CHAPTER 3

RESEARCH METHODS

3.1 Conceptual Framework

This study will develop an approach to determine benefits and costs of using a set of clinical criteria instead of fever alone in presumptive diagnosis and treatment which is a currently using practice in most countries including Myanmar. The idea is to identify one or a set of clinical symptoms or signs that can predict the possibility of being blood slide positive for malaria parasites. This will be coupled with determination of benefits and additional costs incurred when using this or a set of clinical symptoms or signs to select patients to be given presumptive treatment. Details of this approach is discussed below and the whole conceptual framework is presented in Figures 3.1 and 3.2.

3.1.1 The Clinical Criteria

A set of clinical criteria comprising one or more of clinical symptoms or signs, will have to be developed first using logistic regression model. There are typically two goals of modeling in this case: one is to obtain a valid estimate of exposure–disease relationship, the other is to obtain a good predictive model. The latter is one of the intentions of this study.

When the goal is prediction it is appropriate to use computer algorithms, such as backward elimination or all possible regressions, which are built into computer packages for different models. For another goal standard computer algorithms do not apply because the roles that variables such as confounders and effect modifiers play in the model must be given special attention.

At the variable specification stage, clinically or biologically meaningful variables are defined in the model to

provide the largest model to be initially considered. In this study slide positivity for malaria parasite is identified as a dependent variable and oral temperature equal to or more than 38 C, spleen size, cough, vomiting, bowel movement, age, season of the year, sex and area of residence with respect to risk of getting malaria (endemicity) as independent variables.

Figure 3.1 Conceptual Framework: Development of a Set of Clinical Criteria
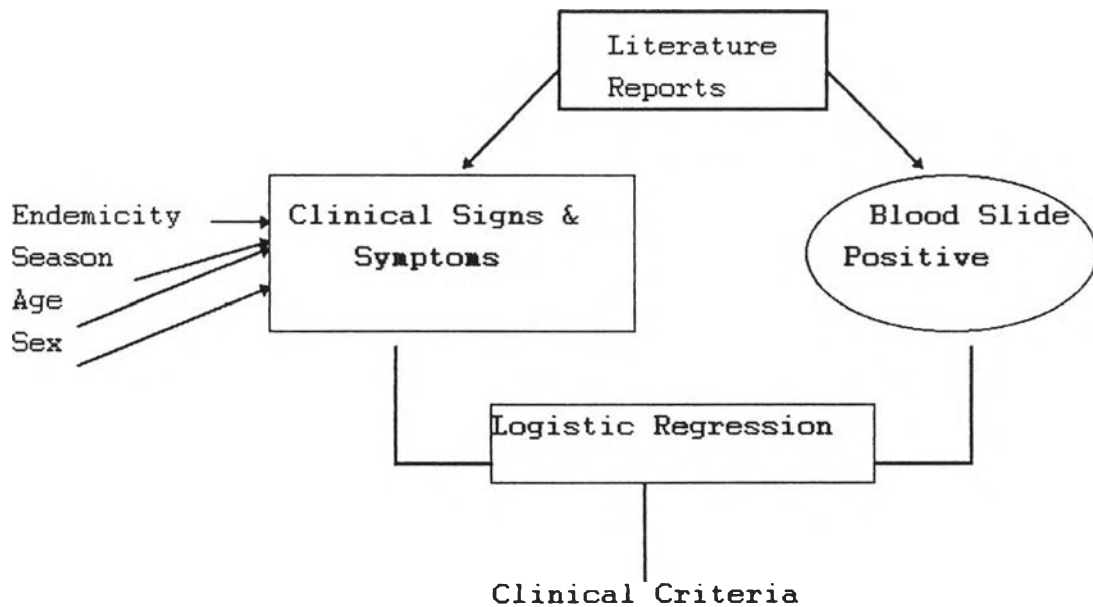
3.1.2 Benefits and Costs

After one or a set of clinical symptoms or signs has been identified as diagnostic criteria, benefits and additional costs of using these criteria were determined. This was based on the inherent properties of a diagnostic process or procedure which are the sensitivity and the specificity of the test. The value of a diagnostic process or procedure depends much on the specificity. In using presumptive treatment approach when fever is the sole criterion for selection of cases for treatment, the proportion of those with blood slide positive, is found to be very low (0.15 or 15%) and it is clear that 85% of those being diagnosed as having attacks of malaria are in fact receiving treatment unnecessarily, causing wastage of drugs and treatment failure of some nonmalaria infections. In addition there are also problems of spread of drug resistance and increased waiting time for the patient to have complete treatment. Kaewsonthi (1988) found that a large proportion of costs incurred by patients was for time cost. When a new diagnostic procedure or technique is introduced into a program the following costs need to be considered:

(i)   Costs for establishing the procedure

(ii) Costs for running the procedure, and

(iii) Costs resulting from the inherent properties of the procedure (i.e. the sensitivity, specificity, positive predictive value and negative predictive value).
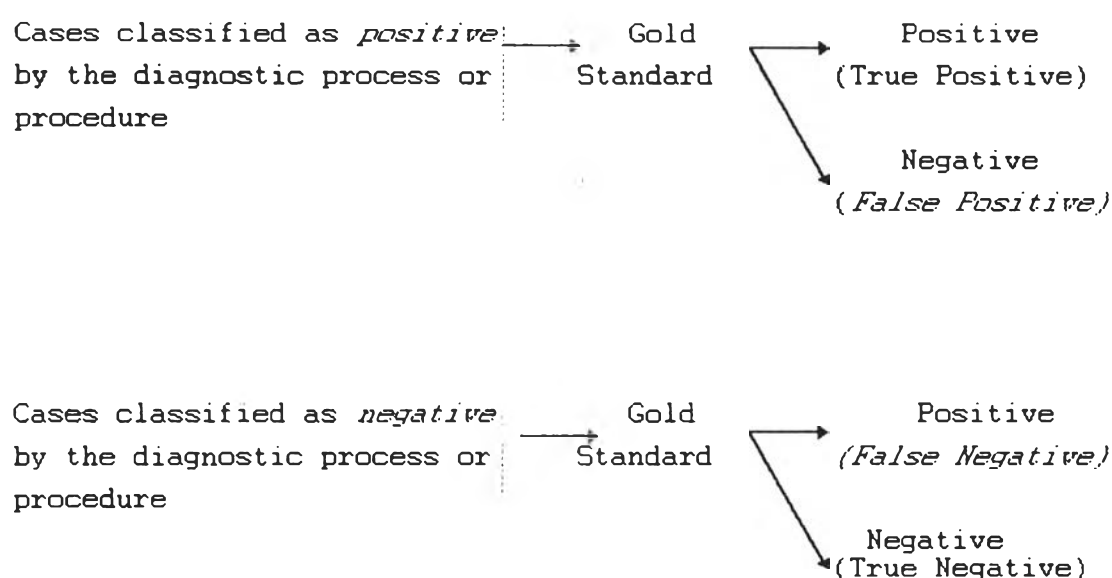
This study emphasizes more on the third component. After being diagnosed as having an attack of malaria using these criteria the patients will receive a course of anti-malarial drug followed by microscopy. The difference from the conventional presumptive treatment is in its selectivity in subjecting the patients to microscopy. The more specific is the procedure the less will be the false positive cases and less wastage of drugs. Among those being labeled as nonmalaria, there can also be false negative cases. These people can serve as the reservoir of infection in the community and then re-visit the clinic for treatment when symptoms appear again and these events

