CHAPTER 2
LITERATURE REVEIW

The literature review in this chapter covers 7 major aspects relevant to the study:

1. Epidemiology and the situation of Congenital Hypothyroidism.
2 Nature of thyroid disease and Congenital Hypothyroidism.
3 Diagnostic technology and procedure of Congenital Hypothyroidism.
4 Health policy of Congenital Hypothyroidism in the world and in Thailand.
5 The health benefit of early detection and treatment.
6 Cost benefit analysis.
7 Economic evaluation of hypothyroidism mass screening.

2.1 Epidemiology and the Situation of Congenital Hypothyroidism

The discipline of epidemiology should be a major pillar in the formulation and implementation of health policy. The relationship between epidemiology and health policy may appear to be simple and straightforward. Health policy would be expected to accommodate to and incorporate the new accretions of knowledge. Thus, it would become increasing formidable in addressing the health problems in society. Indeed, the influence is not always one directional from epidemiological findings to the formulation of health policy. Particular economic, political or ideological factors may strangle any policy reforms or when circumstances are propitious, give birth to new specific regulations laws or policies without impetus from new epidemiological data. Changes in health policy may determine the research priorities and questions that command the attention of epidemiologists. For policy makers may seek to justify their new policies by making use of established or rediscovered epidemiological findings. They may also support funding for studies that are likely to generate data that are relevant for the new health policies.

2.1.1 Diagnostic Technology for Screening Tests

New diagnostic technologies generally develop as a result of advances in the basic sciences. The evolution of new modes of diagnostic imagine are among the most exciting developments in medicine over the past decade. The discovery of new substances that circulate in the blood proceeded from experimentation in biology and

immunology and the clinical application of the measurement of these substances was subsequently established. When the technology moves from the laboratory into the clinical setting it makes sense to apply it to patient with a large number of diverse condition. The goal of this exercise is to delineate the possible uses of the technology. In addition to the clinical uses, diagnostic technologies may contribute to a better understanding of human physiology and mechanisms of disease. For the diagnostic technology to be a clinical useful it must reliably distinguish between disease and non-diseases quantify the severity of an illness or condition or both. The pitfalls encountered in trying to determine the accuracy of diagnostic tests and the best ways around them have been most thoroughly studied for tests that try to determine the presence or absence of disease rather than its extent or severity.

When we choose to buy information in the form of the results of diagnostic or screening tests, we do so because we believe that the value of the information exceeds its price. The value of a test result depends both on its accuracy and on how important the result is in leading to action that bear on the individual's well-being. The accuracy of a test depends on its reliability, the degree to which repeated measurements give the same result, and its validity, the degree to which it intends.

For the decision analysis, it is necessary to assemble information regarding

- The accuracy of the test.
- The frequency of the condition(s) for which testing is being considered.
- The degree to which detection at that time can reduce the likelihood or severity on consequences of the condition.
- The costs of the test of whatever misclassification might ensue and of the consequences of the condition that one is seeking to prevent.

The degree to which accurate estimates can be obtained for these items will vary and for some it will be possible only to specify a range within which the true value is likely to lie. Thus, when performing the decision analysis it may be necessary to conduct sensitivity testing that is to evaluate the decision over a range of values assigned to some or all of the items.

Normally, the objective of the screening test is to prevent or protected from the distribution of the disease. In addition to, the screening test may be a supplemental knowledge in order to educate the size and diffusion of the disease. However, the cost of the screening program, which in the disease that incidence rate is very low, is very high. So it is a questionable that whether is economical worthwhile because every programs need resources, which have opportunity costs, moreover, the screening program may induce the psychiatric effects. Therefore, before implementing the screening program, the decision making should be carefully consideration. The main factors that should be analyzed before deciding the screening program (Indaratana, 1994).

- That disease should be a social concerned disease, which means it is an important disease and people realize the problems from the disease.
- The screening test will detect the disease in the early stage and it can diminish the future violence of the disease or it can prevent the disease.
- The prognosis of the disease is well.
- The health resources should enough for treatment establishment and taking care of patients after the disease is detected.
- There is sufficient appraisal for the screening program with diagnostic of high reliability, sensitivity and specificity, accuracy and repeatability or reproducibility.
- The screening test should be simple and acceptable.
- The cost of the test is reasonable.

Therefore, when the diagnostic is completed the decision arrived at is always the same. If this is the case, the matter is closed. If, however, the choice is influenced by the particular values among the plausible ones, that are uses in the analysis, then either it really makes little difference whether or not testing is done. Because the benefits and costs are nearly equal or there are a different between benefits and costs, but the information available with which to discover it is not sufficient precise. Since it is possible to determine for which items the imprecision is causing particular difficulty in arriving at a choice, it is possible to assign priorities to new research relevant to the question. The research dealing with more clearly determining costs of

tests, illness and death. The main item is the degree of improvement in outcome associate with the patient being tested.

The incidence of Congenital Hypothyroidism has been shown to vary among different parts of the world. This could result from environment or hereditary factors. The average incidence of Congenital Hypothyroidism is approximately 1 per 4,000 live births and it is ranged from 1 per 2,000 to 1per 7,000 live births. It is interesting that the incidence of congenital hypothyroid was markedly increased in the area of iodine insufficiency. In some areas in Zaire the incidence was as high as 10 percent.

In North America, the pilot project for screening of newborn for Congenital Hypothyroidism was begun in 1972 and right now, this program is compulsory for every newborns in North America (Fisher *et al.*, 1979). The average incidence is around 1 per 3,648 live-births and these cases can be divided causes into 1 per 4,254 live-births from primary hypothyroidism, 1 per 68,200 live-births from secondary-tertiary hypothyroidism and the estimated minimum incidence of infants with TBG deficiency is one per 8,913 live-births.

The incidence of Congenital Hypothyroidism in Thailand is around 1 per 3,329 live births. These data comes from the screening program of the Medical Science Department, which covers 40 provinces and 469,344 newborns. The incidence of recall screening in the suspected case is 0.33% and around 75.8% of the Congenital Hypothyroidism patients can be followed up and treatment. The incidence figure in Thailand is nearly in the developed country, which is about 1 per 3,000 to 1 per 4000 live births. However, in iodine deficiency areas, such as Nan province, the Congenital Hypothyroidism incidence has increased up to 1 per 687 live births (1998).

2.2 Nature of Thyroid Disease and Congenital Hypothyroidism

The thyroid is the largest endocrine gland in the body. The weight is about 20 grams and the right lobe is usually being larger than the left. Adult size is reached at age 15. The thyroid grand maintains the level of metabolism in the tissues that is optimal for their normal function. It is not essential for life, but its absence causes mental and

physical slowing and mental retardation. Thyroid tissue is present in all vertebrates. In mammals, the thyroid originates from an evagination of the floor of the pharynx and a thyroglossal duct.

Normally, the principle hormones secreted by the thyroid are thyroxine (T_4) and triiodothyronine (T_3). They are controlled by thyroid stimulating hormone (TSH), which is a glycoprotein. TSH is produced and secreted from pituitary gland by the regulation of thyroid releasing hormone (TRH) from hypothalamus.

