CHAPTER 2
LITERATURE REVIEW

2.1 Medical Facts

2.1.1 Rabies [1]

Definition: Rabies is an acute viral disease of the central nervous system that affects all mammals and that is transmitted by infected secretion, usually saliva. Most exposures to rabies are through the bite of infected animals.

Etiology: The rabies virus is a bullet-shaped, enveloped, single-stranded RNA virus that is 17-85 nm in diameter belongs to the Rhabdovirus family.

Epidemiology: Rabies is found in animals in all region of the world except Australia and Antarctica. Rabies exists in 2 epidemiological forms: *urban,* propagated chiefly by nonimunized domestic dogs and cats, and *sylvatic* rabies, propagated by skunks, foxes, and raccoons. Infection in domestic animals usually represents a " spillover" from exposure to wild animals in locales where rabies is enzootic or epizootic. The worldwide incidence of rabies is estimated at more than 30,000 cases per year. Southeast Asia, the Philippines, Africa, the Indian subcontinent, and tropical South America are areas where the disease is especially common. While focal epidemics of terrestrial rabies have occurred in USA and Europe, human rabies is uncommon, largely because of successful domestic-animal vaccination programs. In most areas of the world, the dog is the important vector of rabies virus for humans. In most areas of the world, the dog is the important vector of rabies virus for human. However, the fox (in Eastern Europe and Arctic Regions), the mongoose (in South Africa and Caribbean), the fox (in Western Europe) and the vampire bat (in Latin Africa) also may be prominent vectors.

Pathogenesis: The first event in rabies is the introduction of live virus through the epidermis or onto a mucous membrane. Initial viral replication appears to occur within striated muscle cells at the site of inoculation. The peripheral nervous system is exposed at the neuromuscular and neurotendinous spindles of unmyelinated sensory nerve cell endings. The virus then spreads centripetal up the nerve to the ventral nervous system. Probable via peripheral nerve axoplasm. at the rate 3 mm per hour. Viremia has been documented in experimental conditions but is thought not to play a role in naturally acquired disease. Once the virus reaches the CNS, it replicates almost exclusively within the gray matter and then passes centrifugal along autonomic nerves to other tissues. The incubation period of rabies is exceedingly variable, ranging form 7 days to 1 year. Host immune responses and viral strains also influence disease expression. The neuropathology of rabies resembles that of other viral diseases of the CNS. The most characteristic pathologic finding of rabies in the CNS is the formation of cytoplasmic inclusions called "*Negri bodies*" within neurons.

Clinical manifestation: The clinical manifestation of rabies can be divided into 4 stages:

1. A non specific prodrome
2. An acute encephalitis similar to other viral encephalitis
3. A profound dysfunction of brainstem centers that produced the classic features of rabies encephalitis
4. Death

The prodromal period usually lasts 1 to 4 days and is marked by fever, anorexia. headache. malaise. myalgias, increased fatigability, etc.

The encephalitic phases usually ushered in by period of excessive motor activity. excitation. and agitation. Confusion. hallucinations, combativeness, bizarre aberrations of thought, muscle spasms. meningismus, opisthotonic posturing. seizures and focal paralysis soon appear. Characteristically, the periods of mental aberration are interspersed with completely lucid period.

The manifestations of brainstem dysfunction begin shortly after the onset of the encephalitic phase. Cranial nerve involvement causes diplopia, facial palsies, optic neuritis, and the characteristic difficulty with deglutition. If the intensive respiratory support is used, a number of late complications may occur.

The difficulty of diagnosing rabies associated with ascending paralysis is illustrated by cases of person-to-person transmission of the virus by tissue transplantation.

Laboratory finding: Early in the disease, hemoglobin values and routine blood chemistry results are normal. Abnormalities develop as hypothalamic dysfunction, gastrointestinal bleeding, and other complication ensue. The peripheral white blood cell count is usually slightly elevated but may be normal or as high as 30,000/uL. The specific diagnosis of rabies depends on

1. Isolation of virus
2. The serologic demonstration of acute infection
3. The detection of viral antigen in infected tissue
4. The detection of viral nucleic acid by PCR

Prevention & Post-exposure prophylaxis: Post-exposure prophylaxis of rabies includes

1. Wound cleaning and treatment
2. Passive immunization with antirabies antiserum of either equine or human origin
3. Active immunization with antirabies vaccine

In an area in which feline or canine rabies is not prevalent, a healthy biting dog or cat can be confined and observed for 10 days.

Pre-exposure prophylaxis: individual at high risk of contact with rabies virus should receive pre-exposure prophylaxis with rabies vaccine.

2.1.2 Rabies Vaccine and Rabies Immunoglobulin [4]

Rabies vaccine

The vaccines those available in Thailand right now are

1. Cell culture rabies vaccine

1.1 Human diploid cell rabies vaccine (HDCV): this vaccine is obtained from the culture of the fixed rabies virus, Pitman Moore's strain, in human diploid cells. Inactivate the virus with beta-propiolactone 0.025% with the viral titer of $\geq 10^7$ MLD $_{50}$/ml (minimum lethal dose in mice) and the antigenic value of $\geq$ 2.5 IU/ml. This kind of vaccine is produced by the Pasteur Merieux Connaught, France. It is a dry vaccine with sterile water for injection. After solute in the sterile water, we will get the 1 ml of clear pink vaccine.

1.2 Purified chick embryo cell rabies vaccine (PCEC): this kind of vaccine is obtained from the culture of the fixed rabies virus, Flury LEP-C25's strain, in the primary chick embryo fibroblast cells. Inactivate the virus with the beta-propiolactone 0.025% with the viral titer of $\geq 10^7$ TCID $_{50}$/ml (Tissue Cuture infectious dose) and the antigenic value of $\geq$ 2.5 IU/ml. This kind of vaccine is produced by Chiron Behring GMbH, Germany. It is a dry vaccine with sterile water for injection. After solute in the sterile water, we will get 1 ml clear colorless vaccine.