Figure 3.2: Conceptual Framework: Determining Benefits and Costs
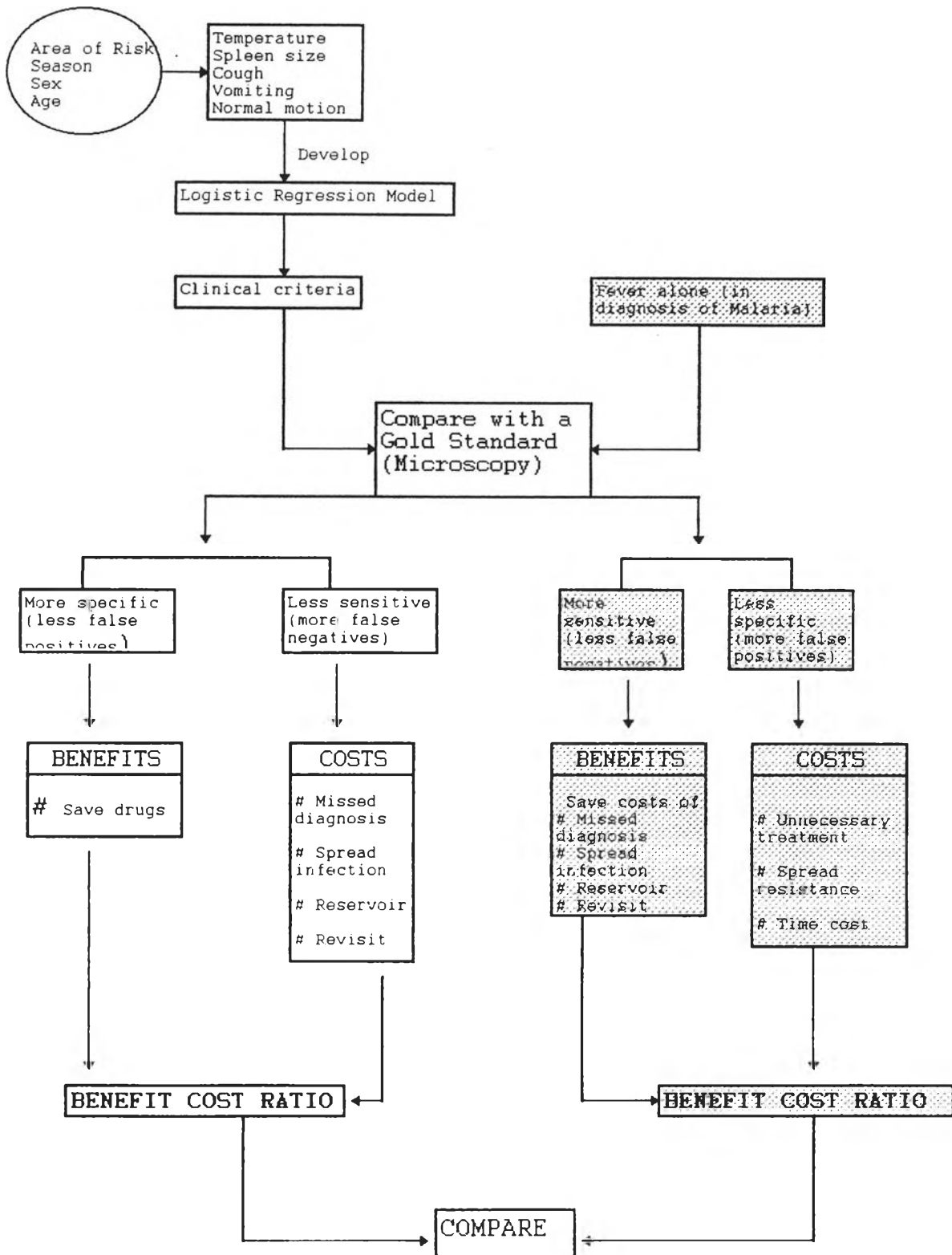
are not without costs. The more sensitive the procedure the less will be these problems. Depending on the specificity and sensitivity of the procedure costs and consequences can be different.

Figure 3.3 Outcomes of Comparing Results of Diagnostic
Process or Procedure to a Gold Standard (Microscopy)

Cases classified as *positive* Gold   Positive
by the diagnostic process or Standard (True Positive)
procedure

                 Negative
                 (False Positive)

Cases classified as *negative* Gold   Positive
by the diagnostic process or Standard *(False Negative)*
procedure

                 Negative
                (True Negative)

When compared to a gold standard, the categories classified by the diagnostic process may either be true or false. False classification will have effect on subsequent costs and consequences as shown in Figures 3.2 and 3.3.

Following the considerations mentioned, benefits and additional costs that can result from using the clinical criteria to diagnose malaria are calculated. Benefits and costs measured in this study are those arising as a result of the false positive and false negative cases respectively. False positive results can lead to unnecessary treatment of cases identified by the clinical criteria as malaria cases which in fact are not. But by being more selective or specific in identifying cases in compared with existing practice of using fever as the sole criterion for presumptive treatment, a substantial amount of drug costs can be saved as there can be

less false positive cases than when fever alone is the criterion for giving treatment. Benefits accrued from using the clinical criteria is measured in terms of drug costs thus saved. Additional costs of using these criteria depend on the number of false negative cases which will infect new cases for whom additional costs for diagnosis and treatment will be needed. Details of calculations are described in the sections to be followed.

3.2 Study Type

Among various types of study Kaewsonthi and Harding (1992) described that design research is concerned with two areas: Initial design and/or improvement in the methods of inquiry and analysis used in other types of study (descriptive, analytic, experimental, evaluative and forecasting), and design of systems such as cadaster information or map production system.