Thyroid hormones have several effects in the body. Such as, they affect to growth and development in mammals, help regulate lipid metabolism and increase the absorption of carbohydrates from intestine. Thus, we can classify the effects into

- Calorigenic Action: T_4 and T_3 increase the oxygen consumption of all metabolically active tissues.
- Effects on the nervous system: Thyroid hormones have marked effects on brain development. The parts of the CNS most affected are the cerebral cortex and basal ganglia. Consequently, thyroid hormone deficiency during development causes mental retardation, motor rigidity and deaf-mutism.
- Effects on heart: Thyroid hormones increase the number and affinity of β adrenergic receptors in the heart. In hypothyroidism, the cardiac output is reduced as a result of both a decreased of stoke volume and heart rate.
- Effects on skeletal muscle: Muscle weakness occurs in most patients with hyperthyroidism and it is also associated with hypothyroidism.
- Effects on carbohydrate metabolism: Thyroid hormones increase the rate of absorption of carbohydrate from gastrointestinal tract.
- Effects on cholesterol metabolism: In hypothyroidism, the level of cholesterol is higher than normal because of the lipid metabolism.
- Effects on growth: Thyroid hormones are essential for normal growth and skeleton maturation. In hypothyroid children, bone growth is slowed and epiphyseal closure delayed. In the absence of thyroid hormones, growth hormones are also depressed and thyroid hormones potentiate the effect of growth hormones on the tissues.

Hypothyroidism is the clinical syndrome that results from decreased secretion of thyroid hormone from the thyroid gland. It most frequently reflects a disease of the gland itself (primary hypothyroidism) or hypothalamic disease (secondary hypothyroidism). Hypothyroidism leads to a slowing of metabolic processes and its most severe from to the accumulation of muco-polysaccharides in the skin, causing a nonpitting edema. The incidence of hypothyroidism varies somewhat with the geographic area. In areas of adequate iodine supply, like the United States, 0.8 to 1% of the population are hypothyroidism. In iodine deficient areas of the world, the incidence is 10- to 20- fold higher. Neonatal hypothyroidism occurs with a frequency of 0.02% in the Caucasian population, whereas among African Americans it falls to 0.003%.

Most frequent causes of Congenital Hypothyroidism come from an abnormal embryological development of the thyroid gland. There are several causes of Congenital Hypothyroidism and they can be divided into

- Thyroid dysgenesis accounts for about 80 to 90% of all causes of Congenital Hypothyroidism All of these cases are sporadic cases that the ratio of girls to boys is 2:1. Developmental anomalies consist either of complete absence of the thyroid gland (athyreosis) or a fault in the migration of thyroid tissue (ectopic thyroid gland).
- Thyroid dyshormonodenesis: There are seven abnormalities of thyroid hormone biosynthesis and hormone function. These conditions are inherited in an autosomal recessive manner.
- Hypothalamic-pituitary deficiency is usually due to the presence of tumors or by necrosis. The incidence occurs in approximately 1:100,000 newborns.
- Others: Such as, drugs, which inhibit thyroid hormone biosynthesis easily cross the placenta, thus, the administration to a pregnant may cause formation of a goiter and hypothyroidism in the infant, which regresses spontaneously during the first week of life. Thyroid failure to TSH, resistance to thyroid hormone and so on.

Signs and symptoms of Congenital Hypothyroidism depend on cause, severity and duration time of thyroid deficiency in a gestational age. In a third to a half of cases,

symptoms of thyroid insufficiency are often hidden and the diagnosis is not suspected during the first year of life. Clinical recognition of hypothyroidism during the first period of life is difficult. At birth, most hypothyroid infants appear to look normal. After that, there are some clinical signs shown in the first month, for instance, peripheral cyanosis, respiratory distress, poor sucking and so on. In the third month, the clinical signs are umbilical hernia, constipation, dry skin, hoarse cry, etc. If the children can not detect, it will be too late to treatment in order to increase brain development.

2.3 Diagnostic Technology and Procedure of Congenital Hypothyroidism

Consequently, the accurate and precise Congenital Hypothyroidism diagnosis should be done in newborns in order to get early treatment. Almost of all Congenital Hypothyroidism are primary hypothyroidism, so, TSH level in blood usually increases before T_4 level in blood will be declined. As a result, in many countries, Congenital Hypothyroidism screening is usually detected by the level of TSH in blood, which is the highest sensitivity to detect primary hypothyroidism. TSH can be determined either in cord blood or in dried spotted blood on filter paper. In 1977, TSH dried blood spotted test was added to the mass newborn screening for metabolic disorders for all children had born in Switzerland.

In the study of Illig *et al.*, (1977), was about the sensitivity of TSH determination by dried spotted blood on filter paper. The result was 47,989 of newborns were tested and 15 cases of Congenital Hypothyroidism were detected and 1 false negative. So, because of the low recall rate, TSH screening seems to be most suitable for a mass screening program. Although, it does not allow the detection of hypothalamic-pituitary hypothyroidism, Thyroid binding globulin (TBG) deficiency and other rare disorders associated with lowT_4 values, which may or may not benefit from early diagnosis and treatment.

Rochiccioli and Dutau (1979) did another study. They studied 48,000 newborns since January 1st in the Midi-Pyrenees district of France. The results were T4 and TSH determination have detected 15 cases of hypothyroidism, so they summarized that the simultaneous determination of T_4 and TSH is an sensitivity and specific screening

method for hypothyroidism. False negative is avoided and the number of false negative results is reduced. All cases of hypothyroidism can be detected (primary hypothyroidism, hypothalamo-hypopituitary hypothyroidism, TBG deficiency, etc). Then, an early and certain diagnosis is made possible.

Moreover, there is one study in Nan province in Thailand by Tananchai and Prosean (1998), which is about the comparative of Congenital Hypothyroidism by using cord blood and blood from neonatal. This study was done during 1994 and 1995 by collecting 1,760 and 3,557 specimens from cord blood and heel prick of 48 hours neonates during 1994 and 1995 respectively. They were analyzed for TSH level by using radioimmunometric assay. The results showed that there is no significant different between two groups. Thus it is possible to collect blood from heel prick because it is more convenience than from cord blood that health personnel does not hurry to collect and probably this blood may contaminate with mother blood. Even though, the dried spotted blood on filter paper is less precision and sensitivity than the serum, it is suitable for Congenital Hypothyroidism mass screening, not for iodine insufficiency.

Pharoah and Madden (1992) did another study of screening for Congenital Hypothyroidism in the Mersey region of England. They had studied the effectiveness and efficiency of the screening program for Congenital Hypothyroidism from 1983 to 1989 by examines an analysis of laboratory, manual and computerized district records, case notes and hospital activity analysis. Their results were the TSH sensitivity was 97% and the specificity was 99.9%. In 10% of positive cases, treatment was delayed beyond 21 days; the latest was 26 days. It is concluded that administrative deficiencies were predominantly responsible for the inefficiencies of the screening program and the long-term follow up should become part of the monitoring process.

