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

L-8

cipal Investigator ROGER GLASS
Trainee Investigator (if any) _____

ication No. 80-006
Supporting Agency (if Non-ICDDR,B) _____

e of Study EPIDEMIOLOGIC AND
LICAL STUDIES OF MULTIPLY
NOTIC RESISTANT VIBRIOS IN MATLAB

Project status:
(✓) New Study
(✓) Continuation with change (ORIGINALLY - PILOT STUDY)
( ) No change (do not fill out rest of form)

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

Source of Population:
(a) Ill subjects (Yes) No
(b) Non-ill subjects (Yes) No
(c) Minors or persons under guardianship (Yes) No

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)

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

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 to Board:
   ___ Umbrella proposal - Initially submit an overview (all other requirements will be submitted with individual studies)
   ✓ Protocol (Required)
   ✓ Abstract Summary (Required)
   ✓ Statement given or read to subjects on nature of study, risks, types of questions to be asked, and right to refuse to participate or withdraw (Required)
   ✓ Informed consent form for subjects
   ___ Informed consent form for parent or guardian
   ___ Procedure for maintaining confidentiality.
   ___ Questionnaire or interview schedule *

* If the final instrument is not completed prior to review, the following information should be included in the abstract summary:
1. A description of the areas to be covered in the questionnaire or interview which could be considered either sensitive or which would constitute an invasion of privacy.
2. Examples of the type of specific questions to be asked in the sensitive areas.
3. An indication as to when the questionnaire will be presented to the Board for review.

gree to obtain approval of the Review Board on the Use of Human Subjects for any change
ving the rights and welfare of subjects before making such change.

Principal Investigator

RECEIVED 3 0 APR 2001

Trainee

80-006
Rec'd 3/3/80

SECTION 1 - RESEARCH PROTOCOL

1. Title: Epidemiologic and Clinical Studies of Multiply Antibiotic Resistant Vibrios (MARV) in Matlab

2. Principle Investigator: Roger I. Glass, M.D.
   Co-Investigators: Mr. Imdadul Huq, S. K. Roy, M.D., and Md. Yunus, M.D

3. Starting Date: February 29, 1980

4. Completion Date: June , 1981

5. Total Direct Cost:

6. Availability of Funds:

   (a) Scientific Director's Remarks:

   (b) Controller's Remarks:

7. Abstract Summary:

This protocol examines the clinical parameters of cholera due to MARVs, the relationship between toxin production and the R-plasmid, the transmission of MARVs within family units, and the distribution of the R-plasmid in Matlab.

Patients entering the Matlab Field Station with signs and symptoms suggestive of cholera will have their stools examined for V. cholerae on admission. Cholera patients will be cultured and the antibiotic

sensitivity of the isolates tested. Clinical features of illness associated with MARVs and normal vibrio will be compared as well as the duration of excretion of vibrios. Vibrio isolates will be tested for toxin production and acute and convalescent sera (2 weeks) of a selected group of patients will be examined for antitoxin response.

Family studies of patients with MARVs will be conducted according to the formats used for previous family studies in Matlab. The families of patients with MARVs and a selected sample of normal vibrio patients will be cultured from day 1 until all cultures in the family are negative for 3 days. Selected environmental water and food samples will be collected for culture. The antibiotic sensitivity patterns of non-vibrio isolates will be examined for the possible presence of a resistance plasmid.

8. Reviews:

(a) Research Involving Human Subjects: _____

(b) Research Committee: _____

(c) Director: _____

(d) BMRC: _____

(e) Controller/Administrator: _____

SECTION II - RESEARCH PLAN

A. INTRODUCTION

1. Objective

To examine (1) the clinical presentation and course of cholera due to MARVs in Matlab; (2) the transmission of MARVs within family units; (3) the distribution of the resistance in the Matlab population; and (4) the clinical and epidemiologic correlates of cholera due to non-toxigenic *V. cholerae*.

2. Background

In December 1979, during sensitivity testing of *V. cholerae* isolates from Matlab, a group were found which demonstrated resistance to five antibiotics (1). Early studies indicated that this resistance was plasmid-borne and had been occurring in Matlab at least since August 1979. A retrospective review of patient charts indicated that patients with MARVs were ill longer and had greater stool volume and prolonged excretion of *V. cholerae* than patients with normal cholera strains (2). A pilot study was implemented to conduct some preliminary family studies and make clinical observations while a full protocol could be written. A clinical trial will be planned when some basic information on the behavior of this illness is gathered.

Over the years, *V. cholerae* have maintained their sensitivity to tetracycline, which has remained the drug of choice worldwide (3).