The present study attempts to develop a model to measure benefits and additional costs of introducing a set of clinical criteria in diagnosing malaria before giving presumptive treatment. The clinical criteria are developed by using a logistic regression model, slide positivity is the dependent variable and temperature equal to or higher than 38° C, splenomegaly, cough, vomiting, normal motion, age, sex, area of residence with respect to risk of getting malaria (endemicity) and season of the year are the independent variables. The aim is to make improvement in evaluating benefits and costs in diagnosis of malaria by providing a supplementary approach. The authors mentioned the steps involved in design study, the first four of which will be followed in this study while the remaining two steps will be attempted when field study becomes feasible. The steps involved are:

(i) Definition of the function and establishment of a specification to be met

(ii) Definition of the criteria by which the performance of the design can be measured

(iii) Design

(iv) Prospective evaluation of the design

(v) Field testing (experimentation) and evaluation using agreed criteria

(vi) Judgment and modification

According to the steps to be followed the design in this study have the two following functions:

(i) To determine the additional costs of using clinical criteria in selecting cases for presumptive treatment, and

(ii) To determine benefits that could arise from using clinical criteria for selecting cases for presumptive treatment.

This model can be used for evaluating benefits and additional costs that could arise from introducing clinical criteria to select cases that are to be given presumptive treatment for malaria before slide confirmation, in cases where the endemicity and level of transmission of malaria are such that there is a low slide positive rate leading to drug wastage from treating cases unnecessarily. A low slide positive rate, as mentioned earlier, means a substantial number of cases being wrongly labeled as malaria and given antimalarials. The clinical criteria to be used will have to be developed in accordance with the situation in each country. The criteria developed in this study were based on findings from the literature available and reviewed, and on the annual report of the VBDC program, Myanmar.

Expected performance of the design is to determine benefits and additional costs of using clinical criteria in selecting cases suspected of having malaria, for presumptive treatment. This performance criteria will be based on the feasibility to determine benefits costs, acceptance by the program managers, availability of the data, generalizibility and applicability.

There are two sets of equations in this model, one for determining benefits and the other for determining additional costs. Prospective evaluation of the design will be accomplished by simulation. Hypothetical data based on the literature reviewed and the annual reports, will be developed followed by a set of clinical criteria. Some real data will also be utilized.

3.3 Developing Clinical Criteria

Although the clinical criteria developed and described in this study are based on hypothetical data, clinical criteria for practical application will have to be developed from real data. This section will thus be described in two parts.
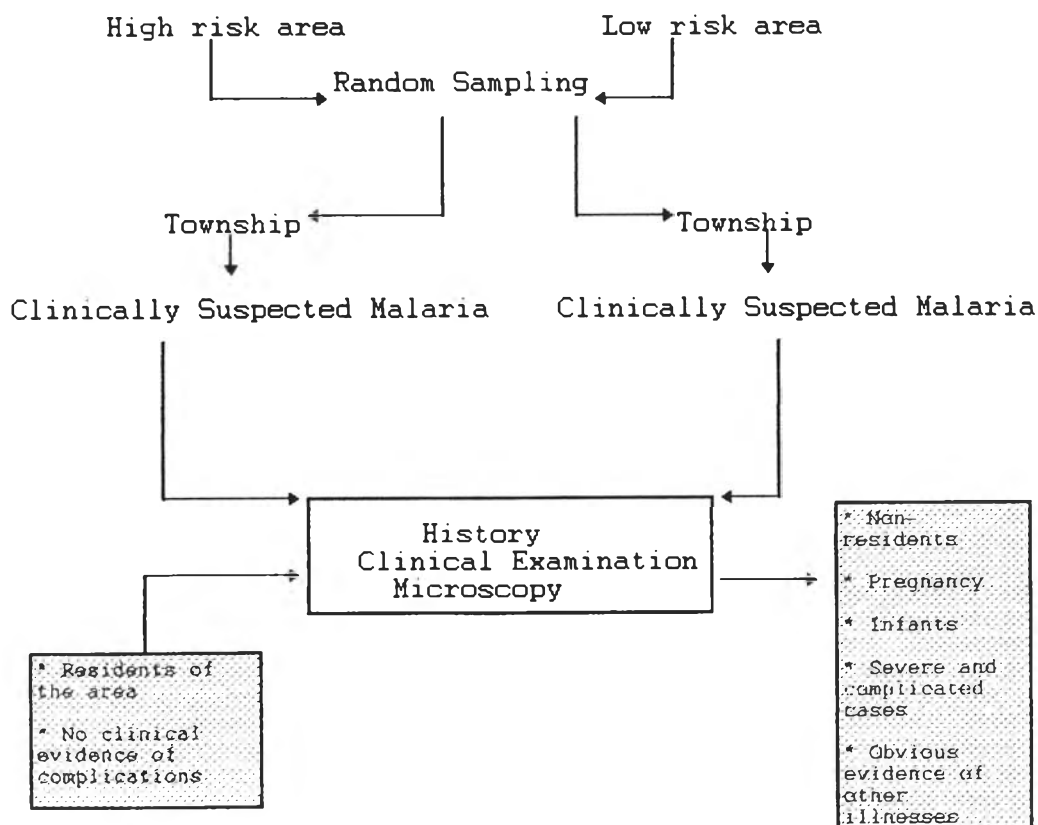
3.3.1 Steps Involved in Field Survey for Developing Clinical Criteria Based on Real Data

(1) Sampling

(i)Sampling Procedure

Sampling procedure is schematically presented in Figure 3.4.

Figure 3.4: Schematic Presentation of Sampling Procedure

i.(a)<u>Population and Sample</u>

Patients having an attack of malaria and residing in areas defined by the Vector Borne Diseases Control Program of the country as having high or low risk for contracting malaria will be the target population to be studied. Number of population living in different risk areas are shown in Table 3.1.

i.(b)<u>Population to be sampled</u>

Patients coming to the public clinics in the aforementioned areas.

<u>Inclusion criteria</u>

Residents of the area

No clinical evidence of complications

<u>Exclusion criteria</u>

Non-residents

Pregnancy

Infants

Severe and complicated cases

Obvious evidence of other illnesses

i.(c)<u>Sampling Technique</u>

Multistage sampling will be conducted. One township as primary sampling unit each from the areas mentioned will be randomly selected first, and from each township all patients coming to the public clinics for the treatment of fever will be selected as secondary sampling units.

All the patients coming to public clinics for fever and fulfilling the selection criteria will be included in the study. The number of patients to be included is according to the sample size determined. Number of patients to be included from each township will be according to the blood slide positive rate (SPR) prevaling in that area at the time of study, after determining the possible number of slide positive cases in that place estimated from the expected sensitivity of the clinical criteria. The townships will be randomly selected from the areas specified by risk of the disease.

i.(d)Study Period

        Survey will be conducted once at the end of rainy season and again before the end of summer (nonrainy season).

