacology

Provide the mechanism of action(s) of the drug

Efficacy studies

- All studies must be referenced individually
- Evaluate the efficacy studies critically
- Tabulate results of important studies whenever possible

APPENDIX 8
Request Form

Drug Co.

Non Standard Drug Application Form A

This form is to be completed in detail and forwarded to the Pharmacy and Therapeutics Committee c/o Drug Information Service, Pharmacy Department.

Section I : (To be filled by applicant)

A) Product Information

i) Non-proprietary (generic) name : .....

ii) Proprietary name : .....

iii) Dosage form and strength : .....

iv) Cost of the drug : .....

B) Therapeutic Indication

.....

.....

.....

C) Submit the following reviews (1 each) on:

i) Pharmacological actions

ii) Pharmacokinetics

iii) Adverse reaction

D) ***Submit published literature on the efficacy studies(from reputable medical journals. Please do not include company brochures or unpublished data.***

Date requested : .....

Company : .....

Representative : .....

Drug Co.

Non Standard Drug Application Form A

This form is to be completed in detail and forwarded to the Pharmacy and Therapeutics Committee c/o Drug Information Service, Pharmacy Department.

Section I : (To be filled by applicant)

A) Product Information

i) Non-proprietary (generic) name : .....

ii) Proprietary name : .....

iii) Dosage form and strength : .....

iv) Cost of the drug : .....

B) Therapeutic Indication

.....

.....

.....

C) Submit the following reviews (1 each) on:

i) Pharmacological actions

ii) Pharmacokinetics

iii) Adverse reaction

D) ***Submit published literature on the efficacy studies(from reputable medical journals. Please do not include company brochures or unpublished data.***

Date requested : .....

Company : .....

Representative : .....

Draft

Non-Standard Drug Request Form B

This form is to be completed in detail and forwarded to the Pharmacy and Therapeutics Committee c/o Drug Information Service, Pharmacy Department, for approval.

A Non-proprietary (generic) name : .....

B Proprietary name : .....

C Dosage form & strength : .....

D Available drugs of the same class with the same therapeutic use in NUH : .....

: .....

E Which similar drug do you recommend to delete : .....

F Quantity of drug to be used : .....

G Reason(s) why this drug is superior to drugs listed in (D). (Use additional sheets if necessary)

.....

.....

.....

.....

Date requested: ..... Requested by: .....

Approved by : .....
(Chief of Clinical Department or Service)

APPENDIX 9
Review

NATIONAL UNIVERSITY HOSPITAL
PHARMACY & THERAPEUTICS COMMITTEE

Review of Drug for Inclusion in Hospital Drug List

(I) Drug Under Review : _____

(Please see attached review of the drug.)

(II) Drugs in the hospital drug list that are prescribed for the same indications:

(IV) Please compare the efficacy, adverse reactions and cost of the drug under review to the existing drugs in the hospital drug list using the following format:

1. is:

a) is ☐ comparable ☐ superior ☐ inferior in efficacy

b) has ☐ comparable ☐ increased ☐ decreased incidence of adverse drug reactions

c) is ☐ comparable ☐ more costly ☐ less costly

Additional comments:

2. Based on the above evaluation, my opinion is to

- ☐ include the drug in the hospital drug list for general use
- ☐ include but restrict usage
- ☐ reject the drug

3. Should any of the current available drugs in the list be deleted? Please tick in the appropriate box.

Thank you.

Please return this form to Pharmacy & Therapeutics Committee c/o Drug Information Service (Department of Pharmacy) by _____

_____ (Signature)

APPENDIX 10
Expert Opinion

(Form where opinion of relevant specialty is sought – atypical report and clinical papers are sent along with it)

Date: _____

_____

_____

_____
National University Hospital

Dear

REVIEW OF _____

The Pharmacy and Therapeutics Committee has received an application for the inclusion of [illegible] tablet in the hospital drug list and would like to seek your opinion about the product.

Kindly return feedback on the attached form provided to Pharmacy & Therapeutics Committee, c/o Drug Information Service, Department of Pharmacy.

Thank you.

Yours sincerely

Yow Kah Lai (Ms)
Secretary
Pharmacy & Therapeutics Committee
National University Hospital

APPENDIX 11
Terms of Reference of the P&T Committee

Pharmacy & Therapeutics Committee Terms of Reference

1. To recommend policies to the medical and nursing staff and the Hospital Administration on all matters relating to the use of drugs in patients, including drugs in the treatment and prevention of disease and drugs for clinical investigation and research.