1.3 Purified vero cell rabies vaccine (PVRV): this kind of vaccine is obtained from the culture of the fixed rabies virus, PM WI 38-1503-3M's strain, in vero cells. Inactivate the virus with the beta-propiolactone 0.025% with the viral titer of $\geq 10^{7.5}$ MLD $_{50}$/ml (minimum lethal dose in mice) and the antigenic value of $\geq$ 2.5 IU/ml. This kind of vaccine is produced by Pateur Merieux Connaught, France. It is a dry vaccine with solution of 0.4%sodium chloride for injection. After solute in this preparing solution, we will get 0.5 ml clear colorless vaccine.

2. Purified duck embryo cell rabies vaccine (PDEV)

This kind of vaccine is obtained from the culture of the fixed rabies virus, PM's strain, in embryonated duck eggs. Inactivate the virus with the beta-propiolactone 0.025% with the viral titer of $\geq 10^{7.5}$ MLD $_{50}$/ml (minimum lethal dose in mice) and the antigenic value of $\geq$ 2.5 IU/ml. This kind of vaccine is produced by Berna Swiss Serum and Vaccine Institute, Switzerland. It is a dry vaccine with sterile water for injection. After solute in this solution, we will get 1 ml turbid solution vaccine because of the Thiomersal as preservative.

Rabies immunoglobulin, RIG

Category: immunizing agent. There are 2 types of immunoglobulin, HRIG and ERIG.

1. Human Immunoglobulin (HRIG) is a gamma globulin obtained form the plasma of hyperimmunized human donors. This kind of RIG is imported from Germany (Centeon) and Switzerland (Berna Swiss Serum and Vaccine Institute). National Blood Bank, TRCS is the main supplier in Thailand right now. Complication of HRIG is rare because it originated form human plasma. Dose of injection is 20 units per kilogram.
2. Equine Immunoglobulin (ERIG) is a gamma globulin obtained from plasma of hyperimmunized horse. This kind of RIG is totally imported from France (Pasteur Merieux Connaught) and Switzerland (Berna Swiss Serum and Vaccine Institute). Purified of nowadays ERIG lowers the rate of allergy known as "serum sickness" to 1-6%. However, most of the complications are minor and occurs 7-10 days after injection. The serious complication such as anaphylaxis shock is rare. Dose of injection is 40 units per kilogram.

Indication: Rabies immunoglobulin is indicated for post-exposure immunizations against rabies infection in person who have not been previously immunize against rabies vaccine. Rabies immunoglobulin is used in conjugated with rabies vaccine.

Mechanism and action: Following intramuscular administration, rabies immunoglobulin provides immediate passive antibodies for a short period of time, this protects the patient until the patient can produce active antibody form the rabies vaccine.

Protective effect: When the post-exposure prophylaxis regimen has included local wound treatment, passive immunization, and active immunization 100% effectiveness has been shown. However, rabies has occasionally developed in persons when key elements of the rabies post-exposure prophylaxis regimen were omitted or incorrectly administered.

Time to protective effect: an adequate titer of passive antibody is present 24 hours after injection.

Duration of protective effect: short. Rabies immunoglobulin has a half-life of approximately 21 days.

Precaution: Pregnancy, breast-feeding, pediatrics, and geriatrics
Side effect: severe systemic adverse effects to rabies immunoglobulin are rare. There are some reports of angioedema, nephrotic edema, and anaphylaxis.

Dosage information: ERIG dosage of use is 40 units per Kg. HRIG dosage of use is 20 units per Kg.

Indication for rabies vaccine and rabies immunoglobulin

1. Pre-exposure immunization

   Inject the 1 ml or 0.5 ml of vaccine (depend on type of vaccine) intramuscularly, IM, or 0.1 ml of vaccine intradermally, ID, at deltoid on day 0, 7, 21 or 28. The date of injection may be postponed 1-2 days.

   This immunization protocol is used for the high-risk personnel such as rabies laboratory researcher. This kind of people should be checked for the rabies antibody every 6 months and boost 1 dose of vaccine whenever the titer is lower than 0.5 IU per ml. And for the other related personnel such as veterinary or pet keeper, should be checked for the rabies antibody annually and boost 1 dose of vaccine whenever the titer is lower than 0.5 IU per ml. In case of the over immunization, the patient may be suffered from the hypersensitivity especially for the HDCV. Thus, the pre-exposure immunization should be given to risk group only.

2. Post-exposure immunization

   2.1 rabies immunoglobulin

   ERIG: inject 40 IU per kg

   HRIG: inject 20 IU per kg

   The patient should be injected with the rabies immunoglobulin on the first day of exposure to the rabies. If the patient receives the vaccine after 7 days, there will be antibody from the rabies vaccine, so that there is no need for RIG after 7 days.

   In case of ERIG use, the patient should be test for hypersensitivity against ERIG. Dilute ERIG 1:10 and inject 0.02 ml with tuberculin syringe intradermally at volar side of arm until the 0.3 mm wheal appear. Inject the other side of arm with normal saline to compare the result. Wait for the result about 15-

20 minutes. If there is a wheal bigger than 6 mm or flare compare with another arm, the test will be reported as "positive"

With the positive test for hypersensitivity, the patient should be injected with HRIG instead. But if the HRIG is not available, the ERIG should be given carefully and under the supervision of the doctor and even in case of the test is negative. However, the symptom of ERIG allergy is only rash, urticaria or arthalgia.