Table 3.1 Population Living under Various Areas of Risks in 1993

State or Division	High Risk	Low Risk	No Risk	Total
Ayeyarwaddy	737,618 (12.1%)	5,358,393 (87.9%)	—	6,096,011 (100%)
Bago	218,153 (4.7%)	4,423,409 (95.3%)	—	4,641,562 (100%)
Chin	450,674 (100%)	—	—	450,674 (100%)
Kachin	1,104,110 (100.%)	—	—	1,104,110 (100%)
Kayah	205,627 (100%)	—	—	205,627 (100%)
Kayin	1,099,171 (85.1%)	192,452 (14.9%)	—	1,291,623 (100%)
Magwe	455,243 (11.5%)	3,503,397 (88.5%)	—	3,958,640 (100%)
Mandalay	380,465 (6.8%)	4,582,369 (81.9%)	632,244 (11.3%)	5,595,078 (100%)
Mon	1,577,798 (76.8%)	476,625 (23.2%)	—	2,054,423 (100%)
Rakhine	2,498,824 (100%)	—	—	2,498,824 (100%)
Sagaing	1,577,735 (33.5%)	3,131,921 (66.5%)	—	4,709,656 (100%)
Shan	4,001,483 (88.1%)	540,495 (11.9%)	—	4,541,978 (100%)
Tanintharyi	1,120,779 (100%)	—	—	1,120,779 (100%)
Yangon	63,096 (1.3%)	1,713,294 (35.3%)	3,077,134 (63.4%)	4,853,524 (100%)
Total	15,490,776 (35.9%)	23,922,355 (55%)	3,709,378 (9.1%)	43,122,509 (100%)

Source : Vector Borne Diseases Control Program, Annual Report, (1993)

(2) Sample size determination

A cross-sectional approach will be used for determining the size of the sample. By using a cohort approach it will be possible to calculate the probability of the event (i.e. slide positivity) (Kleinbaum 1994). Although an odds ratio can only be generated from a cross-sectional approach there is a way to calculate the probability from the odds ratio (Gujarati 1995).