Normally, the level of T_4, Free T_4, TSH will increase after birth by the peak of TSH that will be 80 to 100 mU/L will high in 30 to 60 minutes in order to stimulate thyroid gland to produce and releases T_4. The highest level of T_4 and Free T_4 will be in 12 to 48 hours after birth. After 48 hours, the level of T_4 and Free T_4 will slightly reduce, so

the interpretation of the thyroid function test, especially in infant who is younger than 7 days, should count in hourly of birth life.

In North America and Australia, the primary screening is T_4 and the confirmatory is TSH screening. Their specimens are dried spotted blood on filter paper obtain at age 1 to 5 days of life. Some programs in each area involve simultaneous T_4 and TSH testing on dried blood specimens. Program officials in various geographic areas choose different methods to meet their own particular.

Although, many researches have supported that dried spotted blood is more appropriate to detect Congenital Hypothyroidism, there are several studies about the missed cases of neonatal screening. Most of all missed cases come from technical error. First study, Holtzman *et al.* (1986) conducted a structure telephone survey of state public health laboratory directors of neonatal screening programs to determine the extent of the problem of missed case of Phenylketouria(PKU) and Congenital Hypothyroidism. The result was one missed case of PKU for every 70 cases detected and one missed case of Congenital Hypothyroidism for every 120 cases detected. In other words, two Congenital Hypothyroidism cases were missed for every million infants screened. Regarding the stage of screening in which the missed occurred, 14% occurred during specimens collection, 45% during the laboratory procedures stage, 16% during follow up, 11% were the result of biologic variation and 14% the stage could not identified. They had concluded that neonatal screening programs have been highly successful but there may be additional safeguards to be developed, tested and implemented when practical.

The second study be Gray *et al.* (1997) was about the failure of screening newborns for inborn disorders. It is a cohort study to determine how changes in the structure of the hospital care of infants, such as shortened postnatal stays, affect the completeness of newborn screening. The result was at least one specimen that was missed screening in 8,675 of the birth. Most non-screened patients (93%) had been admitted to the neonatal intensive care unit. Among patients in the health baby nursery, early discharge accounted for 40% of the non-screened cases. Their conclusion was early discharge of healthy newborns was also significant associated with non-screened. This latter finding is of special importance given the current trend toward shorter hospital

stays for newborns. Increased attention to ensuring the collection of specimens from this two-risk population.

Furthermore, there are two studies that are about how to prevent missed cases in mass screening. Allen DB *et al.* (1988) did one and another is done by Fisher DA.(1987). Both are talking about the way to improve the screening program. Allen DB suggested that because of the delayed confirmatory process, the variation of therapeutic and the management autonomy among physicians, the screening should be modified in the area of confirmatory process, the management decision tree for primary care physicians and at least one time subsidy for a visit to pediatric endocrine in order to improve the long term outcome of hypothyroid infants by the screening program. Fisher DA suggested that even though, the screening program is the best, there is still have around 8 to 10% of the total that are missed. Thus, physicians must be aware of the possibility and alert to early clinical evidence of Congenital Hypothyroidism.

In Scotland, Ray M. *et al.*(1997) has audited the screening program for Congenital Hypothyroidism in 1979 to 1993 in order to evaluate the efficiency of the program and to determine the outcome of children with positive testing for TSH. Their conclusion is the current screening program is working well, but efficiency could be increased by earlier and more reliable Guthrie collection. A substantial proportion of children pick up on the screening has a transient rise in TSH rather than true Congenital Hypothyroidism. The incidence of special education and learning support in Scottish children with Congenital Hypothyroidism appears to be no different to that of the general population.

By the year 2003, the Congenital Hypothyroidism screening will be established into every health service unit in Thailand. The process of screening will be in three steps, which are

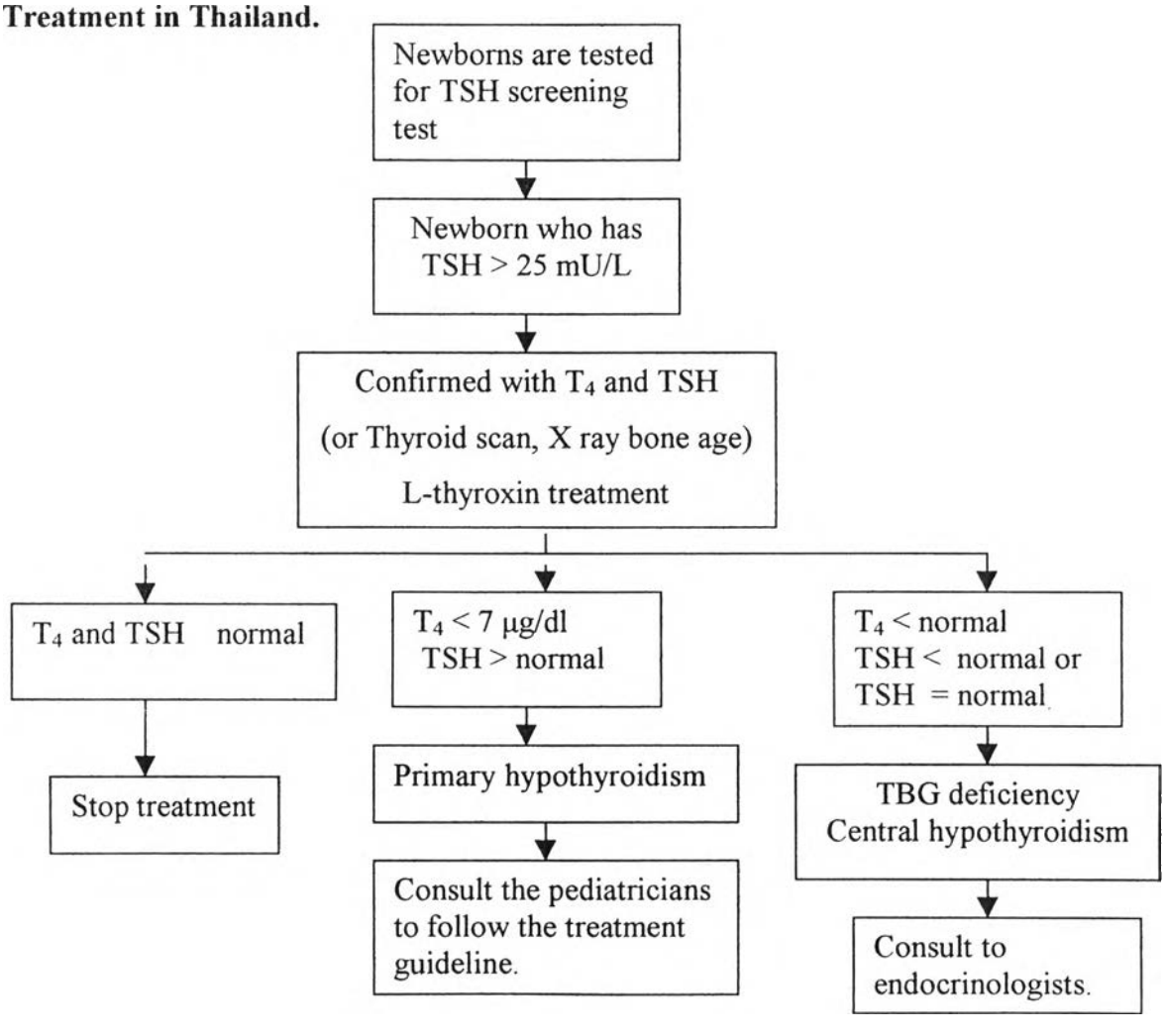
- **The screening process**: All newborns of more than 2 days of age (48 hours) but not more than 7 days, must have TSH screening by using the method of dried spotted blood on the filter paper. In public and private health service facilities, delivery departments will be responsible screening all newborns and for records in mother and child health book. In the case of delivery at home, public health

centers will take the same responsibility for screening and sending a specimens to a regional laboratory center..

