CHAPTER 3

RESEARCH METHODOLOGY

3.1 Research Design

The method of research design was retrospective and descriptive study

The study on efficacy of the two regimens, Art + Dox and Qui + Dox, had been carried out in May, 1994 in a district hospital but it did not identify and measure cost data for cost-effectiveness analysis. For this reason, the study was extended to analyze costs of the two malarial treatment regimens in a district hospital. Descriptive study observed inpatients in hospital over a 28 days period to collect costs and effectiveness data.

3.2 Population and Sample

3.2.1 Sample Unit

Falciparum malarial inpatient followed up for a 28 day period.

3.2.2 Inclusion Criteria

The study has been carried out with these inclusion criteria:

(1) Adult patients, aged between 16 and 60 years, weighing more than 40 kg. These patients were allocated into two groups for comparability.

(2) Positive P.falciparum patients. Number of parasites counted were more than 1,000/microliter of blood. Wheen the number of parasites was lower than 1,000/microliter of blood, it is difficult to measure the effectiveness of the antimalarial drug.

(3) Uncomplicated malaria cases.In severe and complicated cases, including cerebral malaria, the patient may die in 1 or 2 days after treatment due to complications.

(4) Not suffering from other infectious diseases. If patient suffer from other infectious diseases, the illness will be compounded, which make difficult to measure effectiveness.

(5) No use of other antimalarial drugs within 2 weeks before coming to hospital, since if patient used other antimalarial drugs within 2 weeks, some antimalarial drugs may still remain in patient's bloods, complicating evaluation of the test drugs. Urine test for measuring antimalarial drug in patient's urine if patient used antimalarial drug within the preceding 2 weeks.

(6) Patient agreed to remain in the hospital for 28 days to measure effectiveness of antimalarial drugs and avoid malaria reinfection.

(7) Prior to treatment, a medical history was obtained, a physical examination was performed, and laboratory studies were conducted.

3.2.3 Exclusion Criteria

The exclusion criteria of study were:

(1) Pregnant women.
(2) Malarial patient with age less than 16 years or more than 60 years and weighing less than 40 kg.

3.2.4 Allocation Technique

All patients who met eligibility criteria were assigned to one of two groups by simple randomization by drawing lot:

If random number was odd, assigned to group Art + Dox.
If random number was even, assigned to group Qui + Dox.

* In the Art + Dox group, patients were treated with regimen:

Artemisinin (oral): 10 mg/kg/day for 5 day.
Doxycycline (oral): 2 mg/kg/day for 5 day.

The dose per day was divided into 2 times, morning and afternoon.

* In the Qui + Dox group, patients were treated with regimen:

Quinine sulfate (oral): 30 mg/kg/day for 5 day.
Doxycycline (oral): 2 mg/kg/day for 5 day.

The dose per day was also divided into 2 time, morning and afternoon.

After treatment with drugs of those two regimens, patients with resistance level 1 in each group were treated again by the same treatment regimen.

Patients with resistance level 2 or level 3 were treated again by other antimalarial drugs such as mefloquine, falsimef.

3.2.5 Sample Size

- Using cure rate as the primary outcome, we expected that:

Expected cure rate of Ar-D for 5 days would be 98%.
Expected cure rate of Q-D for 5 days would be 80%.

- Sample size of study required:
Two group Art + Dox and Qui + Dox were independent groups

P1 = 0.98
P2 = 0.80
β error = 0.05
LeveL of significance (α level) = 0.05
The power (1- β) = 0.95

Type of data is counted data and difference between the proportions being:

P1 - P2 = 0.98 - 0.80
= 0.18

* N/group required the following formula:

$$N/group = \frac{2(Z\alpha + Z\beta)^2 \times \pi(1 - \pi)}{(P1 - P2)^2} \quad \text{With} \quad \pi = \frac{P1 + P2}{2}$$

$$\pi = \frac{0.98 + 0.80}{2}$$

$$\pi = 0.89$$

$$N/group = \frac{2\ (1.96 + 1.28)^2 \times 0.89\ (1 - 0.89)}{(0.98 - 0.80)^2}$$

$$N/group = \frac{2 \times 10.5 \times 0.89 \times 0.11}{0.032} = \frac{2.056}{0.032}$$

N/group = 64

* Sample size for two regimen groups will be:

N = 64 × 2 = 128

That means that the required sample size for the two together regimen groups will be at least 128 falciparum malaria inpatients.