From the study in the animal, we found that the rabies will multiply itself firstly at the bite site before entering the neuromuscular junction. Thus, the RIG injection around the wound will inhibit and neutralize the rabies virus at wound site. Before injection with RIG, the wound should be cleaned as much as possible. The RIG should be injected by insert the needle underneath the wound and avoid multiple injection

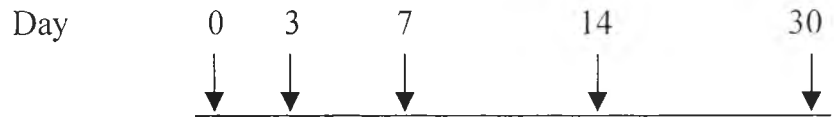
If the wound is at or near the eyeball, HRIG should be dropped into the eye. And if the RIG is left over after injection, the left over part will be injected intramuscularly away from the vaccination site.

There is no need to use RIG more than recommendation because it will suppress the antibody formation. And in case of the RIG in not enough for injection, RIG should be mixed with normal saline to get the enough solution of RIG.

2.2 rabies vaccine

2.2.1 intramuscular injection, IM

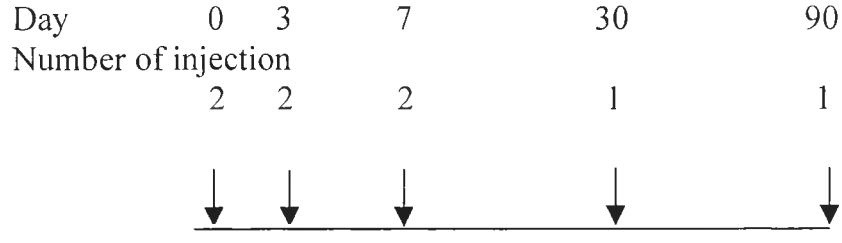
Inject 1 ml or 0.5 ml (depend on type of vaccine) of vaccine intramuscularly at deltoid or the anterolateral aspect of thigh in the children. Do not inject at the buttock because of the low efficacy of the drug at this site.



2.2.2 intradermal injection, ID

2.2.2.1 protocol 2-2-2-0-1-1

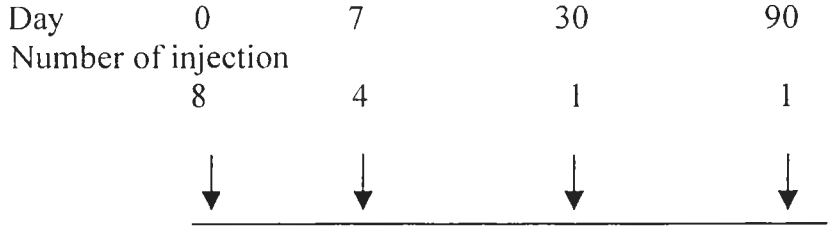
Inject 0.1 ml of the vaccine intradermally at both right and left upper arm on day 1, 3, 7 and at one upper arm on day 30 and 90



This protocol is for PVRV, and it would be possible to use PCEC and HDCV only in case that the antigenic value of vaccine is higher than 0.7 IU per 0.1 ml.

2.2.2.2 protocol 8-0-4-0-1-1

This protocol is applied to the HDCV and PCEC vaccine. On day 0, inject 0.1 ml of vaccine to both sides of upper arms, lateral aspect of thighs, scapulas and lateral aspect of abdomen (8 points). Day 7 inject 0.1 ml of vaccine at both upper arms and lateral aspect of thighs (4 points). Day 30 and 90 inject 0.1 ml of vaccine to one side of upper arm.



Intradermal injection

The aim of intradermal injection is to lower the cost of immunization. Multiple site of injection can activate the antibody in the short time. If we use PCEC and HDCV, the vaccine should have the high antigenic value at least 0.7 IU per 0.1 ml so that the efficacy will be as equal as intramuscular injection. But this kind of protocol should be provided in the places where are well-equipped, well-trained personnel and the high number enough of patient.

The intradermal injection is also appropriate for the multiple exposure, usually more than 2 post-exposure patients.

In case of RIG is not available. The HDCV or PCEC with protocol 8-0-4-0-1-1 should be given. And especially in case that the patient is bitten at face or head and in the low weight children, this protocol should be prescribed conjunct with the RIG. If the patient is on chloroquine or other malaria prophylaxis, the doctor should prescribe only intramuscular injection and conjunct with RIG.

Prophylaxis in the patient with the history of previous vaccination

The patient who is vaccinated with the rabies vaccine at least on day 0, 3, 7 or antibody titer is more than 0.5 IU per ml should be

1. If expose to rabies within 6 month after last injection, the patient will be given only 1 dose vaccine IM or ID on the first day
2. If expose to rabies more than 6 months, the patient will be given 2 doses of vaccine on day 0 and 3

In this type of the patient, there is no need to given the patient with RIG because the antibody against rabies will be activated rapidly.

Notification of rabies vaccine and RIG

1. The incubation period of rabies is usually 1-3 months and 95% are within 1 year. Thus, the patient should be vaccinated with rabies vaccine even in case of coming late
2. The dose of rabies vaccine for children and adult is the same.

3. Pregnancy women and young children can be prescribed with rabies vaccine.
4. The timetable for injection can be postponed for 1-2 days.
5. The cell culture vaccine and the embryonated vaccine can be used interchangeably.
6. The immunodeficiency patient should be given with RIG for every case and only with the intramuscular injection.

Antibody from rabies vaccine and rabies immunoglobulin

Vaccine: rabies vaccine will activate the active antibody against rabies at about day 7, then the level of antibody will be over 0.5 IU per ml on day 14, and at peak on day 30. The antibody will sustain in the body and will last for 1 year.

RIG: this passive antibody can be detected immediately after injection and its half-life is usually 3 weeks.