- **The follow up process**: After the health service centers receive the result of the test for theCongenital Hypothyroidism case, health personnel will recall the patients in order to re-confirm the test and start treating before the age of three months.
- **The report and evaluation process**: Every health service centers will collect all of reports and send back to provincial public health office before the 10^{th} of every month. The provincial public health office will collect all of those reports and send to the regional health promotion center on the 20^{th} of each month in order to send further to bureau of health promotion, where is a responsible unit for registration of Congenital Hypothyroidism cases.

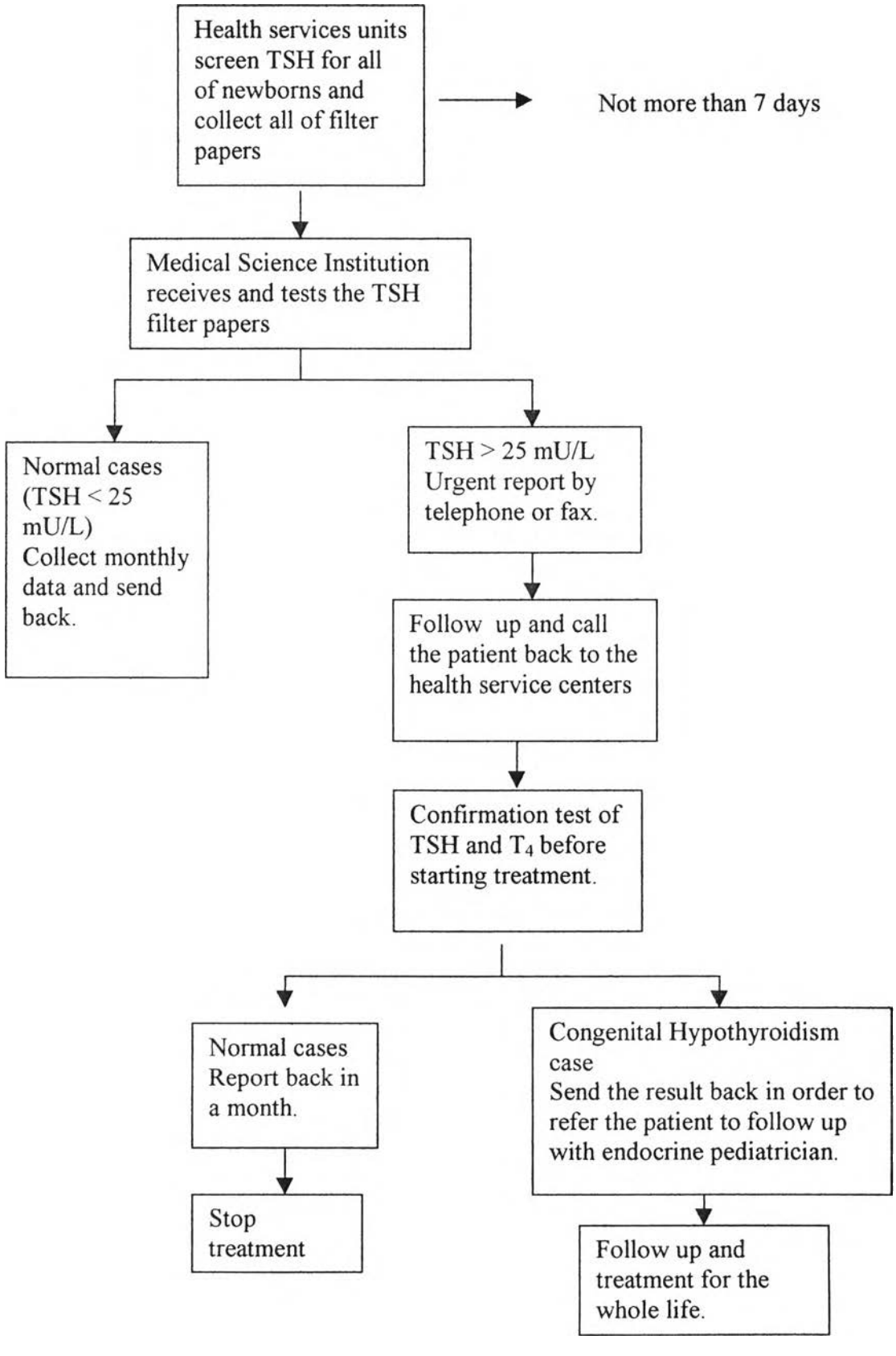
The treatment guideline for the national policy in Thailand is describing in the following.

Figure 2.1: National Policy for the Congenital Hypothyroidism Diagnosis and Treatment in Thailand.



The following figure is the process of the Congenital Hypothyroidism screening in Thailand.

Figure 2.2: The Proposed Process of the Congenital Hypothyroidism-Screening Program to be Introduced in Thailand.



2.4 Health Policy of Congenital Hypothyroidism in the World and in Thailand

In the United States, newborn screening is an individual function of each state, therefore, screening programs are not uniform throughout the United State (Desposito, 1996). Since the test results can affect children and parents in a variety of ways, there are special concerns about how state make decisions to adopt new tests and how they evaluate the current screening panels. For Congenital Hypothyroidism screening, it is performed in all 50 states, including the District of Columbia, Puerto Rico and the US Virgin Islands. All of newborns are collected their blood when they are younger than 24 hours, regarding reliability of the assay results in identifying with this disorder. Generally, the characteristics of screening test and confirmation in North American usually screen with T_4 and followed by TSH level. The costs for newborn screening are variable and generally cited as initial fees for neonatal testing in a state or regionalized laboratory. Historically, program cost of $ 1 to $ 2 for specimen handling, administration and overhead. Currently, state costs range from no fee to $50 for an all-inclusive program including follow up confirmatory testing. These cost figures may not include the total system's cost for repeated and confirmatory testing (additional in some states), educational, patient and physician notification and contact, follow up of affected patients and management (e.g. the cost of dietary supplements).