2. To advise the Chief Pharmacist on the selection of drugs for specified diseases; on selection of drugs to be stocked in patient care areas in the Hospital; on the distribution and administration of medications, including errors in the prescribing, preparation, drawing up and administration of drugs.

3. To evaluate pharmacological and clinical data from all appropriate sources on new drugs or formulations offered or requested for use in the Hospital. In particular, the Committee will from time to time, conduct drug utilization reviews to measure the usage of certain drugs with regard to their safety, cost and prevention or therapeutic efficacy.

4. To maintain and continually upgrade through revision a Formulary of drugs accepted for use in the Hospital. The selection of items to be included in the Formulary will depend on the evaluation of their efficacy, safety and cost. The Committee will attempt to minimise the duplication of similar drug types, drug entities and drug products (formulations) in order to reduce unnecessary expense.

5. To monitor and review unwanted (adverse) drug reactions which occur in the Hospital and relate them to similar information from other appropriate sources.

6. To establish and organise appropriate educational programmes for the Hospital professional staff on matters relating to drug use, including a drug information bulletin and a clinical pharmacy course.

7. To advise the National Healthcare Group Management as to whether the standard drug list requires modification.

APPENDIX 12
P&T Member Questionnaire

QUESTIONNAIRE

1) A P&T Committee is	Yes	No	Not sure
i. Indispensable in every hospital	☐	☐	☐
ii. Essential though not indispensable	☐	☐	☐
iii. Is 'nice' to have	☐	☐	☐
iv. Is not very important	☐	☐	☐
v. Is just a "show"	☐	☐	☐

2) A P&T Committee's most important objective (s) is (are)	Yes	No	Not sure
i. To control the hospital budget	☐	☐	☐
ii. To facilitate efficient management of the hospital as a "health care portfolio"	☐	☐	☐
iii. To control doctors' prescription habits	☐	☐	☐
iv. Management of the hospital inventory	☐	☐	☐

3) Who of the following 'must' be members of the Pharmacy and Therapeutics Committee?	Yes	No	Not sure
i. Physicians	☐	☐	☐
ii. Pharmacists	☐	☐	☐
iii. Financial analysts	☐	☐	☐
iv. Hospital administrators	☐	☐	☐
v. Nurses	☐	☐	☐
vi. Health economists	☐	☐	☐

4) What viewpoints would be considered to add value to your decisions?

	Yes	No	Not sure
i. Financial analysis	☐	☐	☐
ii. Healthcare administration	☐	☐	☐
iii. Pharmacoeconomic analysis	☐	☐	☐

5) How often do you think the committee should meet to achieve a meaningful purpose?

	Yes	No	Not sure
i. Once every month	☐	☐	☐
ii. Once in three months	☐	☐	☐
iii. Once in two months	☐	☐	☐
iv. More often	☐	☐	☐

6) What kind of decisions does the P&T Committee most often make in your hospital?

	Yes	No	Not sure
i. Patient management decisions	☐	☐	☐
ii. Budget management decisions	☐	☐	☐
iii. Formulary drug decisions	☐	☐	☐
iv. Diagnostic and screening procedures decisions	☐	☐	☐

7) A formulary should ideally be

	Yes	No	Not sure
i. An essential drug list	☐	☐	☐
ii. A list of life-saving drugs meant for subsidy	☐	☐	☐
iii. A list of drugs most frequently used	☐	☐	☐
iv. A comprehensive list of drugs avoiding generic duplication	☐	☐	☐
v. Others (Please specify)			

8) How close is your formulary to the aforesaid choice

Not at all | very slightly close | somewhat close | close | very close

9) Which according to you is (are) the factor (s) to be considered when including/ deleting drugs from a formulary?

		Yes	No	Not sure
i.	Cost	☐	☐	☐
ii.	Only clinico-therapeutic properties of drug and alternatives	☐	☐	☐
iii.	Institutional budget	☐	☐	☐
iv.	Economic impact of drug on the therapeutic area	☐	☐	☐
v.	Safety	☐	☐	☐
vi.	Cost-effectiveness	☐	☐	☐
vii.	Brand equity	☐	☐	☐
viii.	Other Quality of Life factors	☐	☐	☐

10) Does your approval process consider all these factors?

Not at all | only little | considers partially | considers | considers completely

11) What does the term “cost” connote to you?