Production process of rabies immunoglobulin [4]

Rabies immunoglobulin complies with the requirements of 3rd edition of European Pharmacopoeia for Human Rabies Immunoglobulin (0723). These requirements are reproduced after the heading "definition" below

Definition:

Human rabies immunoglobulin is a liquid or freeze-dried preparation containing immunoglobulin, mainly immunoglobulin G. The preparation is intended for intramuscular administration. It is obtained from plasma from donors immunized against rabies. It contains specific antibodies neutralizing the rabies virus. Human normal immunoglobulin may be added.

It complies with the monograph on Human normal immunoglobulin, except for the minimum number of donors and the minimum total protein content.

The solvent /detergent treated immunoglobulin is isolated form solubilized Cohn Fraction II. The FractionII solution is adjusted to a final concentration of 0.3% tri-n-butylphosphate; TNBP (solvent) and 0.2% sodium cholate (detergent). The solution is heated to 30 degree Celsius and maintained at that temperature for not less than 6 hours. After the viral inactivation step, the reactants are removed by precipitation, filtration and finally ultrafiltration a diafiltration. BayRab is formulated as a 15% to 18% protein solution at a pH of 6.4 to 7.2. BayRab is then incubated in the final container for 21 to 28 days at 20-27 degree Celsius.

A heat treated immunoglobulin undergoes a heat treatment process step to inactivate viruses that has been added to further reduce any risk of blood-borne viral transmission. The inactivation and removal of model and laboratory strains of enveloped and non-enveloped viruses during the manufacturing and heat treatment process has been validated by spiking experiments. Removal and inactivation of the studied enveloped and no-enveloped model viruses was demonstrated at the precipitation II stage of manufacturing. In addition, inactivation was demonstrated during the 10-hour heat treatment process for the studied enveloped and non-enveloped viruses. Inogam rabies-HT is formulate as 10% to 18% protein solution at a pH of 6.8 adjusted with hydroxide or hydrochloric acid.

Potency:

The potency is determined by comparing the dose of immunoglobulin required to neutralize the infectivity of a rabies virus suspension with the dose of reference preparation, calibrated in International Units, required to produce the same degree of neutralization. The test is performed in sensitive cell cultures and the presence of unneutralized virus is revealed by immunofluorescence.

The International Unit is the specific neutralizing activity for rabies virus in a stated amount of the International Standard of human rabies

immunoglogulin. The equivalence in International Units of the International Standard is stated by the World Health Organization (WHO).

Carry out the test in suitable sensitive cells. It is usual to use the BHK 21-cell line, grown in the medium described below, between the 18^{th} and 30^{th} passage levels counted from the ATCC seed lot. Harvest the cells after 2 to 4 days of growth, treat with trypsin and prepare a suspension containing 500,000 cells per milliliter (cell suspension). 10 min before using this suspension add 10 microgram of diethylaminoethyldextran R per milliliter, if necessary, to increase the sensitivity of the cells.

Use a fixed virus strain grown in sensitive cells, such as the CVS strain of rabies virus adapted to growth in the BHK 21-cell line (seed virus suspension). Estimate the titer of the seed virus suspension as follows.

Prepare a series of dilution f the viral suspension. In the chambers of cell-culture slides (8 chambers per slide), place 0.1 ml of each dilution and 0.1 ml of medium and add 0.2 ml of the cell suspension. Incubate in an atmosphere of carbon dioxide at 37°C for 24 hours. Carry out fixation, immunofluorescence staining and evaluation as described below. Determine the end-point titer of the seed virus suspension and prepare the working virus dilution corresponding to 100 $CCID_{50}$ per 0.1 ml.

For each assay, check the amount of virus used by performing a control titration: from the dilution corresponding to 100 $CCID_{50}$ per 0.1 ml, make three tenfold dilution. Add 0.1 ml of each dilution to four chambers containing 0.1 ml of medium and add 0.2 ml of the cell suspension. The test is no valid unless the titer lies between 30 $CCID_{50}$ and 300 $CCID_{50}$.

Dilute the reference preparation to concentration of 2 I.U. per milliliter using non-supplemented culture medium (stock reference dilution, stored below -80°C). Prepare two suitable predilutions (1:8 and 1:10) of the stock reference dilution so that the dilution of the reference preparation that reduces the number of fluorescent fields by 50 per cent lies within the four dilutions of the cell-culture slide. Add 0.1 ml of the medium to each chamber, except the first in each of two rows, to which add respectively 0.2 ml of the two

predilution of the stock reference dilution transferring successively 0.1ml to the other cambers.

Dilution the preparation to be examined 1 in 100 using non-supplemented medium (stock immunoglobulin dilution) – to reduce to a minimum errors due to viscosity of the undiluted preparation – and make three suitable predilutions so that the dilutions of the preparation to be examine that reduces the number of fluorescent fields by 50 per cent lies within the four dilutions of the cell culture slide. Add 0.1 ml of the medium to all the chambers except the first in each of three rows, to which add respectively 0.2 ml of the three predilutions of the stock immunoglobulin dilution. Prepare a series of twofold dilutions transferring successively 0.1 ml to the other chambers.

To all the chambers containing the dilutions of the reference preparation and the dilutions of the preparation to be examined, add $100CCID_{50}$ per 0.1 ml (working virus dilution), shake manually, allow to stand in an atmosphere of carbon dioxide at 37°C for 90 minutes, add 0.2 ml of the cell suspension, shake manually and allow to stand in an atmosphere of carbon dioxide at 37°C for 24 hours.