In United Kingdom, the national neonatal screening for Congenital Hypothyroidism was established in 1982(Streetly *et al.*, 1995) The aim of the program is to reduce morbidity by complete and timely detection and treatment of affected cases. In 1991, Streetly *et al.*(1994) has studied the coverage of the neonatal screening program. He studied in 1,727 infants who born between October, 1st and December 31st in West Lambert and Camberwell District. His outcomes were the proportion of infants with an identified screening test result. The results were the program covered 96.3% of infants and the incomplete and poorer coverage was infants of African ethnic group. Poorer coverage is also associated with morbidity of the family around the time of birth. He suggested that the arrangements for monitoring the existing screening program are inadequate and an improved system should be established similar to the scheme that monitors the immunization program.

On July 22nd, 1999 the Italian government has announced that the early diagnosis of congenital malformation and neonatal screening of hypothyroidism and phenylketouria are compulsory (Bruno, 1999). The initiative charge is free and includes experimental screening for cystic fibrosis at regional centers. Within the first hours of life and on hospital discharge, newborns will be seen by pediatrician or a neonatologist to identify congenital malformations. Blood tests for hypothyroidism and PKU will be done between 3rd and 5th day of life(or earlier if the newborn is discharge earlier). In home births the physician or midwife helping with the delivery must take the samples. Within 48 hours the filter paper of blood spots are to be forwarded to regional center for processing. In Japan, a nationwide mass screening system for neonatal metabolic diseases was established in 1977 (Hisashige, 1994). This system consists of screening programs for five main congenital metabolic diseases and later the system was extended to include screening for Congenital Hypothyroidism, congenital adrenal hyperplasia(CAH) and neuroblastoma.

In Thailand, Ramathibodi Hospital and Chulalongkorn Hospital have started the Congenital Hypothyroidism screening in 1990. In 1992 the Medical Science Department started to improve the pattern of the nationwide screening program in order to reduce the Congenital Hypothyroidism cases at least 50%. Those newborns will be screened in the 8th national economic and social development plan and the program will cover all of country in this plan. Right now, the Medical Science Institution can screen 300,000 live births per year that account for 30% and the program is covered 39 province.

2.5 The Health Benefit of Early Detection and Treatment

For the babies with Congenital Hypothyroidism, treatment should be started as soon as possible, even if the diagnosis has not yet been confirmed definitively by hormone determinations in serum. In TSH screening procedure, substitution therapy with thyroxin is initiated immediately after blood sampling at the rechecked examination, usually within the second week of life. In cases of questionable diagnosis such as compensated hypothyroidism or possible transient hypothyroidism (normal T_4 and elevated TSH), or in preterm infants (low T_4 and normal TSH), treatment should be started if the thyroid scan shows thyroid dysgenesis. If the scan is normal and the

infants are asymtomatic, the infants may be observed with out treatment. If the serum TSH rises progressively, treatment should be started. Alternatively, these infants may be placed on therapy until age 3 years, when treatment is discontinued and repeated diagnostic studies are undertaken. Infants with TBG deficiency do not have a deficiency of thyroid hormone and require no therapy.

In the cases of diseases and suspected cases should have serial development testing to evaluate intelligence potential until the children reach school age. In infants, who are treated under 3 months age, have mean IQ of 89. In the treated cases between 3 and 6 months have a mean IQ of 70, while infants started on therapy after age 7 months had a mean IQ of 54(La Franchi, 1982). In general, neurological sequelae such as spasticity, hyperkinesis, short attention span speech defects, ataxia and incoordination parallel mental retardation. With the development of programs to screen all newborns for Congenital Hypothyroidism, the average age of diagnosis and treatment is approximately 3 to 6 weeks(La Franchi, 1982). In the oldest regional screening program from Quebec, 30 hypothyroidism infants tested at age 18 months on the Griffith's developmental test scored 105.9 as compared with 111.2 in the control group. It is interesting that a recent study reported an IQ increase of 20 points in-patients with Congenital Hypothyroidism in testing carried out 16 to 26 years after initial IQ testing at age 5 and 6 years.

There are several studies that are supported the idea of the early treatment of Congenital Hypothyroidism will increase the infants intelligent. One study by Glorieux *et al.*(1983) is about the preliminary results on the mental development of detecting hypothyroidism infants who were detected by the Quebec Network for Genetic Medicine in January 1976. Forty- five hypothyroidism, which were mean initial treated at 27 days. There were no statistically significant differences in the various test scores between two populations at age 12 months, but at age 18 and 36 months the hypothyroidism infants had lower scores in hearing speech performance scales and practical reasoning (36 months). The mean scores were still above 100 and only nine in forty five were below 85. The New England Congenital Hypothyroidism collaborate study showed normal IQ, visual motor integration and neuropsychologic profiles when compared with control values (Desposito, 1996). The Ontario study also showed intelligence within the normal range, but the children had cognitive and

neuromuscular impairment that seemed to reflect the severity and time of onset of thyroid hormone deficiency. Recently, the study from England and Netherlands showed that the only correlation with outcome and disease related factors is adequacy of treatment and compliance.

2.6 Cost-Benefit Analysis

Economic logic is based on the notion of scarcity, according to which needs outstrip resources. As resources are scarce it is necessary to make choices not just on which needs should be met, and which should not, but also on assessing up to which point several different needs should be met. The principle of economic analysis is that choice must be made between alternative uses of resources, and these decisions must consider both cost and outcome, since there are not enough resources to provide all the medical care technical possible or that patients might prefer to receive.

The type of economic evaluation, which can assist planners and decision-makers on such issues, is cost benefit analysis (CBA), which is the first analytical study design to have been introduced in health economics. CBA aims to compare all social costs and consequences across different interventions or against a do-nothing option. At the basic of CBA is the concept that social welfare exists and can be maximized by moving additional productive resources to aspects of production where there is greater social benefit at the margin. The key to CBA is the systematic calculation of all costs and consequences accruing to society from different options and the expression of their values in monetary terms. Thus, the enable of the analysis is to make a direct comparison of the program incremental costs with its incremental consequences in commensurate unit of measurement.

2.6.1 Perspective of Analysis

There are several perspectives possible in an economic analysis of medical care. Costs, outcomes and benefits might be seen differently from the point of view of society, the patient, the payer or the provider. The cost to the provider, such as a hospital, is the true cost of providing the service, regardless of the charge and few medical institutions are prepared today to identify their true economic costs. Thus, to determine the provider's cost, it is often necessary to carry out a cost finding exercise

using techniques developed by accountants and industrial engineers. In addition to the perspectives of payer and provider, the cost to the patients and to society as a whole can be considered. The cost to patients is the amount they pay for the service (that is the proportion not covered by insurance) plus the other costs that might incurred because of illness or treatment, including time missed from work. The cost to society is the total net cost of all the different components of society, including the patient's lost productivity and the expenses involved in giving and receiving medical care. Therefore, the cost to society is the social opportunity cost, the result of having given up the opportunity to use the resources for some other purpose. While many analysts have asserted that the societal perspective is the proper to take in an economic analysis from more than one point of view. It is usually helpful to use the perspective of the actual decision-maker.

2.6.2 Determination of Cost

Most economists would define a cost as the consumption of a resource that otherwise could have been used for another purpose. Since the resource has been used, the opportunity ti use it for other purpose is lost. Therefore, its value in the next best use, which is no longer possible, is called its " opportunity cost." In making the determinations of cost, it is important to separate costs that are fixed (and would not be reduced in the short term by a change in the number of services provided) from costs that are variable (those that vary with the volume of services provided).