Based on expected sensitivity of clinical criteria number of possible slide positive cases will be calculated. From the number of slide positive cases thus determined number of cases to be include in the study for each township will again be determined on the basis of the slide positivtity rate at that time. The expected sensitivity is taken as 0.24 and slide positivity as 0.15. The number of cases to be subjected to microscopy thus obtained will be the sample size to be taken.

```
Desired level of significance = 95%
              Type of data = Counted
   Estimate proportion ( P )  = 0.24
   (Expected sensitivity
of clinical cruteria)
         Tolerable error (Δ) = 0.04
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$$n = \frac{Z\alpha^2 \ P \ Q}{\Delta^2}$$

$$= \frac{1.96*1.96*0.24*0.76}{0.04*0.04}$$

$$= \frac{0.7007078}{0.0016}$$

$$= 437.9 \approx 438 \text{ slide positive cases}$$

Slide positive rate (SPR) = 0.15 (average for the whole country)

Number of cases subjected to microscopy (i.e. to be included in the study)

    n = [Number of slide positive cases*100]/SPR

      = [438*100]/0.15

      = 2920 cases to be included in the study for each township.

(3) Data Collection and Analysis

    (i)Data Collection

Variables to be measured are shown in Table 3.2. The dependent variable (i.e. blood slide positive) will be measured by a microscope. As the blood smear result will also be used as a gold standard for calculating sensitivity and specificity of the clinical criteria comprising one or the combination of the independent variables found to be statistically significant, the technical quality and standard of both the microscopy and the microscopist must be ensured. The procedure will be standardized by following the recommended procedure for all cases so as to ensure reliability. Taking the history of illness and physical examination of the patients to elicit clinical symptoms and signs will be done by a medical doctor and the procedures will also be standardized.

    (ii) Data Analysis

Logistic regression will be applied using SPSS software to find out the significant predictors of blood slide positive. From the statistically significant predictors the probability of the slide being positive will be determined as follows:

$$P(Sp) = \frac{1}{1+e^{-Z}} \quad \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots \quad (1)$$

$$Z = \alpha_0 + \sum_{i=1}^{k} \alpha_i x_i$$

Where;

Sp = Slide positivity

α_0 = Constant

α_i = Coefficients of the independent variables

x_i = Independent variables

Logistic regression analysis will be applied using Forward (LR) Stepwise method. The variables found to be significant and retained will be included in the clinical criteria. Probability of being blood slide positive can be calculated as described in the equation (1).

Table 3.2: Variables Used in Developing Clinical Criteria and to be Measured in the Survey

Variable	Operational Definition	Data Source	How to Measure	Scale of Measurement
Dependent Blood slide positive	Presence of malaria parasite in 200 high power fields of thick blood smear	Primary data from field survey	Microscopic examination of thick blood smear (Giemsa stained)	Nominal
Independent 1. Fever	Oral temperature $\geq$ 38 Celsius	Primary. survey	Clinical thermometer	Nominal
2. Enlarged spleen	Spleen palpable on deep or at least more than normal inspiration @	Primary. survey	Clinical examination	Nominal
3. Cough	Statement given by the patient that he/she is coughing	Primary. survey	Interrogation	Nominal
4. Vomiting	Statement given by the patient that he/she is vomiting	Primary survey	Interrogation	Nominal
5. Normal motion	Statement given by the patient that he/she is passing motion regularly	Primary. survey	Interrogation	Nominal
6. Age	Completed age at the time of survey	Primary. survey	Interrogation	Nominal 2-14= children >14 = Adult
7. Sex	Gender	Primary. survey	Interrogation. observation	Nominal
8. Residence with regards to risk of getting malaria	As defined by the VBDC program Myanmar	Secondary. Annual report VBDC 1993	Review. observation	Nominal High risk Low risk
9. Season of the year	Time of the year in relation to the rainy season	Primary. Survey	Observation	Nominal

@ = According to Hackett's classification see APPENDIX I

3.3.2 Specification of Clinical Symptoms and Signs for Hypothetical Data

Using the estimated hypothetical sample size (307) twice the number was allotted to the group representing high risk areas compared to those representing low risk areas because it is expected that the former group will be less symptomatic and thus requiring a larger sample size to detect the symptoms (Rosengburg and others, 1990). There are 204 subjects in the former group and 103 in the latter.

Each risk group was divided into two age groups: those between two and fourteen years as children and those over fourteen years as adults on the basis of age categories available. In actual practice age classification will not be the same. Children composed 25% of each group and the adults the remaining 75% based on the findings in the annual report of the Vector Borne Diseases Control (VBDC) Program in Myanmar 1993. The number of children were 77, 51 in the group representing high risk areas and 26 in the group representing low risk areas. The number of adults were 230, 153 in the former group and 77 in the latter.

Assuming the slide positive rate to be 15% according to the same report of the VBDC Program, the number of subjects who were slide positive was 46 out of the 307 subjects included in the sample. In 1993 around 70% of the slide positive cases were from high risk areas and about 30% were from the low risk areas. Thus, the number of slide positive cases among those representing high risk areas was taken as 33 and the remaining 13 were from the low risk areas. These slide positive cases were then divided into children and adults. Based on the same report slide positive rate among children was 21% and that among adults was 14% in 1993. Thus the number of slide positive cases among children and adults were 11 and 22, respectively in the group representing high risk areas and 5 and 8 respectively in the group representing low risk areas.

To these subjects divided according to area of risk, age groups and slide positivity the variables (clinical signs and symptoms) were allotted. Frequency of each variable in each group was determined in accordance with findings by Genton and others (1994). Existence of signs or symptoms among those having

positive slides were determined using the positive predictive value of each clinical feature reported by the same authors.

Example:
Positive predictive value = Number cases with this symptom or sign and a positive blood slide / total number of cases with this symptom or sign.

Therefore:
Number of cases with this symptom or sign and a positive blood slide = Positive predictive value * total number of cases with this symptom or sign.

The variables (i.e. the symptoms or signs) thus determined and the frequency of each, among total cases and among slide positive cases, was calculated. Each symptom or sign was then made randomly distributed among the subjects. Random numbers were generated using Microsoft Excel software. The remaining variables, sex and season of the year, were distributed randomly, sex was equally distributed and 65% of the cases were in rainy season and 35% in other season.

For developing clinical criteria hypothetical data were generated after reviewing available literature (Genton and others, 1994; Rosengburg and others, 1990; Delfini, 1973), and the annual report of the VBDC, Myanmar (1993). The following clinical criteria and their distribution among the patients (both slide positive and slide negative) were generated and included in the analysis:

