Attachment 1. Date 12/4/86

REVIEW BOARD ON THE USE OF HUMAN SUBJECTS, ICDDR,B.

49

Principal Investigator S. Zimicki Trainee Investigator (if any) _____

Application No. 80-024(P) Supporting Agency (if Non-ICDDR,B) _____

Title of Study Pilot protocols: Risk of child mortality after hospitalization at Matlab Treatment Center (analysis of collected data)

Project status:
(x) New Study
( ) Continuation with change
( ) No change (do not fill out rest of form)

Circle the appropriate answer to each of the following (If Not Applicable write NA).

1. Source of Population:
   (a) Ill subjects — (Yes) No
   (b) Non-ill subjects — Yes (No)
   (c) Minors or persons under guardianship — (Yes) No
2. Does the study involve:
   (a) Physical risks to the subjects — Yes (No)
   (b) Social Risks — Yes (No)
   (c) Psychological risks to subjects — Yes (No)
   (d) Discomfort to subjects — Yes (No)
   (e) Invasion of privacy — (Yes) No
   (f) Disclosure of information damaging to subject or others — Yes (No)
3. Does the study involve:
   (a) Use of records, (hospital, medical, death, birth or other) — (Yes) No
   (b) Use of fetal tissue or abortus — Yes (No)
   (c) Use of organs or body fluids — Yes (No)
4. Are subjects clearly informed about:
   (a) Nature and purposes of study — (Yes) No
   (b) Procedures to be followed including alternatives used — (Yes) No
   (c) Physical risks — Yes (No)
   (d) Sensitive questions — Yes (No)
   (e) Benefits to be derived — Yes (No)
   (f) Right to refuse to participate or to withdraw from study — (Yes) No
   (g) Confidential handling of data — (Yes) No
   (h) Compensation &/or treatment where there are risks or privacy is involved in any particular procedure — (Yes) No
5. Will signed consent form be required:
   (a) From subjects — Yes (No)
   (b) From parent, or guardian (if subjects are minors) — Yes (No)
6. Will precautions be taken to protect anonymity of subjects — (Yes) No
7. Check documents being submitted herewith Board:
   ___ Umbrella proposal - Initially submi overview (all other requirements wi be submitted with individual studi
   X Protocol (Required) p.1-4
   X Abstract Summary (Required)
   ___ Statement given or read to subjects nature of study, risks, types of qu ions to be asked, and right to refu to participate or withdraw (Requir
   ___ Informed consent form for subjects
   ___ Informed consent form for parent or guardian
   X Procedure for maintaining confident ity
   ___ Questionnaire or interview schedule

* If the final instrument is not complet prior to review, the following informat should be included in the abstract sum
1. A description of the areas to be covered in the questionnaire or interview which could be considere either sensitive or which would constitute an invasion of privacy.
2. Examples of the type of specific questions to be asked in the sensit areas.
3. An indication as to when the questi naire will be presented to the Boar for review.

We agree to obtain approval of the Review Board on the Use of Human Subjects for any chan involving the rights and welfare of subjects before making such change.

S Zimicki

031088

80-024(P)
Rec'd 20/6/80

Attachment 1a.

INFORMATION TO INCLUDE IN ABSTRACT SUMMARY

The Board will not consider any application which does not include an abstract summary. The abstract should summarize the purpose of the study, the methods and procedures to be used, by addressing each of the following items. If an item is not applicable, please note accordingly:

1. Describe the requirements for a subject population and explain the rationale for using in this population special groups such as children, or groups whose ability to give voluntary informed consent may be in question.

2. Describe and assess any potential risks - physical, psychological, social, legal or other - and assess the likelihood and seriousness of such risks. If methods of research create potential risks, describe other methods, if any, that were considered and why they will not be used.

3. Describe procedures for protecting against or minimizing potential risks and an assessment of their likely effectiveness.

4. Include a description of the methods for safeguarding confidentiality or protecting anonymity.

5. When there are potential risks to the subject, or the privacy of the individual may be involved, the investigator is required to obtain a signed informed consent statement from the subject. For minors, informed consent must be obtained from the authorized legal guardian or parent of the subject. Describe consent procedures to be followed including how and where informed consent will be obtained.

   (a) If signed consent will not be obtained, explain why this requirement should be waived and provide an alternative procedure.

   (b) If information is to be withheld from a subject, justify this course of action.