- **Direct Cost**

Direct costs essentially are transactions and may be expenditures for medical or non-medical products and services. The types of direct medical costs usually considered include those hospitalization, drugs, physician's fees, laboratory tests, radiological procedures, rehabilitation, durable medical equipment and long term care. These are costs that are traditionally counted as health care expenditures and represent the outlays that contribute to the proportion of the gross national product spent on health care.

However, substantial portions of direct costs are for non-medical services. These expenditures, such as food, transportation, lodging, family care, home aids and clothing, are results of an illness but do not involve purchasing medical services. In

addition to these non-medical expenses for the patient when a member of the family is ill, there may be substantial transportation and lodging expenditures incurred by others in family.

Costs and charges.- In the calculation of direct costs it is essential to remember that charges are not the same as costs. Charges are often set by the marketplace or by regulation and may not reflect the true costs of providing a product or service. Usually, there is not even a consistent price, since different purchasers may be able to negotiated different rates. The true cost of medical care is the set of revenues that are consumed in providing care. The value of these resources is the value of the lost opportunity to use resources in other way. Therefore, the charges measure cost only to those who pay those charges.

- **Indirect Cost**

In addition to direct medical and non-medical costs, indirect cost also have substantial impact. Indirect costs are those that occur because of loss of life or livelihood and may result from morbidity and mortality. Indirect morbidity costs may occur because of being absent from work, because of a decreased earning ability when working or because of long term disability that necessitates a change in type of work. Indirect mortality is, in essence, the costs of premature death. Two ways of calculating these costs are the human capital approach and the willingness to pay approach.

- **Intangible Cost and Benefit**

Intangible costs represent another categories of costs and like indirect costs are difficult to measure. These are the costs of pain, suffering, grief and the other non-financial outcomes of disease and medical care.

2.6.3 The Principle of the Cost Benefit Approach

The feature that distinguishes among techniques of economic evaluation is the way in which the consequences of health care programs are valued. Cost Benefit analysis (CBA) requires program consequence to be valued in monetary units, thus enabling the analyst to make a direct comparison of the programs incremental cost with its incremental consequences in commensurate units' measurement. In the simple terms,

the goal of this analysis is to identify whether a program's benefits exceed its costs; a positive net social benefit indicating that program is worthwhile.

2.6.3.1 Efficiency and Equity

In the absence of resource allocation using the cost benefit approach, the resulting resource use could be "inefficiency" and/or "inequitable". Efficiency is a state where the costs of producing any given output are minimized and the utility of individuals' preference is maximized. The cost benefit approach adopts the societal perspective in order to ensure consistency between the pursuit of maximum utility for society as a whole and the pursuit of maximum profitability. In the other word, the cost benefit approach should simply try to identify potential Pareto improvements.

The analysis of equity in conjunction with efficiency is still controversial subject amongst economists. For example, Williams (1985, p.326 quoting McGurie, 1988) has suggested that "the objective of economic appraisal is to ensure that as much benefit as possible is obtained from the devoted to health care". Culyer (1979, p.45 quoting McGurie, 1988) has written that "If the underlying rationale of the NHS is ... concerned with the health status of individual members of the population, it is a natural extension to suppose that the general objective of the NHS might be summarized as being to maximize, given the budget allocated, the health of the population".

Certainly, it is simpler to analyze only whether a project is socially efficient or inefficient. To use such analysis in decision making, however, requires the additional value judgement that the gainers ought to gain and loser lose. The value judgement trading-off the distribution and efficiency effects can be built into the social welfare function (SWF). Thus, the essential difference between social efficiency and social welfare lies in the incorporation of an equity criterion. Social efficiency takes no account of who gains which benefits or who bears which costs. Social welfare may take account of desert, need, rights, justice, fairness and other criteria in judging projects by their equity as well as their efficiency.

2.6.3.2 Measuring Efficiency

Gains and losses, or benefits and costs, are usually measured with reference to the consumer surplus. It is usually measured by the compensating variation. This is the maximum that a consumer would be willing to pay for a benefit, or the minimum a consumer would be willing to receive to accept some loss. Thus the compensating variation is measured with reference to the consumer's existing utility level.

An alternative measure is the equivalent variation. This is a minimum that a consumer would be willing to receive rather than forgo a benefit, or the maximum that a consumer would be willing to pay rather than suffer some loss. Thus, the equivalent variation is measured with the reference to the consumer's new utility level. Therefore, compensating variation of a potential benefit = equivalent variation of a potential cost. Or compensating variation of a potential cost = equivalent variation of a potential benefit

The compensating variation and equivalent variation will differ where there are income effects, that is where moving to a higher level of real income through the receipt of a benefit, or the lower level though suffering a cost, changes the consumer's real income and hence the valuation of the goods gained or lost. Thus for normal goods equivalent variation > compensating variation and for inferior goods compensating variation > equivalent variation.

2.6.3.3 Shadow Pricing

Where there are external effects in consumption, or where there are constraints on what individuals may demand, observed valuations must be replaced by "shadow prices". If no market exists then, obviously, the demand for a commodity cannot be observed at all. In such situations shadow prices are imputed to measure the CV that would have been present in the absence of market distortions. A particular issue in this context is "valuing life" since many health care projects will affect some individuals' probabilities of death or life expectancy.

2.6.3.4 Time Preference and Discounting

The effects of a project may be spread over time and, hence, it is necessary to weight future *vis-à-vis* present effects. Individuals may have positive time preference rate,

which means that they will discount future costs and benefits. There are two approaches to weighting future, as compared with present, benefits and costs. The former involves the social time preference (STP) rate and the latter the social opportunity cost of capital (SOC). The first approach is determined with direct reference to individuals' preferences regarding the future *vis-à-vis* the present. While the second references to the prevailing real rate of interest.

The weighting of future costs and benefits is accomplished by means of a discount rate whereby CVs in different years are summed as follow:

$$\Sigma^{t}_{t=0} CV_t (1+ r)^{-t}$$

Where t = 0 is the present, t = 1 is one year hence, and so forth, and r is the discount rate.

2.6.3.5 Risk and Uncertainty

The effects of the project may not be certain. The value of CVs in such circumstances may diverge from where effects are certain. Risk is where the probability of an effect happening is less than certain, but the probability is known. Generally, risk gains are less highly preferred than certain equivalents and this must be taken into account in valuing CVs, which ideally should be valued at certain equivalents.

Uncertainty is a more difficult problem. Uncertainty refers to where the possible effects are known, but their probabilities are not. In response to uncertainty individuals may adopt different strategies that had the least bad worst outcome, the maximin strategy. Again the value of the CV will be affected by the extent of uncertainty.

No matter how careful the analysis, the data used in clinical economics studies will include some uncertainties and potential biases. There will be limits to precision with which data on costs and outcomes can be determined. Sensitivity analysis is a determination of the degree to which this uncertainty could influence conclusion about the economic impact of clinical decisions.