		Yes	No	Not sure
i.	Acquisition cost	☐	☐	☐
ii.	Total cost of treatment	☐	☐	☐
iii.	Budget impact	☐	☐	☐
iv.	Cost to the patient	☐	☐	☐

12) What does the term “cost-effectiveness connote to you?

		Yes	No	Not sure
i.	Cheap	☐	☐	☐
ii.	Value for money	☐	☐	☐

iii. Optimizing the clinical efficacy, economic impact and patient quality of life ☐ ☐ ☐

iv. Effectively controls the institutional budget for drugs ☐ ☐ ☐

13) What according to you is (are) the prerequisite (s) for good review of a product?

	Yes	No	Not sure
i. Extensive literature search	☐	☐	☐
ii. Proper interpretation of clinical data	☐	☐	☐
iii. Compilation of evidence that is most relevant to the decision	☐	☐	☐
iv. Good presentation of available information about the product	☐	☐	☐
v. All of the above	☐	☐	☐

14) To what extent would you say the literature search for review of formulary inclusions in your hospital, is complete/comprehensive?

i. 50%

ii. 60%

iii. 70%

iv. 80%

v. 90% and more

15) What kind of evidence are your formulary decisions usually based on?

	Yes	No	Not sure
i. Local clinical (and/or marketing) trials of the product/(s) conducted for registration purposes	☐	☐	☐
ii. Experience of senior colleagues with that product either in Singapore, or elsewhere	☐	☐	☐
iii. International and multicenter clinical trials	☐	☐	☐
iv. Your own experience with that product and/or a member	☐	☐	☐

of the same and/or similar class

v. "Expert" opinion (of senior consultants in your hospital) ☐ ☐ ☐

vi. Review of all/most of the available literature ☐ ☐ ☐

16) Which of the following question (s) do you ask before making decisions?

	Yes	No	Not sure
i. Is this drug completely revolutionary or does it have other members of the same class and/or a different class for the same indication?	☐	☐	☐
ii. How does the new drug compare with other drugs and / or treatment modalities in terms of safety, efficacy and cost?	☐	☐	☐
iii. Would this new drug be more "cost-effective" as compared to other drugs and / or treatment modalities for the same indication?	☐	☐	☐
iv. Would this new drug radically alter the quality of life experienced by the patients treated using this drug?	☐	☐	☐

About the approach used by the evaluator

17) How satisfactory would you consider the literature search of the evaluator?

i. Very satisfactory

ii. Good

iii. Okay but not good

iv. Unsatisfactory

18) How "relevant" would you consider the "evidence" presented by the evaluator to your decision at hand?

i. 90% relevance and above

ii. 80-90% relevance

iii. less than 80% relevance

19) What do you think of this new approach to drug evaluation?

Not at all useful | little useful | useful | quite useful | very useful

i. Search for evidence relevant to the decision has been more comprehensive/complete

ii. Interpretation of evidence

   a. Looks for "quality" in evidence

   b. Interprets statistical calculations accurately and in terms of impact on real-world practice settings

   c. Reviews literature critically to derive the most important benefit rather than clinical features

iii. "Synthesis" of evidence

- collects as much evidence from as many sources as possible
- collects evidence important for decision and combines them to generate one "grand" evidence

iv. Presentation of evidence

- Presented in an easy-to-read format
- Presented not in an easy-to-read format
- Presented in a form so as to make decisions easier
- Presented in a difficult-to-comprehend format

20) Do you think this new method considers a more comprehensive gamut of factors?

Considers completely | considers | somewhat | not at all

21) The approach is:

Fully satisfactory | somewhat satisfactory | Satisfactory | fairly satisfactory | not at all satisfactory

22) What in your opinion is (are) the major advantage (s) and drawback (s) of the current approach?

Advantages	Yes	No	Not sure
i. The approach is very comprehensive	☐	☐	☐
ii. The approach objectively attends the decision-situation at hand	☐	☐	☐
iii. The approach raises a number of pertinent issues which give a wider perspective to the whole decision	☐	☐	☐
iv. The approach conducts sensitivity analysis that makes the decision more robust	☐	☐	☐
v. The approach quantifies in economic terms the impact of a particular decision	☐	☐	☐
vi. All of the above	☐	☐	☐
vii. Others (please specify)			

Disadvantages	Yes	No	Not sure
i. The approach is too roundabout	☐	☐	☐
ii. The report is far too long	☐	☐	☐
iii. The approach leaves no room for personal experience	☐	☐	☐
iv. It requires special expertise that may be lacking at the moment	☐	☐	☐
v. Others (please specify)			

23) What recommendation (s) would you have to overcome the aforementioned drawback(s)?