While tetracycline is not essential in the treatment of cholera, it does decrease the duration of diarrhea, length of hospitalization, and period of excretion of vibrios (4). In 1977, plasmid-borne multiply antibiotic-resistant vibrios were identified in the epidemic of cholera in Tanzania (5). This plasmid, which is different from that identified in Matlab, has remained in the vibrio of that region for 2 years suggesting that it is stable and will be long-lasting. This stability of the plasmid has been unexpected since laboratory studies with vibrio plasmids have given markedly different results (6). The emergence of this plasmid-borne resistance among vibrios in Bangladesh and its persistence already for 5 months suggest that a new antibiotic therapy will be needed and that further areas of the country and region should expect this sort of occurrence.

R-plasmids are of importance in many areas of diarrheal disease control in Bangladesh. Plasmid-borne antibiotic resistance in Shigella has led to the need for continually changing the antibiotic regimen given to Shigella patients (7). Plasmid-borne toxin of E. coli has led to difficulties in clearly associating ETEC serotypes with toxin production. To date, however, these plasmids were specific to the organisms in which they were originally found. During the early studies in Matlab, an isolate

of E. coli was found to possess a multiply antibiotic-resistant pattern of the vibrio. This suggests that other E. coli may be encoded with the plasmid and further epidemiologic studies could provide important information on the transfer of this genetic material between individuals and microorganisms in an environment already under intense epidemiologic and microbiologic surveillance.

Recently, many strains of V. cholerae isolated at ICDDR,B have failed to demonstrate toxin production in the normal assays used for LT - Y-1 adrenal cell, CHO cell, rabbit skin, and rabbit ileal loop. These findings are preliminary in Bangladesh, but have been observed in Calcutta and in earlier studies of toxin production among vibrios. While it has not been determined where cholera toxin lies in the DNA of the vibrio, its closest relative, LT toxin of ETEC, is plasmid-borne which could explain some of the instability noted in toxin production by selected strains of ETEC. Since toxin is needed to cause antitoxic immunity, we would like to know whether non-toxigenic strains of V. cholerae make no toxin, or an incompetent toxin, and what the immune response to this non-toxigenic strain would be.

3. Rationale

V. cholerae is an important cause of severe diarrhea in Bangladesh

and tetracycline has long been an effective drug of choice. The emergence of resistance to tetracycline will prolong the clinical course of all patients with MARVs. The identification of the resistant plasmid in an isolate of E. coli might suggest that a similar resistance pattern may appear in E. coli and other micro-organisms as well.

This study will allow us to identify the clinical illness of these patients, the transmission of V. cholerae in family studies, and the transmission of the plasmid in the Matlab setting. We will also be able to determine the prevalence of non-toxigenic strains of V. cholerae and the antitoxic response to these strains.

B. SPECIFIC AIMS

1. To identify the clinical illness associated with MARVs vs. normal cholera.
2. To examine the mode of transmission of cholera using this unique antibiotic-resistance marker.
3. To examine the epidemiology of resistant plasmids and other micro-flora of the Matlab population and field area.
4. To identify the prevalence and the descriptive epidemiology of non-toxigenic V. cholerae in Matlab and to examine the antitoxic response of patients ill with this organism.

C. METHODS AND PROCEDURES

1. Time Period

The study will continue for 1 year with an additional 6 months required for data analysis.

2. Matlab Hospital Study

(a) Population: All patients at Matlab found to have cholera will be eligible for this study. Patients with moderate-to-severe dehydration will be screened on admission with darkfield. Currently, all patients who live in the VTS area are cultured for V. cholerae and patients positive on culture will be admitted as well.

(b) Bacteriologic Procedures

(i) Isolation: Patients with moderate-to-severe dehydration will have a stool specimen examined by darkfield on admission. VTS patients found to be culture-positive for V. cholerae will be included in the study on day 2 even if they were not moderately dehydrated on admission.

(ii) Quantitative cultures: These cultures will be performed at 12-hourly intervals from 0 to 48 hours and daily until cultures are negative, and patients will be kept in hospital until their cultures are negative for 24 hours. Isolates will be stocked on trypticase agar and tested for toxin production afterwards using the CHO cell and Y-1 adrenal cell assays.

(c) Clinical Assessment: All cholera patients will be systematically studied. Upon admission, they will be queried using a standard form about gastrointestinal symptoms, illness duration and severity, and will receive a physical examination. Admission and discharge heights and weights will be determined. A stool specimen will be taken from all patients with moderate-severe dehydration by rectal chatheter for darkfield examination and quantitative culture count if vibrio are found. A specimen will be sent for microscopic examination for fecal WBCs and parasites. Two hundred lambda of sera will be drawn on admission from all patients to measure specific gravity and to determine acute serology. Patients from the VTS area identified by culture to have vibrio who were not originally moderately dehydrated and admitted into the study will enter the study when their cultures become positive.