2.6.3.6 Approached in Value of Life

There are three general approaches to the monetary valuation of health outcomes:

I The human capital approach.

II The revealed preferences.

III The stated preferences of willingness-to-pay.

I The Human Capital Approach

The human capital approach is the oldest and most easily applied. This method is based on an individual's worth to society calculated on the basis of his or her present and future earnings. Each person represents a productive resource to society and illness diminishes that person's productive capacity, which is usually valued in this approach by his or her loss of earning. In the other words, this concept has been widely used to value of life and absence from work due to illness. For example, life has been valued on the basis of its expectancy multiplied by the annual average income of that person or that social class.

There are a number of measurement difficulties with human capital approach. Firstly, although in theory wage rates reflect the marginal productivity of a worker, there are often imperfections in labor markets and wage rates may reflect, *inter alia,* inequities such as discrimination by race and gender. Secondly, if the study were from a social perspective that analyst would need to consider the value of healthy time gained that is not sold for a wage. This raises a general class of problems of how economists place shadow prices on non-marketed resource. Therefore, there are two methods for attaching a shadow prices: (1) An opportunity cost of time and (2) A replacement cost.

The timing of health effects over the life span has implications for the economic contribution of the individual, as productive days are lost from acute illness, disability and premature death. Weights for productivity were added to the Ghana model by estimating the age earning profile. Using labor force participation rates derives the profile by age group to correct for unemployment. It is also assumed that entry into labor force occurs at age 14 with an income of one half the mean for all age groups. Income then increases at regular increments up to the age of thirty. In addition per capita productivity is projected to grow by 2.5 percent per annum. Dividing the expected income of all wage groups by the income expected at age thirty gives the profile expressed in terms of productivity weights. Productivity days lost to disease

are obtained by multiplying health days lost by the productivity weights for each age group and then discounting and summing over the expected remaining life span to get the present equivalent number of productivity days lost.

II The Revealed Preferences

A number of wage-risk studies have been published, in which the goal is to examine the relationship between particular health risks associated with a hazardous job and wage rates that individuals require to accept the job(Martin and Psacharopoulos, 1982 quoting Drummond *et al.*1997). This approach is consistent with the welfare economics framework because it is based on individual preferences regarding the value of increased (decreased) health risk.

The strength of the wage-risk approach is that it is based on actual consumer choices involving health versus money, rather than hypothetical scenarios and preference statements. However, a weakness of this approach is that estimated values have varied widely and estimations seem to be very context and job-specific. This approach is a review of past decisions, such as court awards for injury compensation, to elicit the minimum value that society place on health outcomes.

III The Stated Preferences of Willingness-to-Pay

The willingness-to-pay (WTP) relies on the view of samples of the general public who are asked how much they would be prepared to pay to accrue a benefit or to avoid certain events. WTA is based on the minimum amount a person or population would have to be paid to accept the loss or reduction of a good or service. The classic WTP (the most frequently used technique) approach relies on questioning an individual's willingness to pay to diminish the probability of a health state (usually adverse) coming into being. WTP values, on the other hand, whether they derive from surveys or involves the prospective use of revealed preferences, are ex ante (before the fact) measures of the monetary values individuals attach to changes in welfare that would accompany changes in the probability of an event. WTP could be helpful in indicating how individuals value health and life and in deriving social preferences regarding health policy. Furthermore, WTP might be especially helpful in assessing the burden of pain and suffering, which have an intangible quality that is not amenable to evaluation in terms of the monetary value of resources used or forgone.

2.6.4 The Process of the Cost Benefit Approach

There are nine processes of the cost benefit approach. The process can usefully be divided into a series of stages, which form a helpful sequential classification for the purposes of expositions.

- **Specifying Alternatives for Appraisal**

Since the objective of economic appraisal is to seek efficient and equitable uses of resources, it is important that all potentially efficient and equitable options should be examined. However, the options examined have to be selected as being those considered offering the greatest potential because the potential uses of health care resources are virtually infinite. This emphasizes how economic appraisal builds on epidemiological evaluation and clinical trials.

- **Specifying the Appraisal Objective**

Ultimately, the appraisal objective is to seek social efficiency and equity, however, where particular constraints are binding, it may be sufficient or necessary to assess technical efficiency instead. Moreover, the appraisal objective should also be set in terms of the criteria to be used in assessing equity. For instance, variance in health care accesses costs or even in health, or else the value judgement should be made explicit that the gainers, whoever they are found to be, ought to gain, and the losers, whoever they are, to lose.

- **Identifying All Effects**

This stage will rely on evidence from epidemiological studies showing what effects upon health there will be. Ideally, the appraisal should at this stage identify all the beneficiaries and cost-bearers of each of the alternatives. It should identify the direct effects and the indirect effects, such as the immediate or long-term effects on health and the effects on employment, consumption and so on.

- **Measuring All Identified Effects**

Again this stage will rely on evidence from epidemiological studies to indicate the magnitude of the health effects. Measures of these may require special development

for particular appraisals. Ideally, the improvements in health should be quantified in terms of measures such as QALYs gained.

- **Valuing All Measured Effects**

CBA is necessary to take the step of putting a money value on the QALY (or other measurements) so that their value can be compared directly with that of the costs. From the above discussion, there are three methods to value the human life, human capital approach, the revealed preferences and willingness to pay approach.

- **Discounting Future Costs and Benefits**

It was suggested that there are three basic reasons why individuals hold positive time preference rates. Firstly, myopia or impatience would seem as likely to apply to health improvements as to anything else. Secondly, risk of never enjoying the benefits would imply that individuals' time preference rate should increase with their age, although in practice the difference that this makes may be negligible. Lastly, diminishing marginal utility may suggest a negative rate, at least for certain periods of deferment.

- **Assessing Risk and Uncertainty**

Measurement of costs and benefits should allow for individuals' aversion to risk in gaining benefits or preference for risk in accepting costs. Uncertainty in economic appraisal can be dealt with by sensitivity analysis, where all known possible outcomes are tried successively in the calculations, to show to what extent the analysis is sensitive to the uncertainty.

- **Assessing Equity**

This stage involves examining the distribution of costs and benefits of each project to determine the gainers and losers and whether the gains and losses seem fair. Summarizing the equity of a project in terms of a single measure may be as difficult as summarizing efficiency in terms of the social aggregate CV. Some measure such as the variance of health care access costs may be appropriate or a Gini coefficient of health status levels might be constructed and used to compare the equity of health care interventions.

- **Choosing**

In CBA, a project will be declared socially efficient if the gains exceed the losses or, if a choice must be made between several such mutually exclusive projects, the one with the largest excess of gain over loss would be chosen. The decision-makers responsible for the final choice of project(s) may not choose the project(s) declared to be efficient. The data on which the analysis was based may be inaccurate and the decision-makers may feel that, with their more extensive knowledge, some other projects are more efficient. Hence, the claim of CBA is not that they make decisions, rather it is that they assist in the decision-making.

There are several evaluating methods for the capital investment decision. In the health investment usually uses present value methods including the net present value method, the internal rate of return method and benefit cost ratio to evaluate the health program. Nearly all of managers agree that methods using present value (the time value of money) give the best assessments of long term investments.