(i) *Temperature greater than or equal to 38 C*

It is assumed that 19% of the adult patients residing in the high risk areas will have temperature equal to or higher than 38° C. The positive predictive value of this clinical feature was assumed to be 24%, an adjusted value based on the finding by Genton and others(1994). The number of cases having blood positive slides and temperature equal to or higher than 38° C would thus be calculated as 7 and the remaining cases having that specified temperature would then be blood slide negative. A similar method of calculation was used in determining the number of cases having that level of temperature

in adults cases residing in the low risk area and for the children residing in both areas. Detailed figures are shown in Tables 3.3 and 3.4.

(ii) *Enlargement of spleen*

Among the adult cases residing in the high risk area 41% were assumed to have enlargement of spleen, the positive predictive value being 14% adjusted on the basis of the finding by Genton and others (1994), according to the prevalence of slide positives in that area.

(iii) *Cough*

It was found out in the study by Genton and others (1994) that cough as a symptom occurs in 49% of children and 41% of adults coming to the clinics. History of having no cough is found to be significantly associated with blood slide positives both in children and adults. This finding was applied in the same way in this study to determine the distribution of this symptom among both the adults and the children.

(iv) *Normal stool*

This sign is a significant predictor for blood slide positivity both in adults and in the children in the study by Genton and others (1994).

(v) *Vomiting*

This sign is included in the analysis because it is found to be significantly associated with *P. falciparum* parasitaemia $\geq$ 10,000/µl in the literature (Genton and others, 1994).

Table 3.3: Variables and Their Distributions according to Slide Positivity in High Risk Area.

	Adults (n = 153)				Children (n = 51)			
	Total	PPV	Slide(+)ve (n=22)	Slide (-)ve (n=131)	Total	PPV	Slide(+) ve (n=11)	Slide(-) ve (n=40)
Tmp≥38	29 (153*0.19)	24	7	22	22 (51*0.43)	24	6	16
Spl(+)	63 (153*0.41)	14	14	49	31 (51*0.61)	26	9	22
Cough	63 (153*0.41)	—	7	56	25 (51*0.49)	—	4	21
Normal Stool	143	14	20	123	46	21	9	37
Vomit	11 (153*0.07)	16	2	9	9 (51*0.17)	—	1	8
Sex(M)	76 (153*0.5)	—	11	65	25 (51*0.5)	—	6	19
Season	100 (153*0.65)	—	18(22*0.8)	82	33 (51*0.65)	—	9(11*0.8)	24

Table 3.4: Variables and Their Distributions according to Slide Positivity in Low Risk Area.

	Adults(n = 77)				Children(n = 26)			
	Total	PPV	Slide(+) ve (n=8)	Slide (-)ve (n=69)	Total	PPV	Slide (+)ve (n=5)	Slide (-)ve (n=21)
Tmp≥38	20 (77*0.25)	17	4	16	16 (26*0.6)	21	4	12
Spl(+)	20 (77*0.25)	10	2	18	10 (26*0.4)	22	3	7
Cough	32 (77*0.41)	—	3	29	16 (26*0.6)	—	3	13
Normal Stool	58	10	6	52	22	18	4	18
Vomit	11 (77*0.14)	12	2	9	5 (26*0.17)	—	1	4
Sex(M)	39 (77*0.5)	—	4	35	13 (26*0.5)	—	4	9
Season	50 (77*0.65)	—	6(8*0.8)	44	17 (26*0.65)	—	4 (5*0.8)	

3.4 Costs and Consequences

Attempt is made in this study to follow the steps described by Mills and Gilson (1988) in determining costs and consequences (benefits). The steps involved in this study in evaluating costs and consequences will be:

(1) identification and specification of costs;

(2) identification and specification of consequences;

(3) aprroach for determining benefit cost ratio.

3.4.1 Identification and Specification of Costs

Various ways of classification of costs of health care projects/programs or interventions have been described and each type of classification has its own merits and demerits (Creese and Parker,1991; Drummond and Stoddard, cited by Mills and Gilson, 1988). An attempt was made in this study to classify the costs that had been identified according to the method described by Drummond and Stoddard, (see Table 2.1). After classification, not all the costs identified but only those that are feasible and relevant for the objectives of the study were measured. In this study costs to be measured and valued were defined as the additional costs to be borne if the clinical criteria developed were introduced into existing practice where fever only is used as an indication for giving presumptive treatment for malaria.

(i) <u>Direct Costs</u>

Additional costs within the health care sector for developing and using the clinical criteria

(a) Costs for developing the clinical criteria (i.e. costs for conducting the field survey)

<u>Salaries</u>

Principal investigator

Assistant researcher

Clerical and typing services

Travel Expenses
Domestic travel

Computer and other machine costs

Contingencies (for underestimates of other items)

(b) Cost for training health workers

(c) Costs resulting from false negative cases
        – costs for treating these cases when they come back
to the clinic again
        – costs for treating new cases arising as a result
of transmission by the false negative cases __

(ii) Indirect costs

        (a) Costs borne by the patients and their families:
        – Psychological or emotional costs

        (b) Costs borne externally to the health care sector,
        patients and their families
        – Not identifiable in this study.

        Costs were expressed in Kyats taking 1993 as the base year.
No discounting was done because calculation was done only for a
one year period and both the costs and consequences are assumed
to be occurring in the same time period.

        From the costs that had been identified the following costs
were measured:

(a) Costs for training health workers
(b) Costs resulting from false negative cases

- costs for treating new cases arising as a result of transmission by the false negative cases __

These costs are the additional costs that are to be borne by the health care sector (provider) if the clinical criteria are introduced and used to select patients who are to be given presumptive treatment. Costs for developing the clinical criteria are actually protocol driven costs and were not measured in this study. Additional costs for diagnsis and treatment for the new cases infected by false negative cases will be the additional costs that arise from false negative cases. Before being detected and treated completely these new cases will again infect more new cases which will again infect more new cases in the same manner. Additional costs resulting from false negative cases will thus be costs for diagnosis and treatment of these sucessive crops of new cases. These costs will be considered for benefit cost analysis in this study because when compared to the existing practice in selecting cases for presumptive treatment they are the additional costs to be borne by the health care sector.

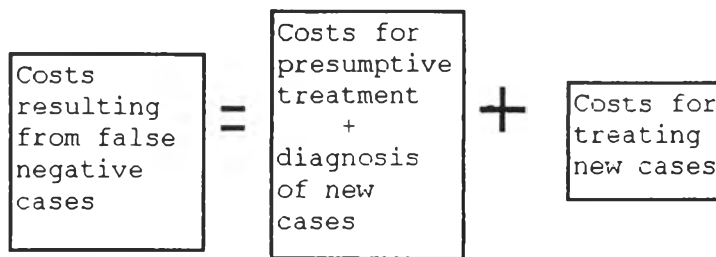| Additional costs to be incurred by the health care sector	=	Costs for training health workers	+	Costs resulting from false negative cases
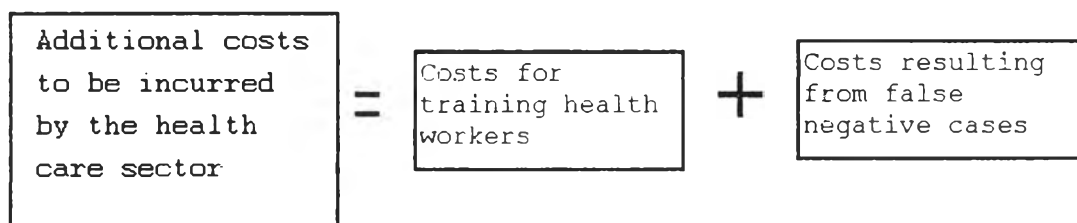
$$C_{Ad} = C_{Tr} + C_{FN}$$

Where:

C_{Ad} = Additional costs to be incurred by the health care sector

C_{Tr} = Costs for training health workers

C_{FN} = Costs resulting from false negative cases

Costs resulting from false negative cases

$$C_{FN} = Z + \delta + \rho$$

Where;

Z = Drug costs for presumptive treatment of a new case

δ = Costs for diagnosing a new case

ρ = Drug costs for radical treatment of a new case

3.4.2 Identification and Specification of Consequences

Consequences in this study were expressed as benefits of introducing the process. Benefits were again expressed as costs saved. A certain portion of costs for treating patients unnecessarily where fever alone is used as an indication for giving presumptive treatment would be saved by using the clinical criteria for selecting patients to be given presumptive treatment. The costs saved here can be regarded as changes in resource use for organizing and operating services within the health sector for the original condition (presumptive treatment). The costs saving can be expressed as benefits because the funds freed by a project can finance other benefit entailing health projects (Carrin, 1984).