After 24 hours, discard the medium and remove the plastic walls. Wash the cell monolayer with phosphate buffered saline pH 7.4 R and then with mixture of 20 volumes of water R and 80 volumes of acetone R and fix in a mixture of 20 volume of water R and 80 volumes of acetone R at –20 °C for 3 minutes. Spread on the slides fluorescein-conjugated rabies antiserum R ready for use. Allow standing in an atmosphere with a high level of moisture at 37 °C for 30 minutes. Wash with phosphate buffered saline pH 7.4 R and dry. Examine twenty fields in each chamber at a magnification of × 250, using a microscope equipped for fluorescence readings. Note the number of fields with at least one fluorescent cell. Check the test dose used n the virus titration slide and determine the dilution of the reference preparation and the dilution of the preparation to be examined that reduce the number of fluorescent fields by 50 per cent, calculation the two or three dilutions together using probit analysis. The test is not valid unless the statistical analysis shows a significant slope of

the dose response curve and no evidence of deviation form linearity 9or parallelism.

The stated potency is no less than 150 I.U. per ml. The estimated potency is no less than the stated potency and is not greater than two times the stated potency. The fiducial limits of error (P=0.95) of the estimated potency are not less than 80 per cent and not more than 125 per cent.

2.2 Economic Theory

2.2.1 Capital Budgeting and Cost Analysis [6]

Facing the challenge of balancing long-run and short-run issues. How can managers systematically incorporate financial and non-financial assets into their long-run planning decision? The methods of analysis will be discussed are called capital budgeting method because they deal with how to select project that increase rather than decrease the capital of an organization. These methods assist managers in analyzing projects that span multiple years.

Stage of capital budgeting is the making of long-run planning decisions for investments in projects and programs. It is decision-making and control tool that focuses primarily on projects or programs that span multiple years. These planning decisions should be guided by the objectives of an organization and its strategies. Strategy describes how an organization matches its own capabilities with the opportunities in the marketplace to accomplish its overall objectives. There are six stages in capital budgeting

- **Stage 1: Identification-** to distinguish which types of capital expenditure projects are necessary to accomplish organization objectives.
- **Stage 2: Search stage-** to explore alternative capital investments that will achieve organization objectives.
- **Stage 3: Information-Acquisition stage-** to consider the expected costs and the expected benefits of alternative capital investments.

- **Stage 4: Selection stage-** to choose projects for implementation.
- **Stage 5: Financing stage-** to obtain projects funding.
- **Stage 6: Implementation and control stage-** to get projects underway and monitor their performance.

Discounted cash flow (DCF) method measure all expected future cash inflows and outflow of projects as if they occurred at a single point in time. DCF methods incorporate the time value if money. The time value if money takes into account that a dollar (or any other monetary unit) received today is worth more than a dollar received at any future time.

Relevant cash flows in discounted cash flow analysis. One of the biggest challenges in DCF analysis is determining which cash flows are relevant to making the investment selection. Relevant cash flows are expected future cash flows that differ among the alternatives.

Intangible Assets and Capital Budgeting. Intangible assets, whether or not they are recognized for external reporting purposes, are critical to most organizations. Examples include brand names, the customer base.

Sensitivity analysis to examine how a result will change if the predicted financial outcomes are not achieved or if and underlying assumption changes, mangers can use sensitivity analysis

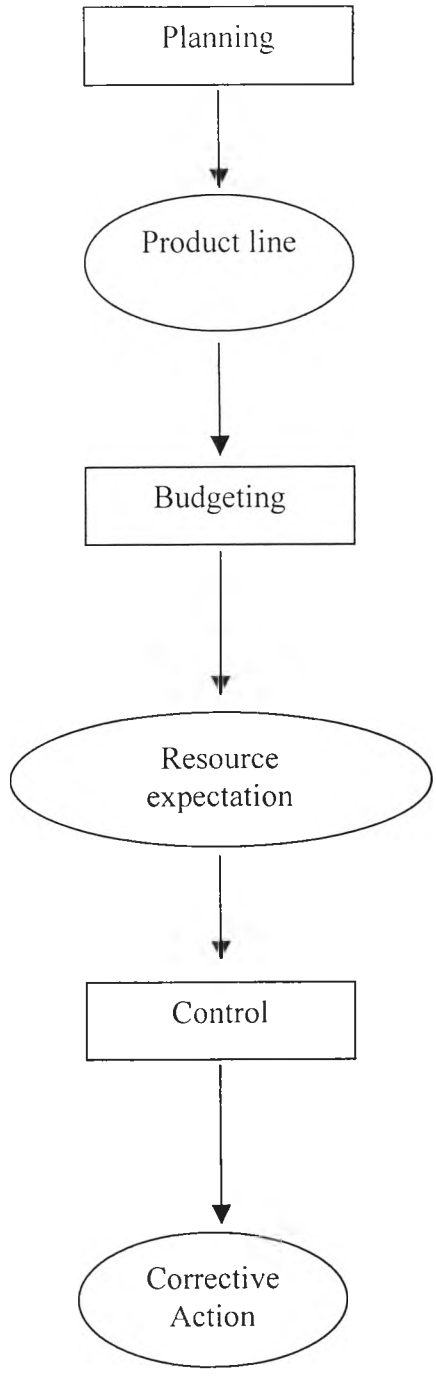


Figure 2.1: planning, budgeting, and control process

2.2.2 Cost Allocation [7,9]

Cost allocation refers to taking costs from one area or cost objective and allocating them to others. There are 2 types of cost allocation that concern us. The first is the allocation of indirect costs within a department to specific individual patients. The second type of allocation is from one department or cost center to another.

Many allocated costs are referred to as overhead. Overhead refers to costs that are generally indirect and cannot be easily associated with individual patients. Overhead cost therefore requires some form of aggregation and then allocation to patients.