24) Would you recommend that this approach be followed for all drug evaluations?

Yes	No	Not sure
☐	☐	☐

APPENDIX 13
P&T Committee Member Responses

INSTITUTION											NUH			
No of responses	10										10			
Respondent code:	P&TMBR 1	P&TMBR 2	P&TMBR 3	P&TMBR 4	P&TMBR 5	P&TMBR 6	P&TMBR 7	P&TMBR 8	P&TMBR 9	P&TMBR 10				
A P&T committee is														
											Y	N	NS	
Indispensable in every hospital	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100%	0%	0%	100%
											Y	N	NS	
Essential though not indispensable		N	N	N		N	N		N	N	0%	100%	0%	100%
											Y	N	NS	
Is 'nice' to have		N	N	N		N	N	N	N	N	0%	100%	0%	100%
											Y	N	NS	
Is not very important		N	N	N		N	N	N	N	N	0%	100%	0%	100%
											Y	N	NS	
Is just a "show"		N	N	NS		N	N	N	N	N	0%	88%	13%	100%
A P&T Committee's most important objective (s) is (are)														
											Y	N	NS	
To control the hospital budget	N	Y	N	N	NS	N	Y	Y	Y	N	40%	50%	10%	100%
											Y	N	NS	
To facilitate efficient management of the hospital asa "health care portfolio"	Y	Y	Y	N	Y	Y	Y	Y	Y	N	80%	20%	0%	100%
											Y	N	NS	
To control doctors' prescription habits	N	NS	N	N	Y	N	Y	Y	Y	N	40%	50%	10%	100%
											Y	N	NS	
Management of the hospital inventory	N	Y	Y	Y	Y	N	Y	Y	Y	N	70%	30%	0%	100%
'must' be members of the Pharmacy and Therapeutics Committee														
											Y	N	NS	
Physicians	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100%	0%	0%	100%
											Y	N	NS	
Pharmacists	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100%	0%	0%	100%
											Y	N	NS	
Financial analysts	N	Y	Y	N	Y	N	NS	Y	Y	N	50%	40%	10%	100%
											Y	N	NS	
Hospital administrators	Y	Y	NS	Y	Y	N	N	Y	Y	NS	60%	20%	20%	100%
											Y	N	NS	
Nurses	N	Y	N	Y	NS	N	NS	N	Y	N	30%	50%	20%	100%
											Y	N	NS	
Health economists	Y	Y	Y	N	Y	NS	Y	NS	NS	Y	60%	10%	30%	100%
Viewpoints considered to add value to P&T decisions														
											Y	N	NS	
Financial analysis	Y	Y	N	N	Y	N	Y	Y	Y	N	60%	40%	0%	100%
											Y	N	NS	
Health care administration	N	Y	N	N	Y	Y	Y	Y	Y	N	60%	40%	0%	100%
											Y	N	NS	
Pharmacoeconomic analysis	Y	Y	Y	NS	Y	Y	Y	Y	Y	Y	90%	0%	10%	100%
Frequency of meeting to achieve a meaningful purpose														
											Y	N	NS	
Once every month	Y	Y	Y	N	Y		Y		Y	Y	88%	13%	0%	100%
											Y	N	NS	
Once in three months				N	N		N		N		0%	100%	0%	100%
											Y	N	NS	
Once in two months				Y	NS	Y	N	Y	N		50%	33%	17%	100%
											Y	N	NS	
More often				N	NS		N		N		0%	75%	25%	100%
Kind of decisions made most often by the P&T Committee														
											Y	N	NS	
Patient management decisions		Y	N	N	NS		Y	NS	Y		43%	29%	29%	100%
											Y	N	NS	
Budget management decisions		Y	N	N	NS		Y	NS	Y		43%	29%	29%	100%
											Y	N	NS	
Formulary drug decisions	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100%	0%	0%	100%
											Y	N	NS	
Diagnostic and screening procedures decisions		N	N	N	N		N	NS	NS		0%	71%	29%	100%
A formulary should ideally be														
											Y	N	NS	
An essential drug list	Y	Y	Y	N	Y	Y		Y	Y	Y	89%	11%	0%	100%
											Y	N	NS	
A list of life-saving drugs meant for subsidy	N	Y	Y	N	Y			Y	Y		71%	29%	0%	100%
											Y	N	NS	
A list of drugs most frequently used	N	Y	Y	N	NS			Y	Y	Y	63%	25%	13%	100%
											Y	N	NS	
A comprehensive list of drugs avoiding generic duplication	Y	Y	Y	N	NS		Y	NS	Y		63%	13%	25%	100%
											Y	N	NS	
Others				a lsit of drugs hosp stacks based on need and patient demand							0%	0%	0%	0%
How close is NUH formulary to the aforesaid choice														
Not at all											0%			
very slightly close											0%			
somewhat close					#	#					20%			
close	#	#		#			#	#	#		60%			
very close										#	10%			