3.4.3 Approach for Determining Benefit Cost Ratio

Two sets of equations were developed for measuring and valuing benefits and costs. These equations were based on the inherent properties of the clinical criteria viz. specificity and sensitivity. The more specific are the clinical criteria the less will be the false positives. This will reduce the quantity of drugs to be given unnecessarily. This reduction in number of cases treated unnecessarily can save the costs which will be the basis for valuing benefits. The more sensitive are the clinical

criteria the less will be the number of false negatives.
Although both the specificity and sensitivity are the inherent
properties of any diagnostic procedure or process which is
desirable it is rare to have a perfect diagnostic procedure or
process which have both high specificity and sensitivity. A
trade-off must be made. Although high specificity of the
clinical criteria may be desirable to reduce costs of treating
patients unnecessarily we have to face with the problem of costs
resulting from false negative cases, a consequence of low
sensitivity.

The most straight forward method of displaying the
comparison of a diagnostic test and a gold standard is with a
''two by two'' or ''four fold'' table, Table 3.5. The key words
in such comparisons are specificity, sensitivity, and predictive
values. Here only the specificity and sensitivity are relevant
to the study. The gold standard refers to a definitive diagnosis
attained by biopsy, surgery, autopsy, long-term follow-up or
another acknowledged standard. Consider the columns of Table
3.5. The gold standard has identified (a+c) patients as having
the disease of interest, and ''a'' patients had positive
diagnostic test results. Thus an index of the diagnostic test's
ability to detect the disease when it is present is a/(a+c),
usually expressed as a percentage and referred to as sensitivity
(Canadian Medical Association Journal, 1981). Sensitivity is
also known as pick up rate of diagnostic test or positivity in
disease. It is the proportion of all diseased individuals (true
positives and false negatives) in whom the test will be positive
(true positive) (Kamol-Ratanakul, 1996). Similarly, the ability
of the diagnostic test to correctly identify the absence of the
disease is shown in the next vertical column as d/(b+d); this is
the specificity. Specificity is proportion of non-diseased
individuals (true negatives and false positives) who will have a
negative test (true negative). It is also known as negativity –
in- health (see Appendix II).

Table 3.5 Four Fold Table Demonstrating Comparison of a Diagnostic Test with a Gold Standard

		Gold Standard		
		Patient *has* the disease	Patient does *not* have the disease	
Test result (conclusion drawn from the result of the test)	Positive: Patient appears to *have* the disease	True Positive (a)	False Positive (b)	(a+b)
	Negative: Patient appears *not to have* the disease	(c) False Negative	(d) True Negative	(c+d)
		(a+c)	(b+d)	(a+b+c+d)

Source: <u>Canadian Medical Association Journal</u>, 1981; 124: 704

a/(a+c) = Sensitivity

d/(b+d) = Specificity

Table 3.6 Comparing Results of Clinical Criteria with Gold Standard

Microscopy
(Gold Standard)
(+)   (-)

	Microscopy (Gold Standard)	
	(+)	(-)
(+)	TP (a)	FP (b)
(-)	FN (c)	TN (d)
	SPR (a+c)	1-SPR (b+d)

Diagnosis using clinical criteria

Using fever as a sole criterion for selecting cases for presumptive treatment

T = Total cases

Comparing the results of clinical criteria with that of the gold standard (microscopy) a two by two table can be constructed from which the specificity and sensitivity of the clinical criteria can be calculated (Table 3.6). Terminology used in determining benefits and costs will be explained together with approach to determine benefits and costs.

Sensitivity

Similar to standard definition (see Appendix II) sensitivity in this study is proportion of all cases identified by microscopy (Gold Standard) as slide positive (i.e. True Positive + False Negative or a+c) whom will be identified by the clinical criteria as having malaria (i.e. True Positive or a). It can be written as:

$$\text{Sensitivity} = \text{True Positive (TP)} / \text{True positive (TP)} + \text{False Negative (FN)}$$

$$= a/a+c \quad \ldots \ldots \ldots \ldots \ldots \ldots \quad 3.4.1(a)$$

then,

$$1-\text{Sensitivity} = 1- \text{TP}/\text{TP+FN}$$

$$= \text{FN}/\text{TP+FN}$$

$$= c/a+c \quad \ldots \ldots \ldots \ldots \ldots \ldots \quad 3.4.1(b)$$

Specificity

Proportion of individuals identified by microscopy as slide negative (i.e. FP+TN or b+d) who will be identified by clinical criteria as not having malaria (TN or d). It can be written as:

$$\text{Specificity} = \text{TN}/\text{FP+TN}$$

$$= d/b+d \quad \ldots \ldots \ldots \ldots \ldots \ldots \ldots \quad 3.4.1(c)$$

Then,

1- Specificity = 1- TN/FP+TN

          = FP/FP+TN

          = b/b+d . . . .   3.4.1(d)

Slide Positive Rate (SPR)

Proportion   of   all   cases   subjected   to   microscopy
(TP+FP+FN+TN or a+b+c+d) who are identified by microscopy as
slide positive (TP+FN or a+c). It can be written as:

SPR = (TP+FN)/(TP+FP+FN+TN)

    = a+c/a+b+c+d
if T (total cases) = a+b+c+d,

SPR = TP+FN/T

SPR = a+c/T . . . .   3.4.1(e)

then,

1-SPR   = 1-[TP+FN/TP+FP+FN+TN]

        = FP+TN/TP+FP+FN+TN

        = b+d/a+b+c+d

        = b+d/T . . . .   3.4.1(f)

Valuing Benefits

Benefits in this study means   costs saved for treating
false positive cases unnecessarily.

Notations,

β = Benefits

χ = Costs for treating false positive cases

fv = Subscript index for cases in which fever alone is the
    indication for giving presumptive treatment

ccr = Subscript index when clinical criteria are used to
    diagnose cases for presumptive treatment

Equation for benefits can be written as

$$\beta = \chi_{fv} - \chi_{ccr} \quad \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots \quad 3.4.2$$

Determining drug costs for treating false positive cases

(i) When fever alone is the indication for giving presumptive
treatment costs for treating false positive cases will be number
of false positive cases times drug costs of presumptive
treatment for each patients.

Notations,

Z = Drug costs for giving presumptive treatment to each
    case

π_0 = Number of false positive cases when fever alone is the
    indication for presumptive treatment

Drug costs can be written as:

$$\chi_{fv} = Z\pi_0 \quad \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots \quad 3.4.2(a)$$

π_0 can be determined from the Table 3.6 as follows:

Number of false positive cases(π_0) = b+d

$$= b+d/T * T$$

In fact,

b+d/T = 1-SPR $\quad \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots$ [Eqn. 3.4.1(f)]

then,

$$\pi_0 = (1-SPR)T$$

$$\chi_{fv} = Z\pi_0$$

$$= Z\ T(1-SPR) \quad \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots \quad 3.4.2(b)$$

(ii) When clinical criteria are used to diagnose cases to be given presumptive treatment costs of presumptive treatment are number of false positive cases times drug costs for each patient.

Notations,

Z = Drug costs for giving presumptive treatment to each case

π_1 = number of false positive cases when clinical criteria are used to diagnose cases to be given presumptive treatment

$$\chi_{ccr} = Z\pi_1 \quad \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots \quad 3.4.3(a)$$

π_1 can be determined from the Table 3.6 as follows;

Number of false positive
cases when clinical