The Steps in the overhead application process:

1. Selecting a base for assigning costs to patients and department: The first step is to select an overhead cost application base. This base serves as the denominator of the fraction to be used to calculate the based on the existence of a cause-and-effect relationship between production volume and overhead costs. In addition, the base should be applicable to all patients. Common industrial bases are direct labor hours, direct labor cost and machine hours. Health care organizations could use hours or cost for staff as an application base along these lines. Other bases also could be developed if the result in a more accurate cause-and –effect relationship between overhead costs and volume of patients. Age, sex, and diagnosis were suggested above.
2. Determining budgeted cost and volume: The second step is to determine a budgeted overhead cost and a budgeted volume of production. In the case of a health care organization, we would need to ascertain all departmental budgeted amounts that cannot be assigned to patients as either direct labor or direct materials. We would also need to estimate the expected volume. Note that volume does not necessarily mean the number of patients .We are concerned here with the volume of the item

used for the base. For example, each department would have to estimate the number of hours of housekeeping service that they expect to consume for the coming year, if the housekeeping base is the total number of hours of service.

3. Computing overhead rate: the third step is computation of an overhead rate y dividing the total expected overhead cost by the total expected production volume. For example if a health car organization expects to have overhead cost of $10 million and 500,000 nursing hours, then a rate could be developed by dividing the overhead cost by the nursing hours base to result in an application rate of $20 per nursing hour. This rate is base on annual budgets. As noted earlier, the use of annual rather than monthly budget smoothes out some unwanted seasonal impacts. Similarly, use of monthly budgets for rate calculations would cause us to charge major maintenance costs only to patients rather than spreading those costs across all patients' whole benefit from them over the course of the year.
4. Measuring the actual base: The forth step is to keep track of actual base data as the year unfolds. That is, we must track how many nursing hours are actually consumed for each patient or how many housekeeping hour of service are actually provided to each department.
5. Applying the budgeted overhead application rate to the actual volume: The fifth step is to apply the budgeted overhead application rate to the actual units of the vase consumed to determine the overhead applied. Thus, suppose that a specific department consumed 1,500 hours of housekeeping service. Since the application rate is $10 per hour, a total of $15,000 would be applied to that department. This application would generally be done monthly throughout the year.
6. Accounting for year-end differences between actual total overhead and the amount of overhead applied throughout the year: The sixth and the final step is to account for any year end differences between actual total

overhead and the amount of overhead that has been applied to patients throughout the year.

Various methods for allocating shared cost [7,9]

1. Direct allocation: Each overhead cost is allocated directly to final cost centers/ Program Z's allocated share of central administration is equal to central administration cost times. Note program Z's proportion center, not total paid hours for the whole organization. The later method would underestimate the costs in all finals cost centers.
2. Step down allocation: the overhead departments are allocated in a stepwise fashion to all of the remaining overhead departments and to the final cost center.
3. Step down with iterations: The overhead departments are allocated in a stepwise fashion to all the other overhead departments and to the final cost centers. The procedure is repeated a number of times to eliminate residual unallocated amount.
4. Simultaneous allocation: This method uses the same data as 2 and 3 but it solves a set of simultaneous linear equations to give the allocations. It gives the same answer as method 3 but involves less work.

2.3 Previous Studies

2.3.1 Rabies and Rabies Immunoglobulin

Hanlon, A., et al. (2001) studied about modern human post-exposure prophylaxis instead of using the conventional regimen which consists of potent vaccines and local infiltration of rabies immune globulin (RIG). Monoclonal antibodies (Mabs) offer several theoretical advantages over RIGs. To this end, several human and equine RIGS, alone or in combination with vaccine, were investigated for post-exposure efficacy in a Syrian hamster model, compared with a single neutralizing murine Mab. Preliminary results suggest that: (1)

animal models continue to provide utility as human surrogates in the demonstration of product efficacy against rabies; (2) RIG preparations differ substantially in experimental effectiveness and clearance; and (3) relevant alternatives, such as Mabs, should be pursued for future improvements to human rabies prevention.

Wilde, H., et al. (1991) studied about situation of rabies in Thailand the study found that there were100,000 courses of postexposure rabies treatment given in Thailand annually, 95% consist of brain tissue-derived vaccine without immune globulin. Rabies tissue culture vaccines and immune globulins are expensive by the standards of developing countries. The study also suggested another alternative for Thailand. That was when the vaccine were given according to either of two proven intradermal post-exposure schedules, significant savings can be achieved without loss of efficacy. Purified equine rabies immune globulins account for approximately 10% of the cost of human products administered to exposed individuals and have been shown to be safe and effective. The studies showed the failure of domestic immunization. A canine pre-exposure immunogenicity study with a potent, inactivated tissue culture vaccine revealed that 12.5% of Thai dogs failed to develop protective antibody titers 2 months after one subcutaneous injection.

2.3.2 Cost of Intervention, State of Health Approach (Cost of Life Loss and Cost of Health)

Andersen, K., et al. (2000) studied about the cost function estimation to apply to dementia. The author suggested using the regression model to estimate the cost because of the highly skewed of clinical data from few patients incur high costs relative to the majority of patients and even worse in case of zero cost observation. The study suggests that one should choose a regression model based on the quality of its predictions. The objective of this study was to estimate a cost function in order to estimate the annual health care cost of

dementia. In this study, using different models, the health care cost was regressed on the degree of dementia, sex age, marital status and presence of any co-morbidity other than dementia. The choice in the model had a substantial impact on the predicted health care costs e.g. for a mildly demented patient, the estimated annual health care costs varied form DKK 71273 to DKK 90940 (1 US$ =DKK7) depending on which model was chosen. This study has shown that health care cost is substantially higher for demented patients than for non – demented elderly people in general. Furthermore, the degrees of dementia and marital status have been shown to be important factors. In this study, the costs of informal care and of pharmaceutical drugs are not included.