Following hospitalization, patients will be treated with IV and oral solution as usual and tetracycline will be initiated on patients identified to have cholera. If the average duration of diarrhea for the first 20 MARV patients is more than 5 days, i.e. the mean duration of untreated patients from historical studies, then tetracycline will be withheld from these patients until a full clinical trial can be started.

All patients will remain hospitalized until they go 24 hours without a liquid stool or are culture-negative for 1 day.

While in hospital, the following parameters will be measured at 4-hourly intervals: (i) stool volume; (ii) duration of diarrhea, vomiting, fever, and other signs and symptoms; (iii) IV requirements; (iv) urine output.

All patients will be asked to return 10-14 days after admission to ascertain that they are again healthy and to obtain a convalescent sera by fingerstick as before.

(d) Serology: Acute and convalescent sera will be collected from all patients. All patients found to have non-toxigenic V. cholerae and the control group with normal, toxigenic V. cholerae will be tested for anti-cholera toxin, and anti-B subunit antibodies.

3. Family Studies

The families of index patients will be visited within 24 hours of a confirmed diagnosis of cholera and queried about recent diarrheal illness, common water exposures, antibiotic use, and recent travel. Rectal swabs will be collected and cultured on day 1 and daily thereafter until all cultures are negative for 2 days. Samples of water from the household will be taken as well as surface water from surrounding sources and tested for vibrio and other pathogens.

Bacteriology - vibrios will be cultured following routine transport and isolation techniques. Plasmids among other intestinal flora will be identified using a selective antibiotic plate to be developed in the microbiology lab - probably incorporating tetracycline with or without kanamycin.

4. Data Analysis

From this study, data will be obtained on the following:

(a) The clinical course of illness caused by MARVs with and without tetracycline use.

(b) The mode of transmission of V. cholerae within families using the pattern of multiple antibiotic resistance as a

specific marker.

(c) The distribution of the R-plasmid within the family and the Matlab community.

(d) The distribution of non-toxigenic V. cholerae in Matlab and its clinical and epidemiologic correlates.

D. SIGNIFICANCE

This study will provide us detailed information on the clinical course of cholera due to a MARV organism and its mode of transmission in Matlab, information about the distribution of the R-plasmid in Matlab, and data on the prevalence of non-toxigenic strains of V. cholerae and their ability to produce an antitoxic immune response.

This information will provide background for a clinical trial to identify a new treatment regimen for resistant cholera and information about the potential spread of the resistant plasmid in the community.

E. FACILITIES REQUIRED

1. Office Space - no additional space required.
2. Laboratory Space - one 1/4 Revco to store frozen specimens.
3. Hospital Resources - no additional space.
4. Animal Resources - 1500 infant mice will be needed if we see approximately 500 cases of cholera.
5. Logistic Support - none.
6. Major Items of Equipment - none.

E. COLLARBORATIVE ARRANGEMENTS

None at present.

REFERENCES

1. ICDDR,B - New Release, January 31, 1980. The emergence of multiply antibiotic-resistant vibrios in Bangladesh
2. Unpublished data - Glass RI, Huq, MI, Alim ARMA, Yunus M
3. Hirschhorn N, Pierce NF, Kobari K, Carpenter CCJ. The treatment of cholera in Cholera (D Barua and W Burrows, editors), WB Saunders Co, Philadelphia 1974, pp 235-252
4. Lindenbaum J, Greenough WB, Islam MR. Antibiotic therapy of cholera. Bull Wld Hlth Org 1967, 36:871-883
5. Mhalu FS, Mmari PW, Ijumba J. Rapid emergence of El Tor Vibrio cholerae resistant to antimicrobial agents during first six months of fourth cholera epidemic in Tanzania. Lancet 1979; i:345-347
6. Yokota T, Kasuga T, Kaneko M, Kuwakara S. Genetic behavior of R-factors in Vibrio cholerae. J Bacteriol 1972; 109:44-442
7. Mutanda LN, et al. Unpublished data.

SECTION III - BUDGET

A. DETAILED BUDGET

1. PERSONNEL SERVICES

Name	Position	% or # of Days	Project Requirements Taka	Dollar
Dr. Class	Scientist	20%	-	10,000
Dr. Yunus	Physician-in-Charge, Matlab	20%	15,150	-
Dr. Roy	Physician	40%	20,740	-
Mr. I. Huq	Microbiologist	10%	9,500	-
Mr. Khan	Supervisor	30%	15,350	-
Mr. Azizul Huq	Asst. Supervisor	100%	38,490	-
(To be named)	Field Asst.(5)	100%	118,510	-
Mr. Alim	Sr. Research Asst.	10%	4,930	-
Mr. Belayet	Research Technician	20%	4,300	-
Mr. Faijur Rahman	Pathology Technician	20%	2,860	-
(To be named)	Keypunch Operator	10%	1,600	-
"	Programer	10%	3,990	-
"	Supvr - Epidemiology	100%	32,080	-
Dr. Mahmud	Veterinarian	5%	4,150	-
	Sub-Total		271,650	