criteria are used to
diagnose cases for
giving presumptive
treatment (π_1) = b

$$= b/b+d \ * \ b+d/T \ * \ T$$

in fact,

$b/b+d$ = 1-specificity $\quad \dots\dots\dots\dots\dots$ [Eqn.3.4.1(d)]

$b+d/T$ = 1-SPR $\quad \dots\dots\dots\dots\dots\dots\dots\dots$ [Eqn.3.4.1(f)]

then,

$$\pi_1 = (1-specificity)(1-SPR)T$$

$$\chi_{ccr} = Z\pi_1$$

$$= ZT(1-specificity)(1-SPR)$$

Let specificity = ξ

then,

$$\chi_{ccr} = ZT(1-\xi)(1-SPR) \ldots\ldots\ldots\ldots\ldots \qquad 3.4.3(b)$$

(iii)Determining costs saved (β)

Substituting equations 3.4.2(b) and 3.4.3(b) in 3.4.2

$$\beta = \chi_{fv} - \chi_{ccr}$$
$$= [ZT(1-SPR)] - [ZT(1-\xi)(1-SPR)]$$
$$= [ZT(1-SPR][1-(1-\xi)]$$
$$= ZT(1-SPR)\xi \ldots\ldots\ldots\ldots\ldots\ldots\ldots \qquad 3.4.3(c)$$

Valuing Costs

Applying the same contingency table additional costs to be borne by the health care sector can be calculated. These costs have three components; costs of developing clinical criteria, costs of training health workers and costs resulting from false negative cases. First two components can be calculated from costs incurred by these activities and the last component costs resulting from false negative cases can be determined from Table 3.6.

Notations,

Y = Additional costs to be borne by the health care sector in introducing and using clinical criteria

T = Total cases subjected to microscopy after giving presumptive treatment

X = Costs of of training health workers

C_{FN} = Costs resulting from false negative cases

Z = Drug costs for presumptive treatment of a new case

δ = Costs of diagnosis for a new case

ρ = Drug costs of radical treatment for a new case

ν = Number of false negative cases

η = Number of new cases infected by each false negative case

$\nu\eta$ = Total number of new cases infected by false negative cases

then,

Additional costs (Y) = X + C_{FN} .... 3.4.4(a)

Costs resulting from false negative cases include additional costs for new cases infected by false negative cases. False negative cases without receiving needed treatment will serve as reservoir of infection in the community and new cases can be infected by them. If "η" is designated as number of new cases infected by each false negative case this component need consideration in calculating costs resulting from false negative cases. These new cases will serve as the reservoir of infection in the community before being correctly diagnosed and completely treated. Some of them will be correctly identified by the clinical criteria and completely treated while other not being correctly identified will infect new cases again before receiving correct diagnosis and complete treatment. Costs of presumptive treatment, diagnosis and radical treatment of these successive crops of new cases were the additional costs considered and measured for benefit cost analysis. Considering these, costs resulting from false negative cases (C_{FN}) were considered under the following three components:

(i) Drug costs for presumptive treatment of new cases
(ii) Costs for diagnosis (microscopy) of new cases
(iii) Drug costs for radical treatment of new cases

$$(C_{FN}) = \kappa\nu\eta P + \kappa(1-\kappa)\nu\eta(1+\eta)P + \kappa(1-\kappa)^2\nu\eta(1+\eta)^2P$$
$$+ \kappa(1-\kappa)^3\nu\eta(1+\eta)^3P + \ldots$$

$$= \kappa\nu\eta P[1+(1-\kappa)(1+\eta)+ (1-\kappa)^2(1+\eta)^2 + (1-\kappa)^3(1+\eta)^3$$

$$+ (1-\kappa)^4(1+\eta)^4 + \ldots] \quad\ldots\ldots\ldots\ldots\ldots \qquad 3.4.4(b)$$

Equation 3.4.4(b) can be reduced as follows:

$$C_{FN} = \kappa\nu\eta P\left[\frac{1}{1-(1-\kappa)(1+\eta)}\right] \quad\ldots\ldots\ldots\ldots\ldots \qquad 3.4.4(c)$$

Notations,

    κ = Proportion new cases correctly diagnosed (i.e. sensitivity of the clinical criteria)

    P = Costs of diagnosis and radical treatment for new cases (i.e. $\delta + Z + \rho$)

Number of false negative cases (ν) can be determined from the Table 3.6.

then,

    ν = c

       = c/a+c $*$ a+c/T $*$ T

in fact,

  c/a+c = 1-sensitivity $\quad\ldots\ldots\ldots\ldots\ldots\ldots$ [Eqn. 3.4.1(b)]

  a+c/T = SPR $\quad\ldots\ldots\ldots\ldots\ldots\ldots\ldots$ [Eqn. 3.4.1(e)]

and,

    ν = (1-sensitivity)(SPR)T

let sensitivity = σ

then,

    ν = (1-σ)(SPR)T $\quad\ldots\ldots\ldots\ldots\ldots\ldots$ 3.4.4(d)

and,

$$\kappa = \sigma$$

Substituting equation 3.4.4(d) in 3.4.4(c)

$$C_{FN} = \kappa v \eta P \left[\frac{1}{1-(1-\kappa)(1+\eta)} \right] \quad \dots \dots \dots \dots \quad 3.4.4(c)$$

$$= \sigma(1-\sigma)(SPR)T\eta(\delta+Z+\rho)\left[\frac{1}{1-(1-\sigma)(1+\eta)}\right] \quad \dots \dots \quad 3.4.4 \ (e)$$

Additional costs (Y) will then be

$$Y = X + C_{FN}$$

$$= X + \sigma(1-\sigma)(SPR)T\eta(\delta+Z+\rho)\left[\frac{1}{1-(1-\sigma)(1+\eta)}\right] \quad \dots \quad 3.4.4 \ (f)$$

Determining costs for diagnosis (microscopy), drug costs for presumptive treatment and radical treatment

Costs for diagnosis consist of costs for personnel, equipment and supplies, and were estimated from available data from the VBDC, Myanmar.

For presumptive treatment average drug costs for giving a required dose of chloroquine was used in calculation. Number of patients in each group, dose in tablets to be given to a patient in each age group and costs of each tablet were taken into consideration.

Radical treatment for falciparum malaria is different from that for other species (i.e. vivax, malariae and ovale). *P. falciparum* was found to be about 85% and the remaining species 15% of the slide positive cases in 1993 (VBDC, 1993) and it was considered in calculating drug costs for radical treatment. After determining average drug costs of radical treatment for cases with *P. falciparum* infection and that for other species in the same way as in determining average drug costs for presumptive treatment, average drug costs for radical treatment were determine as follows

$$\rho = F_f * \rho_f + F_{v+} * \rho_{v+}$$

$$= 0.85\rho_f + 0.15\rho_{v+} \quad \dots\dots\dots\dots\dots\dots\dots\dots \quad 3.4.4(g)$$

Notations,

F_f = Proportion of cases with *P. falciparum* infection

ρ_f = Average drug costs of radical treatment for cases with *P. falciparum* infection

F_{v+} = Proportion of cases with *P. vivax* or other parasites

ρ_{v+} = Average drug costs of radical treatment for cases infected with *P. vivax* or other parasites

In summary,

Benefits

$$(\text{Costs saved}) = ZT(1-SPR)\xi \quad \dots\dots\dots\dots\dots\dots \quad 3.4.3(c)$$

Costs saved (Benefits) can then be calculated by substituting the values of specificity and slide positive rate which were obtained from the comparing clinical criteria and gold standard, the total number of cases subjected to presumptive treatment in a year and the drug costs for presumptive treatment into the equation 3.4.3(c)

$$\text{Additional costs} = X + C_{FN}$$

$$Y = X + \sigma(1-\sigma)(SPR)T\eta(\delta+Z+\rho)\left[\frac{1}{1-(1-\sigma)(1+\eta)}\right] \quad \dots\dots\dots \quad 3.4.4 \ (f)$$

By substituting values of costs for training health workers which were calculated from figures on existing payment system in Myanmar, values for sensitivity and slide positive rate which were derived from the results of the comparison of clinical criteria with gold standard and value for ''η'' which was estimated, into equation 3.4.4(f) additional costs of introducing the clinical criteria was calculated.

Benefit cost ratio

Benefits (costs saved) and additional costs that had been calculated in the ways described were used to find the benefit cost ratio.

Benefits
(costs saved) $= ZT(1-SPR)\xi$ .... 3.4.3(c)

Additional Costs

$$Y = X + \sigma(1-\sigma)(SPR)T\eta(\delta+Z+\rho)\left[\frac{1}{1-(1-\sigma)(1+\eta)}\right] \quad .... \quad 3.4.4\ (f)$$

$$\text{Benefit cost ratio} = \frac{[\text{Equation } 3.4.3(c)]}{[\text{Equation } 3.4.4(f)]}$$