Boonyahodhara, V., (1987) studied about the epidemiology and economic impact of accident. The study showed that there were 2 million injured and about 30,000 million baht loss annually for the accident but this figure did not include the indirect cost-opportunity cost which was much more than this. The author showed that the direct cost is only "*tip of iceberg*". The direct cost account for only 6 % of the total cost. Therefore, Thailand maybe loss about 700,000 million baht every year. The study calculated the indirect cost from the cost of mortality, morbidity and disability. The cost of premature death was calculated from working year loss in each age group. Then convert the total working year loss into monetary term using the discounting factor.

Eisenring, C., (2000) studied about whether an individual maximizes lifetime or trades off longevity for quality of life in Grossman's pure investment (PI) model. This study shown that the answer critically hinges on the assume production function for healthy time. If the production function for healthy time produces a trade-off between life span and quality of life, one has to solve a sequence of fixed time problems. The one offering maximal intertemporal utility determines optimal longevity. Comparative static results of optimal longevity for a simplified version of the PI-model are derived. According to Grossman's seminal contribution was to treat health as a stock

variable, which depreciate over time, but which can be augmented by investments. To investigate the longevity-quality of life trade-off, a simplified version of Grossman's pure investment model is analyzed. In the PI model, healthy time and, therefore, the health status does not enter the utility function. Health is solely an investment commodity. Thus, the existence of a trade-off between longevity and quality of life in PI model critically hinges on the assumptions about the production function for healthy time. The result of this study is that higher initial endowments of wealth and health, a rise in the wage rate, or improvements in the technology of producing healthy itme, all increase the optimal length of life. On the other hand, optimal longevity is decreasing in the depreciation and interest rate.

Forsberg, C., et al. (1998) studied about the costs of diarrhea and saving form the control program. The study compared the reduction of treatment costs before and after implementation of the program, and the potential saving to be made form its continuation. The study shows that cost that can be saved from the diarrhea control program was benefit from the program. Thus, in case that the program is success, the over all cost will be lower.

Gravelle, H., and Smith, D., (2001) studied about discounting for health effects in cost-benefit and cost-effectiveness analysis. This study is an ongoing methodological debate about the appropriate way to take account of future health effects in evaluations. They said that cost and benefits should be discount at the same rate. They suggested to discount health when it is valued in monetary term, as in cost-benefit analysis, a t the same rate as costs. If health effects are measured in quantities (e.g. quality adjusted life years) as in cost-effectiveness analysis) and the value of health effects is increasing over time, discounting the volume of health effects at lower rate than costs is a valid method of taking account of the increase in the future value of health effects. And then they concluded that the value of future health effects in terms of future income grows over time, this must be allowed for, either directly by

adjusting the health effects used in the evaluation, or indirectly by using a lower discount rate used for health effects than for costs. For the direct method of allowing for change in the value of health over time, CBA in all health effects should be valued in the income of the period in which they occur and then discount back to a present value using the rate of discount appropriate for costs, and CEA the minimal volume of health effects should be adjusted to a real volume to reflect the growth in the value of future health effects and the same discount rate be applied to costs and the real volume of health effects. In case of that the indirect method of allowing for growth in the value of health by means of a lower discount rate on health effects is used, the discount rate on health effects will be 1-3.5% less than the discount rate on costs depending on the assumptions made about the pure utility discount rate.

Gow, J., (1999) studied about the total cost (direct and indirect cost) associated with the operation of an Australian community based screening program for colorectal cancer. The aim of this study is to calculate the economic costs to Australian society of the 1995 Bowelscan program. These included direct costs, such as the cost of test kits and their processing and the subsequent costs of treating test-positive participants, as well as direct costs, such as lost productivity and travel costs which enable to estimate the cost per cancer detected by the program.

Hout, V., (1998) studied about discounting costs and effects. This study showed the important of calculation of present value (PV) to assessment of cost effectiveness and cost utility analysis for both costs and the effects. The study shows that discounting benefits at a lower rate than costs may have important implications for the outcome of the cost effectiveness of a program such as in considering the costs and effects of vaccination strategies for hepatitis B, the difference may be as large as between US $3696 per life year gained (both costs and effects discounted at 5%) and US $ 375 per life year gained (only costs discounted). The study suggests that different discount rates may be

appropriate. This does not only concern health: similar arguments might come up when considering the environment or other commodities for which there are substantial market imperfection.

Johnson. F., et al. (2000) used stated-preference (SP) analysis to measure willingness to pay (WTP) to reduce acute episodes of respiratory and cardiovascular ill health. The SP survey employs a modified version of the health state descriptions based in the Quality of Well Being (QWB) Index. The four health state attributes are symptom, episode duration activity restrictions and cost. This study demonstrates the feasibility of applying SP techniques to elicit values for health conditions described in terms of symptom, activity restriction and duration. Furthermore by combining two SP elicitation methods, graded pair and discrete-choice, the estimates presented in this study are more valid and robust measures of benefits than could be obtained from a single format. The two formats collect slightly different evaluation strategies. Thus, combining both formats allows capitalizing on the information provided by each format and on the different cognitive processes. The grade-pair format elicits value for marginal trade-off among health states, whereas the discrete-choice format exhibits total values to avoid a given condition subjective to the subject's current health.

Liu, J., et al. (2000) studied mother's willingness to pay for her own and her child's health: a contingent valuation study in Taiwan. This study uses the contingent valuation (CV) method to estimate mothers' willingness to pay (WTP) to protect themselves and their children from suffering a minor illness-a cold- in Taiwan. WTP is specified as a hedonic function of the duration and severity of the cold and of respondent's socioeconomic characteristics. The average mother is willing to pay before to protect her child than herself form suffering a cold. This study uses data from a developing country and estimates value for an illness described by the respondent. For the model of hedonic function, the regression analysis suggests a strong relationship between family

income, health and WTP. These measures of health values provide a foundation for evaluating public health or environmental regulations that may influence the prevalence of minor morbidity in a developing country.