Net Present Value Method is to evaluate a long-term investment opportunity, the time value of money should be part of the analysis. The net present value method includes this cost of money by using an interest rate that sets the desired rate of return or at least sets a minimum acceptable rate of return. The decision rule is " given a minimum acceptable rate of return, if the present value of incremental cash inflows is greater than the net incremental cash investment outflow, approve the project" (Anderson, 1992). The net cash investment is subtracted from the sum of the present values of the cash inflows. When the residual is positive, the project's rate of return is greater that the interest rate used for discounting. If incremental investment cash outflows are less or equal the present value of incremental cash inflows then minimum acceptable rate of return is less or equal project's rate of return. Therefore, the net present value is positive and the project should be approved. When the sum is negative, the project's rate of return less than the discount rate. If incremental investment cash outflows are greater than present value of incremental cash inflows, then minimum acceptable rate of return is greater than the project's rate of return. So the net present value is negative and the project should be rejected. The internal rate of return method, which is the discount rate for a project which will have the effect of producing a zero net present value, finds the project's rate of return. This is the point

where the incremental initial investment cash flow equals present value of the incremental cash inflows. In other words, the net present value is zero.

2.7 Economic Evaluation of Hypothyroidism Mass Screening

To make judgements about efficiency economic evaluation of health care has to compare health outcomes, however measured, with costs. There are three main approaches exist to measuring outcomes: clinical end points, quality of life measures and willingness to pay. The simplest outcome measure to use in a trial is a clinical one, such as an early-detected cases of Congenital Hypothyroidism. Health economists use such measure to construct cost effectiveness ratio or benefit cost ratio.

In Congenital Hypothyroidism screening, there are several studies in the part of economic evaluation. One is a cost benefit analysis for Congenital Hypothyroidism control programs by Layde *et al.* This study was applied in Quebec in 1977.The benefit calculation was calculated from net costs to society of rearing and maintaining a hypothyroidism child for each age interval. The present value of future costs and benefit was calculated using a discount rate of 7.5%. Since all figures were in terms of constant dollars and this amount need to allow for future inflation, but rather represents the lost opportunity value of money spent on screening program. In other words, the yield that could be expected, irrespective of inflation, if the cost of the screening programs were put into long term investment. Additionally, this study assumed that real earnings and the labor, intensive costs of medical care and education increase at 2.5% per year primarily due to increasing productivity. In the cost calculation, there were two components comprise the Congenital Hypothyroidism disease control, whish were neonatal screening and the treatment of those cases detected. In neonatal screening, the total costs of the screening program were calculated including costs of specimen collection and laboratory testing as well as a definitive follow-up.

The treatment of detected case costs were estimated to be the same as for PKU in the first six years of life because of the various health care system. Thereafter, the costs were assumed that no extraordinary follow-up would be necessary, so that the costs would equal with the average of those patients with Congenital Hypothyroidism. The

results were the average cost per child screened for Congenital Hypothyroidism was $1.55 in the terms of 1977 US dollars. With an incidence of one per 6,000 lives birth, the detection of a single cases of Congenital Hypothyroidism would cost about $9,300. The cost of treatment for those with Congenital Hypothyroidism detected added a present value of $2,500 to the cost of Congenital Hypothyroidism screening program. The benefits of detecting and treating a case of Congenital Hypothyroidism were the saving of the averted costs of child with Congenital Hypothyroidism plus the net increase in the productivity of the treated child. It was $13,824, yielding a net benefit to society of more than $105,00 for each case detected and child treated. The cost benefit ratio was 1:8.9 or in the other words, society got a return of approximately $8.90 for each dollar spent on Congenital Hypothyroidism screening program.

Another study of economic evaluation of cost benefit ratio of neonatal screening procedure for PKU and Congenital Hypothyroidism was done in France by Dhondt *et al.* in 1991. The aim of this study to evaluate the cost benefit ratio per detected case. The evaluation was done in monetary term. The calculated cost process of the screening was on the basis of the expenses of the Nord-Pas-de-Calais Regional Screening Center, including the treated costs. The medical costs were analyzed from the medical records and the additional costs were evaluated from patient and family interviewing. In monetary calculation, they used costs in1985 French Frances with a discount rates of 4.5%. The major benefit was avoidance of the burden to society that was the costs of caring for the mentally retarded child. The result was the benefit cost ratio per case detected of Congenital Hypothyroidism prophylaxis was 13.8.

In Japan, Hisashige had done the health economic analysis of the neonatal screening program for metabolic disorder, especially PKU. He analyzed a cost and benefit of PKU screening program in order to evaluate the efficiency of the mass screening system. The cost of cases detection and the treatment program were compared with the projected benefit (avoided costs) that results from preventing of the mental retardation associated with the disorders due to PKU. Costs and benefit were discounted at an annual rate of 7%. In his study, the screening program was assumed to be compared with do nothing alternative. In the case of the do nothing alternative, mental retardation of several degrees occurred. This study was done under a societal

viewpoint for estimating costs as well as benefits. Directs costs consisted of the actual expenditure for screening, confirmation of diagnosis and subsequent treatment of detected cases. Screening costs included the costs related to the collection of the blood specimen and laboratory testing. Treatment costs for a child with PKU included for initial admission and treatment, special dietary supplements and costs related to monitoring frequent blood tests. The present value of future costs was estimated by discounting. An annual rate of 7% was used as the discounting rate during the period of screening, treatment and follow-up.

The benefits were represented by avoided costs that would result from untreated PKU. These avoided costs comprised two elements: expenditure related to the lifelong care of a person with untreated PKU (direct benefits) and loss of productivity (indirect benefits) resulting from disability. The direct benefits included cost of institutional care, special care and special education. Indirect benefits were defined as the loss of production of affected children and the mother, who cared for them. These costs were calculated on the basis of the annual loss of wages for work. The production loss among affected persons, who could not employed, was estimated on the basis of lifetime earnings. These benefits were also discounted at an annual rate of 7% during follow-up. Furthermore, the sensitivity analysis was performed to assess the effects of changes in the assumption about the incidence rate of PKU on the cost benefit ratios and net benefits. The results of this study is assuming the incidence rate of PKU was 1 per 80,500 and the total number of infants screened was 1.2 million, net benefits for the screening program were $283,000 and the cost benefit ratio was 1:2.5. The sensitivity analysis for the incidence of PKU showed that the cost benefit ratio exceeded one.

In Thailand, Rajatanavin study the cost benefit of hypothyroidism screening program at Ramathibodi Hospital in 1992. He calculated costs and benefits on the basis incidence at Ramathibodi Hospital and the sensitivity analysis of the incidence was done in the range of the Congenital Hypothyroidism found. All cost incurred including capital cost, labor cost and material cost. The estimated opportunity cost was calculated in a less inspected fashion. The cost calculation was discounted at an annual rate of 8% per year. The supported spent was also calculated in a less rigid. It

was done without inclusion of opportunity cost of supporters and based on the assumption that there would be no increase in medical expenses.