Factor (s) to be considered when including/ deleting drugs from a formulary														
											Y	N	NS	
Cost	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	90%	10%	0%	100%
											Y	N	NS	
Only clinico-therapeutic properties of drug and alternatives	Y	Y	Y	Y	N	N	N	N	Y		56%	44%	0%	100%
											Y	N	NS	
Institutional Budget	N	Y	Y	N	Y	N	Y	Y	Y		67%	33%	0%	100%
											Y	N	NS	
Economic impact of drug on the therapeutic area	Y	Y	Y	N	Y	Y	Y	Y	Y		89%	11%	0%	100%
											Y	N	NS	
Safety	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100%	0%	0%	100%
											Y	N	NS	
Cost-effectiveness	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100%	0%	0%	100%
											Y	N	NS	
Brand equity	N	N	N	N	NS	N	N	NS	Y		11%	67%	22%	100%
											Y	N	NS	
Other Quality of Life factors	NS	Y	Y	Y	Y	Y	Y	Y	Y		89%	0%	11%	100%
Does NUH approval process consider all factors														
Not at all											0%			
only little											0%			
considers partially											0%			
considers	#	#		#	#	#			#		60%			
considers completely							#	#			20%			
Connotation of the term "cost"														
											Y	N	NS	
Acquisition cost	Y	Y	N	Y	N		N		Y		57%	43%	0%	100%
											Y	N	NS	
Total cost of treatment	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100%	0%	0%	100%
											Y	N	NS	
Budget impact	Y	Y	Y	Y	Y		Y		Y	Y	100%	0%	0%	100%
											Y	N	NS	
Cost to the patient	Y	Y	Y	Y	Y		Y	Y	N	Y	89%	11%	0%	100%
Connotation of the term "cost-effectiveness"														
											Y	N	NS	
Cheap	N	NS	N	N	N		N		N		0%	86%	14%	100%
											Y	N	NS	
Value for money	Y	Y	Y	NS	Y		Y	Y	Y	Y	89%	0%	11%	100%
											Y	N	NS	
Optimizing the clinical efficacy, economic impact and patient quality of life	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100%	0%	0%	100%
											Y	N	NS	
Effective control of the institutional budget for drugs	N	Y	Y	N	NS		Y	N	Y		50%	38%	13%	100%
The prerequisite (s) for good review of a product														
											Y	N	NS	
Extensive literature search	Y	Y	Y	Y	Y		Y	Y	Y	Y	100%	0%	0%	100%
											Y	N	NS	
Proper interpretation of clinical data	Y	Y	Y	Y	Y		Y	Y	Y	Y	100%	0%	0%	100%
											Y	N	NS	
Compilation of evidence most relevant to the decision	Y	Y	Y	Y	Y		Y	Y	Y	Y	100%	0%	0%	100%
											Y	N	NS	
Good presentation of available information about the product	Y	Y	Y	Y	Y		Y	Y	Y		100%	0%	0%	100%
											Y	N	NS	
All of the above	Y	Y	Y	NS	Y	Y	Y	Y	Y		89%	0%	11%	100%
Extent to which literature search for review of formulary inclusions is comprehensive														
50%			#	#							20%			
60%											0%			
70%					#	#					20%			
80%	#	#									20%			
90% and more							#	#	#	#	40%			
Kind of evidence formulary decisions are usually based on														
											Y	N	NS	
Local clinical (and/or marketing) trials of the product (s) conducted for registration purposes	Y	Y	Y	Y	N		Y	N	Y	Y	78%	22%	0%	100%
											Y	N	NS	
Experience of senior colleagues with that product either in Singapore, or elsewhere	N	Y	Y	N	N		Y	N	Y	Y	56%	44%	0%	100%
											Y	N	NS	
International and multicenter clinical trials	Y	Y	Y	Y	Y		Y	Y	Y	Y	100%	0%	0%	100%
											Y	N	NS	
Own experience with the same product and/or a member of the same and/or similar class	N	Y	Y	N	Y		Y	Y	N	Y	67%	33%	0%	100%
											Y	N	NS	
"Expert opinion" (of senior consultants) in NUH	Y	Y	Y	N	Y		NS	N	Y	Y	67%	22%	11%	100%
											Y	N	NS	
Review of all or/most of the available literature	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100%	0%	0%	100%