   (c) If there is a potential risk to the subject or privacy of the individual is involved in any particular procedure include a statement in the consent form stating whether or not compensation and/or treatment will be available

6. If study involves an interview, describe where and in what context the interview will take place. State approximate length of time required for the interview.

7. Assess the potential benefits to be gained by the individual subject as well as the benefits which may accrue to society in general as a result of the planned work. Indicate how the benefits outweigh the risks.

8. State if the activity requires the use of records (hospital, medical, birth, death or other), organs, tissues, body fluids, the fetus or the abortus.

The statement to the subject should include information specified in items 2, 3, 4, 5(c) and 7, as well as indicating the approximate time required for participation in the activity.

SECTION I - RESEARCH PROTOCOL

Title: Pilot protocol: Risk of child mortality after hospitalization at Matlab Treatment Center (Analysis of collected data)

Principal Investigator: S. Zimicki, L. Chen, (others as appropriate)

Starting Date: July 1980

Completion Date: September 1980

Total Direct Cost: < US $ 1000

Scientific Program Head:

This protocol has been approved by the Community Services Research Working Group.

Signature of Scientific Program Head:

Date: 12/6/80

Abstract Summary: Although various authors have estimated the number of deaths averted through use of Matlab Treatment Center (MTC), no one has yet quantitated the net effect on mortality. As a first step in that direction, this pilot protocol is a proposal to link already collected data to follow up children hospitalized at MTC between 1 February 1977 and 31 January 1978. Cohort mortality (crude and cause-specific) and rehospitalization incidence density rates and survival curves for the risk of death and the risk of rehospitalization will be produced and compared using appropriate statistical methods. (Cohort characteristics to be considered singly or multiply are age, sex, month of hospitalization, etiology of diarrhea, dehydration status, and distance of home from the treatment center.) One specific aim of the study is to produce a generalized computer program which will allow similar analysis of other data sets.

This protocol involves no additional collection of data; procedures to ensure confidentiality were implemented at the time of original data collection.

Abstract Summary — particular items

1. Not applicable

2. No risks; not applicable

3. Not applicable

4. See next page

5. No additional informed consent required

6. No interview; not applicable

7. No benefits to individual; to society in general, better understanding of the effect of episodic treatment for diarrhea, which may in future allow improvement of hospital services

Confidentiality Statement

Study involves use of collected data only; consent was obtained at the time of original data collection.

a) Data to be used in the study was collected as part of Dr. Black's *E. coli* surveillance

b) All data are on tape or in DSS volumes

c) Not necessary to record any identifying information

d) No follow-up required

e) Access to data; S. Zimicki, L. Chen, personnel in Statistics

f) Data will be published only in aggregate; no possibility of identifying individuals

g) Raw data will remain on tape; any new files constructed will, if not useful to other investigators, be deleted

Cholera Research Laboratory

Memorandum

TO CSRMC

FROM Susan Zimicki, L. Chen (Others as appropriate) DATE June 11, 198

SUBJECT Pilot Study: Risk of child mortality after hospitalization at Matlab Treatment Center (analysis of collected data)

The purpose of this analysis is to establish the survival curves of cohorts of children hospitalized at Matlab Treatment Center (MTC) at least once between 1 February 1977 and 31 January 1978.

This is a pilot study; it is expected to lead to a full protocol which will have as its aim the quantitation of the effect of MTC on mortality. Before this larger project is undertaken some information is needed to refine hypotheses. It is generally assumed that episodic hospitalization at MTC saves lives: Mosely et al. (1) estimated that 50% of hospitalized cholera patients would have died without hospitalization and Oberle et al. (2) estimated between 435 and 924 deaths averted (survivors) in a hospitalized population of 1916 (rate of 23-48%). It seems likely, however, that even though a life may be saved by treatment, the net effect on mortality will be different from that estimated by simply counting the deaths averted. To answer the question of how different, several assumptions need to be examined: (i) Survivors will be subject to the same risks of mortality due to all causes as the non-hospitalized population. (ii) Survivors, because of characteristics such as a higher rate of malnutrition, may indeed be at a continuing higher risk of mortality from some causes; (iii) The risk of subsequent death from diarrhoea is mediated by repeat hospitalization.

This preliminary study does not propose to quantitate the net effect on mortality of Matlab Treatment Center, but the information obtained should allow some refinement of the above-stated assumptions into hypotheses that can be tested when more data is available (when the yotis come back from Hopkins).