3.3 Methods of Data Collection

3.3.1 Effectiveness Data Collection

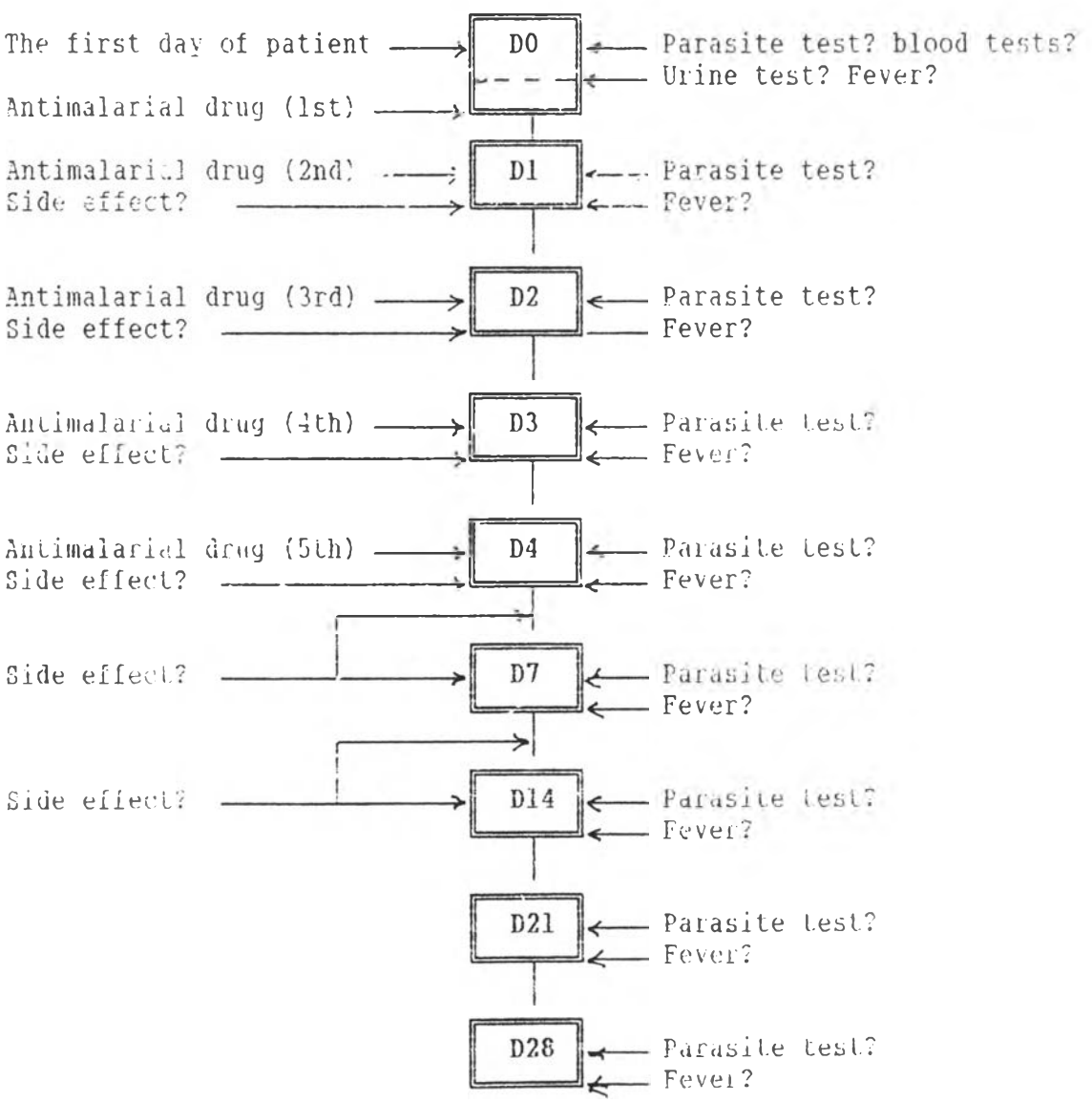
Patients were admitted in to hospital and remained there for 28 days. The effectiveness data was collected from clinical records by list of patient's name, side effects, the parasitemia clearance time and resistance level (R1, R2, R3) to evaluate and calculate effectiveness as follows:

Number of patients with side effects: Side effects were defined as signs that first occurred or become more severe following treatment.