Questions asked before making decsions														
											Y	N	NS	
completely revolutionary or other members of the same class and/or a different class for the same indication	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100%	0%	0%	100%
											Y	N	NS	
How new drug compares with other drugs /trmnt w.r.to safety , efficacy and cost	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100%	0%	0%	100%
											Y	N	NS	
Is new drug more "cost-effective" compared to others for same indication	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100%	0%	0%	100%
											Y	N	NS	
Does new drug radically alter quality of life experienced by patients	N	Y	Y	Y	Y	NS	Y	Y	Y	Y	80%	10%	10%	100%
Satisfaction with literature search of evaluator														
Very satisfactory								#			10%			
Good	#	#	#		#	#	#		#	#	80%			
Okay but not good				#							10%			
Unsatisfactory											0%			
Relevance of evidence presented by the evaluator														
90% relevance and above			#						#	#	30%			
80-90% relevance	#	#			#		#	#			50%			
less than 80% relevance				#							10%			
New approach to drug evaluation is														
Not at all useful				#							10%			
Little useful											0%			
Useful			#		#						20%			
Quite useful	#	#				#	#			#	50%			
Very useful									#		10%			
Search for evidence is comprehensive/complete	NR	#	#				#				30%			
Interpretation	NR													
Looks for "quality in evidence"			#							#	20%			
Interprets tats well and in terms of impact on real-world practice settings		#	#								20%			
Reviews lit critically to derive most important benefit rather than clinical features			#								10%			
Synthesis of evidence	NR													
Collects as much evidence from as many sources as possible			#							#	20%			
Collects evidence important for decision and combines them to generate one "grand" evidence		#	#								20%			
Presentation of evidence														
Presented in an easy-to-read format	#	#								#	30%			
Presented not in an easy-to-read format											0%			
Presented in a form so as to make deisions easier			#								10%			
Presented in a difficult-to-comprehend format											0%			
Whether the new method considers more comprehensive gamut of factors														
Considers completely											0%			
Considers	#	#	#					#	#		50%			
Somewhat					#	#	#			#	40%			
Not at all				#							10%			
The approach is														
Fully satisfactory								#			10%			
Somewhat satisfactory		#			#				#		30%			
Satisfactory	#		#			#				#	40%			
Fairly satisfactory							#				10%			
Not at all satisfactory				#							10%			
Major advantages														
											Y	N	NS	
Comprehensive	N	Y	Y	Y	Y	Y	Y	NS	Y	NS	70%	10%	20%	100%
											Y	N	NS	
Objectively attends decision at hand	Y	Y	Y	NS	Y	NS	Y	Y	Y	Y	80%	0%	20%	100%
											Y	N	NS	
Raises pertinent issues for a wider perspective to decision	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	90%	10%	0%	100%
											Y	N	NS	
Conducts sensitivity analysis for more robust decision	N	Y	Y	N	NS	NS	Y	NS	Y	Y	50%	20%	30%	100%
											Y	N	NS	
Quantifies in economic terms the impact of a particular decision	Y	Y	Y	N	NS	Y	Y	NS	Y	Y	70%	10%	20%	100%
											Y	N	NS	
All of the above		Y	Y	NS			Y		Y		80%	0%	20%	100%
Others														
Disadvantages														
											Y	N	NS	
Approach is too roundabout	N	NS	N	N	NR	Y	N	N	N	N	10%	70%	10%	90%
											Y	N	NS	
The report is far too long	N	Y	Y	N	NS	Y	NS	N	NS	N	30%	40%	30%	100%
											Y	N	NS	
Leaves no room for personal experience	N	Y	Y	N	NS	NS	N	N	Y	N	30%	50%	20%	100%
											Y	N	NS	
Requires special expertise that may be lacking at the moment	N	Y	N	N	Y	Y	NS	N	Y	Y	50%	40%	10%	100%
Others														
Any recommendations to overcome the aforementioned drawbacks	NR	NR	NR	raw data as o	NR	NR	NR	NR	more concise i	NR				
											Y	N	NS	
Recommend approach to be followed for all drug evaluations	Y	Y	Y	N	NS	NS	Y	Y	N	NS	50%	20%	30%	100%