Murray, C., et al. (2000) studied the development of WHO guidelines on generalized cost-effectiveness analysis. They posed the question that evaluation of specific intervention used the concept of CEA which is dominated by studies of prospective new interventions compared with current practice. This type of analysis does not explicitly take a sectoral perspective in which the costs and effectiveness of all possible interventions are compared, in order to select the mix that maximizes health for a given set of resource constraints. WHO guidelines on generalized CEA propose the application of CEA to wide range of interventions to provide general information on the relative costs and health benefits of different interventions in the absence of various highly local decision constraints. This general approach will contribute to judgments on whether interventions are highly local decision constraints. This general approach will contribute to judgments on whether intervention is highly cost-effective, highly cost-ineffective or something in between. Generalized CEAs require the evaluation of a set of interventions with respect to the counterfactual of the set of the related interventions, i.e. the natural history of disease. This relative cost-effectiveness, which do not pertain today specific decision-maker, can be useful reference point for evaluating the direct is for enhancing allocative efficiency as well as opportunities presented by new interventions.

Postnett, J., and Jan, S., (1996) studied about the indirect cost of the unpaid inputs. This paper is intended as an exposition of conventional welfare economics principles to the valuation of unpaid inputs into the production of health. The sorts of unpaid activity which may be expected to be of interest in an economic evaluation of health care provision will be of two kinds; (i) non-market activity- time inputs of the patients and relatives spent in travel,

waiting, etc. (ii) quasi-market activity- the provision of caring, nursing and housework for patients by relatives and others. The study focused on unpaid time which represents a potentially significant input into the health production function. The notion of opportunity cost. Such analysis requires consideration of whether time displaced in the production of heath involves lost work or lost leisure. Furthermore. because valuation of opportunity cost requires the consistent treatment of costs and benefits, the study also considers the valuation of outputs. The basis for valuing the shadow price of work time is examined by firstly assuming perfect competition. The basis for valuing the shadow price of leisure is restricted to an examination of methods used to value unpaid housework. The two methods examined are the replacement cost and the opportunity cost method.

Ried, W., (1996) investigated the relationship between the willingness to pay and the cost of illness approach with respect to the evaluation of economic burden due to adverse health effects. Cost of illness approach is commonly used in applied work in any situation where individual willingness to pay can be taken to encompass the effect on medical care resource use as well, cost of illness should be considered as the rival approach in program evaluation. Of course, relying on the later approach will yield valuable information only to the extent that a relation between cost of illness and willingness to pay can be established. The main purpose of this paper to study the relationship between the willingness to pay and the cost of illness approach by relying on Grossman's pure investment model while effects on individual morbidity are taken to be generated by marginal changes in the rate of health capital depreciation. The analysis generates two principal findings. First, for a class of identical individuals cost as measured by the cost of illness approach is demonstrated to provide a lower bound on the true welfare cost to the individual, i.e. cost as given by the willingness to pay approach, moreover, the cost of illness is increasing in the size of the welfare loss. Second, if one takes into account the possible heterogeneity of individuals, a clear relationship

between the cost values supplied by the two approaches no longer exists. As an example, the impact of variations in either financial wealth or health capital endowment is discussed. Thus. diversity in individual type turns out to blue the link between cost of illness and the true economic cost.

Stein, H., and Wemmerus, V., (2001) studied about the cost of life loss using a life course perspective, the research examines personal accounts of adults with schizophrenia, and their parents and well- siblings from six families. Accounts of multiple members of the same family, including the family member with schizophrenia, are used to describe how families understand and accommodate life changes that result from the illness. Families describe the loss of a "*normal life*" as one of the most devastating aspects of schizophrenia. The study presented the personal and social losses described by adults with schizophrenia and their well family members, and document families' search for ways that their ill family member can achieve or maintain valued social roles. The concerns of well family members for the future of the ill family member and ways families contemplate transfer of care issues are described. Implications of the study for community research and action are discussed.

Ungar, W., et al. (2000) studied about measuring productivity loss days in asthma patients. According to the economic burden of illness, it is important to assessment the productivity losses arising from short-and long- term absences due to disability and premature death. These indirect costs may account for a large proportion of total cost. Since indirect costs are not borne directly by payers, such as public or private health plans, they often receive little attention, despite the large cost to society in the form of lost productivity. The study aims to develop a method to measure restricted days and to quantify total productivity loss days (PLDs) in adult asthma patients. Patient and disease characteristics, occupation, annual wage, work absences, restricted days, level of functioning on restricted days, and travel and waiting time were collected to

calculate PLDs. This study suggests disaggregating indirect cost into PLDs an wage rates. This study revealed that most productivity loss in asthma patients could be attributed to restricted days than absence or waiting and travel time.

Veravaidaya, M., et al. (1991) studied about the economic impact of HIV/AIDS in Thailand. The study divided the economic impact into 2 categories. The first one was the direct cost which included system cost e.g. blood examination, health care expenditure. The second was indirect cost which included income earning forgone. The result found that the cost of HIV/ AIDS was high as US $1,400 million in year 1998 and will be US $1,800-2,000 million in year 2000. But the estimation of HIV patient is much higher when compared with the estimation of the National Economic and Social Development Board (3.4-4.3 million and 1.1-1.3 million respectively)

Vongsaroj, R. (1998) studied about the economic loss due to HIV/AIDS in Phayao, Thailand. The study calculated the both direct cost and indirect cost of HIV/AIDS. The direct and the indirect cost were about 18 million and 573 million respectively. The direct cost is costs such as cost of treatment; cost of programs, etc. the concept of cost of premature death (income foregone loss) was used to calculate the indirect cost as well. The study also confirmed that the indirect cost such as the human capital loss is much higher than direct cost.