Specific aims

I. For cohorts of children hospitalized at Matlab Treatment Centre between 1 February 1977 and 31 January 1978 (distinguished by age, sex, dehydration status, etiology and distance of home from hospital).

1. to produce survival curves for the risk of death and the risk of repeat hospitalization.

2. To produce mortality (crude and cause-specific) and hospitalization incidence density rates.

3. To compare these curves and rates, using appropriate statistical tests, to determine if risk of subsequent death or hospitalization is concentrated in any particular subgroup.

II. An essential component of the study is writing a computer program to carry out 1 and 2 above. A specific aim of the study is to do this in such a way that it will be easily applicable to other data.

Methods

Two sources of data will be used. The first is the record of hospitalizations of children < 5 from the VTS area between 1 February 1977 and 31 January 1978. This information was collected by Dr. Robert Black as part of E. Coli surveillance and includes age, sex, dehydration status and etiology (Vibrio, Salmonella, Shigella, E. Coli, Rotavirus). The second is the DSS mortality and migration data for the period 1 February 1977 through July 1979.

The first step in analysis will be to identify deaths, migrations and repeat hospitalizations that occurred in the study population between the time of hospitalization and the end of the followup period. This will allow at least 1½ years followup for death and migration, and at least 1 year for repeat hospitalization (Figure 1). Information recorded and linked to the index hospitalization will be date and cause of death, date of migration, and the same hospitalization information as recorded for first hospitalization.

The second step will be to form cohorts characterized by stratifying variables considered singly or multiply (age, sex, month of first hospitalization, dehydration status, etiology, distance of home from hospital). Then for each cohort Table 1 will be produced (3,4) for several combinations of outcome and withdrawal (Table 1). The resulting survival curves with confidence limits can be plotted with either

calendar month of outcome or interval since first hospitalization on the x-axis. This will allow visualization of the relative effect of interval and season on risk of outcome. If it seems useful to test the statistical significance of differences between curves, the method recommended by WHO will be used (5). Incidence density rates (outcome/person-time) will be calculated as summary rates (4).

Comparisons which will be made and tested for significance if appropriate, will include different ages at hospitalization, male vs female, dehydration status 0-1 vs 3-4 and different etiologies, as well as month of hospitalization and distance of home from hospital. Mortality incidence density rates for age and sex cohorts of the general population can be estimated from DSS data and compared with those generated in this analysis. (It might be possible to estimate the survival curves for children in the population as a whole by making some simplifying assumptions and using Lexis diagrams. It seems preferable, however, to wait until the data tapes are available to allow true curves for nonhospitalized children to be generated. This will allow a much cleaner analytic comparison.) The hypotheses to be tested in each case will be that rate or survival curve x is no different from rate or survival curve y.

An additional interesting comparison will be the percent of deaths attributed to various causes in the study population and in the population <5 as a whole. The comparison year for the DSS data can be either 1977 or 1978, whichever is easier.

Potential sources of bias will be handled as outlined below and presented in Table 2. If there is no census number and the record cannot be linked through the hospital record number, the child will be excluded from the study. The characteristics of this excluded population will be compared with those of the study population to assess the extent of possible bias. The number of wrong census numbers detected during the linking process will be counted, and the rate calculated as an estimation of the rate of recording/coding/keypunching error. A random sample of the children included in the study (size of sample determined on basis of estimation above) will be cross-checked against DSS data to ascertain the rate of error in age and sex assignment and to test for randomness of these errors.

Methodologic considerations include treatment of death in hospital and repeat hospitalizations. Those dying in hospital should be excluded from the analysis. This will be accomplished by listing those dying within 2 weeks of hospitalization and examining the hospital records.

The problem of whether it is appropriate to exclude those who come to hospital again as if they had died depends on the interpretation of the different survival curves generated because of it is directly related to the question of the survival effect of hospitalization.

Significance

The benefits of doing this study are (1) [illegible]tion of a generalized computer program to calculate survival curves and incidence density rates from followup data and (2) an idea of the survival effect of hospitalization at MTC, including identification of the groups of children benefitting most.

Budget

The incremental cost of this study will be less than 1000 dollars. The major expense will be computer time and supplies; other items will be a consultant programmer's time, secretarial supplies and a literature search.