Number of days to clear parasite in patient's blood to identify sensitivity, resistance level R1, R2, R3: Blood slide was taken for thick and thins film at day D0, D1, D2, D3, D7, D14, D21, D28 (D0 is the day before treatment).

Parasite density was determined by counting the number of parasites per 200 white blood cells in a thick film and was expressed as number of parasites per microliter of blood. Blood films were declared negative if no parasite was seen in 200 oil immersion fields on a thick film.

Figure 3.1 Malaria Treatment and 28 Days Follow Up Period



3.3.2 Costs Data Collection

1) Cost Incurred by Patient

Costs incurred by patient were collected by interviewing patient and accompanying person.

* Interview patients for direct cost and indirect cost data incurred by patient:
  - Drug costs (non antimalarial drug)?
  - Time costs-income loss due to illness and treatment period?
  - Total household income per year?
  - Number of people in his or her family who worked to earn the income?
  - Travel costs: Money paid for travel to hospital and from hospital to their home?
  - Cost of food during treatment period: Average expenditure for food per day in treatment period in hospital?

* Interview patient's accompanying person:

  - Travel costs: money paid for travel from home to hospital and from hospital to their home?
  - Time cost: Number of days he or she stayed in hospital to take care of the patient?
  - Total household income per year?
  - Number of people in his or her family who worked to earn the income?
  - Number of working days?
  - Cost of food: Average money paid for food per day when staying with patient in the hospital?

2) Costs incurred by provider

Costs incurred by provider were collected by interviewing relevent persons: manager in hospital or district health service for direct and indirect costs.

* Personnel cost:

  - List the medical staff: Doctors, nurses, etc. in clinical room, where malaria patient is treated and personnel in other departments.
  - Record their salary and any allowance received by them per month?
  - To determine what proportion of time used per bed per month?
  - Estimating the costs of each medical staff per bed per month?
  - Proportion of bed used for malaria patient or average number of beds used per day, per month in hospital.

* Drugs costs.

Data from inpatient record for drugs used include antimalarial drugs and non-antimalarial drug.
Cost of drugs and transport cost of drug to hospital.

* Small equipment, medical supplies in laboratory and their cost.

* Building maintenance cost.
  Record the building maintenance expenditure per year.
  Estimate the proportion of space used.
  Estimate number of bed day used per year.
  Calculate building maintenance per bed used per day.

* Operating costs.

  - Furniture costs?
    List the office furniture.
    Estimate the current value.
    Find out the discount rate used by economic planning office.
    Estimate useful life of furniture, resource from economics office.
    Use the annualization factor (From annualization factor table) to calculate the annual cost of furniture by dividing the current value of item by annualization factor.
    Calculate furniture cost per bed used per day.

  - Cost of electricity per month?
    Calculate cost of electricity per bed used per day.

  - Cost of telephone per month?
    Calculate the cost of telephone per bed per day.

3.4 Method of Data Analyses

3.4.1 The Costs - Effectiveness Analyses

Cost effectiveness analysis is a comparison of the cost of different drug regimens to achieve a unit effectiveness which is the cost of each drug regimen divided by its effectiveness: that is cost effectiveness. The more cost-effective drug regimen is that for which the lower costs per unit of effectiveness is achieved. The lower cost-effectiveness ratio is reflects the better treatment regimen.

3.4.2 Sensitivity Analysis

To measure costs and effectiveness of antimalarial drugs, patients were kept in hospital for a 28 days follow up period (in vivo test, WHO extended test 28 days observation).

In normal treatment conditions, malarial patients are treated in hospital when they get fever and positive parasite test. The days of

treatment depend on antimalarial drug treatment duration. If patients are treated by Art + Dox and Qui + Dox drug regimens, they only stay in hospital 5 days. Therefore the cost includes provider cost and cost incurred by patient which will change.

Sensitivity analysis was used to analyze the costs and effectiveness of two drug regimens in normal treatment practice with 5 days of treatment in hospital.

3.4.3 Statistical Significant Test

The study included two independent groups, so the Chi-Square test was used to test the statistical significance of outcome between two two treatment regimens by general two-way contingency. If one of observation was less than 5, Fisher's exact test was used.