References

1. Mosely WH, Bart KJ, Sommer A. An epidemiological assessment of cholera control programs in rural East Pakistan. Int. J. Epi. I: 5, 1972.

2. Oberle MW, Merson MH, Islam S, ASMM Rahman, Huber DH, Curlin G. Diarrheal disease in Bangladesh: Epidemiology, mortality averted and costs at a rural treatment center. In preparation.

3. Rothman KJ, Estimation of confidence limits for the cumulative probability of survival in life table analysis. J. Chron. Dis.31:557, 1978.

4. Rothman KJ, Boke JD,Jn. Epidemiologic analysis with a programmable calculator. NIH Publication No. 79-1649, June 1979. US Government Printing Office, Washington D.C.

5. Chiang CL. Life table and mortality analysis. World Health Organization, Geneva. 1977.

Interval since hospitalization	A Alive at beginning of interval i	Outcome during i	W ?Withdrawn during i	S Survival probability during i	SE($\hat{S}$)	Lower 90% confidence limit	Upper 90% confidence limit

Combinations of outcome and treated as withdrawal

	Outcome	Treated as withdrawal	Outcome ignored
1.	death	migrated out	repeat hosp.
2.	death	migrated out & repeat hospitalization	-
3.	2nd hospitalization	death migrated out	-

	ERROR	EFFECT	TREATMENT
1.	No Census number or wrong census number	No link with DSS data possible	Exclude from Study; compare excluded and included population with regard to age, sex, etc.
2.	Wrong census number but linkable	None	Calculate rate as estimate of reporting/coding/keypunch error.
3.	Age, sex, etc. misreported, miscoded, mispunched.	Misclassification	Cross-check sample against DSS data (determine sample size from error rate estimated in 2) determine rate, assess randomness.

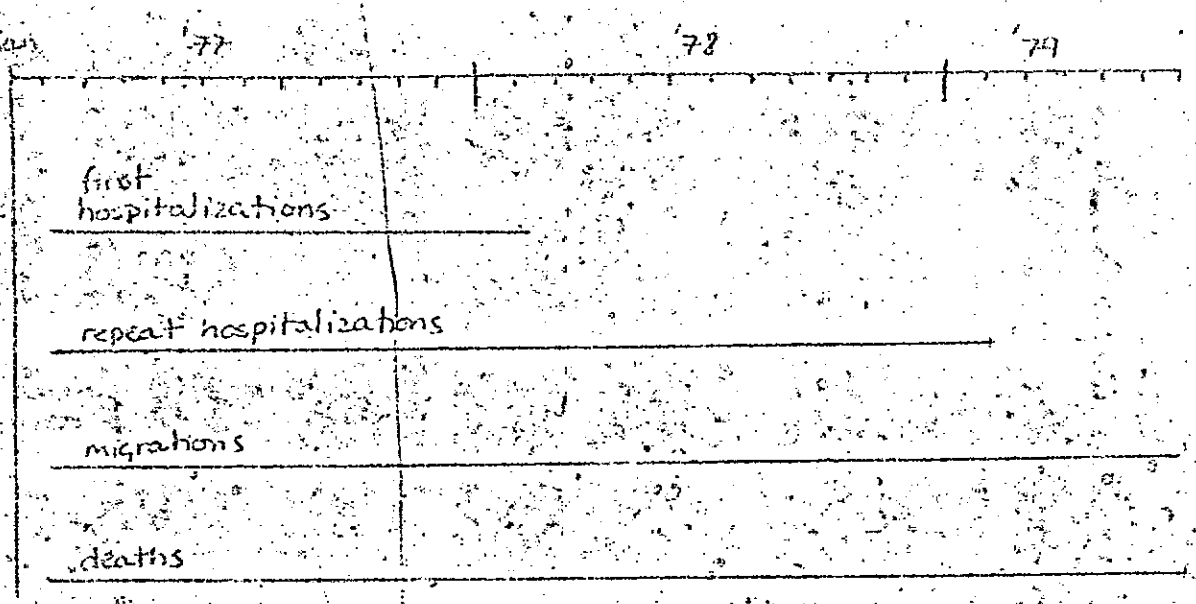

Figure 1. Chronogram of data to be used in the study. The line for first hospitalizations indicates dates for eligible entry into the study; those for repeat hospitalizations, migrations and deaths indicate periods for which followup data is readily available. Thus the minimum followup period will be one year for repeat hospitalizations and one and a half years for migrations and deaths.