2. SUPPLIES AND MATERIALS

Item	Unit Cost		
Rectal swabs for vibrio - 500	Tk. 11.00	55,000	-
Water for culture - 1,000	7.50	7,500	-
Cholera antitoxin tests - 1,000	5.00	5,000	-
Cholera toxin testing - 500	5.00	2,500	-
Stationery, office supplies, computer paper and cards		2,500	-
	Sub-Total	72,500	

3. EQUIPMENT

None

	Unit Cost	Project Requirements Taka	Dollars
4. PATIENT HOSPITALIZATION			
Number of patient days (150 patients x 4 days)	600 @ 130T/d	78,000	-
Sub-Total		78,000	
5. OUTPATIENT CARE			
None			
6. ICDDR,B TRANSPORT			
Dacca-Matlab - 40 round trips	400T/trip	16,000	-
Hours water transport - 4 run hrs/day x 180 days	100T/hour	72,000	-
Sub-Total		88,000	
7. TRAVEL AND TRANSPORTATION OF PERSONS			
International travel		-	3,500
Sub-Total			3,500
8. TRANSPORTATION OF THINGS			
Importation of supplies		-	200
Sub-Total			200

	Project Requirements	
	Taka	Dollars
9. RENT, COMMUNICATIONS & UTILITIES		200
Sub-Total		200
10. PRINTING AND REPRODUCTION		200
Sub-Total		200

11. OTHER CONTRACTUAL SERVICES

None

12. CONSTRUCTION, RENOVATION, ALTERATIONS

None

B. BUDGET SUMMARY

	Category	Taka	Dollars
1.	Personnel	271,650	10,000
2.	Supplies	72,500	-
3.	Equipment	-	-
4.	Hospitalization	78,000	-
5.	Outpatients	-	-
6.	ICDDR,B Transport	88,000	-
7.	Travel Persons	-	3,500
8.	Transportation Things	-	200
9.	Rent/Communication	-	200
10.	Printing/Reproduction	-	200
11.	Contractual Services	-	-
12.	Construction	-	-
	Total	510,150	14,100
	Grand Total	$47,013	

ABSTRACT SUMMARY

This protocol examines the clinical parameters of cholera due to MARVs, the relationship between toxin production and the R-plasmid, the transmission of MARVs within family units, and the distribution of the R-plasmid in Matlab.

Patients entering the Matlab Field Station with signs and symptoms suggestive of cholera will have their stools examined for V. cholerae on admission. Cholera patients will be cultured and the antibiotic sensitivity of the isolates tested. Clinical features of illness associated with MARVs and normal vibrio will be compared as well as the duration of excretion of vibrios. Vibrio isolates will be tested for toxin production and acute and convalescent sera (2 weeks) of a selected group of patients will be examined for antitoxin response.

Family studies of patients with MARVs will be conducted according to the formats used for previous family studies in Matlab. The families of patients with MARVs and a selected sample of normal vibrio patients will be cultured from day 1 until all cultures in the family are negative for 3 days. Selected environmental water and food samples will be collected for culture. The antibiotic sensitivity patterns of non-vibrio isolates will be examined for the possible presence of a resistance plasmid.

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1. Since the study seeks to define the associated illness and laboratory features of these organisms in all age groups, patients of all ages must be studied.
2. There are no significant risks to this study. Only rectal swabs, stool specimens (via rectal catheter), and blood (via fingerstick or antecubital vein) will be collected.
3. There are no risks; therefore, this section is not applicable.
4. Confidentiality of the data collected will be ensured. Patient names will not be used in analysis or publication of the data. The original data will be locked in a file in the custody of the principle investigator who will restrict its use. In all laboratory studies only the hospital numbers will be used to identify patients.
5. A signed consent form will not be used since the study risks are minimal. For ICDDR,B patients only routine diagnostic procedures will be done - rectal swab, stool collection, and blood drawing; standard therapy will be given for the participants.

   Information on what diagnostic procedures will be performed will be provided verbally and verbal consent obtained. For minors, consent will be obtained from the authorized legal guardian or parent of the child. The verbal statement made will include (a) the nature and purpose of each procedure,

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(b) the physical risks, (c) the benefits derived, (d) the right to refuse to participate, and (e) confidentiality of data.

6. The only interview performed will be the routine taking of a medical history from ill persons.

7. Individual patients with diarrhea will benefit in that the cause of their illness will be more clearly understood and they will be followed longer than patients without the normal-non-resistant strains. Family contacts will learn whether they are carriers of pathogenic organisms.

   The potential benefit to society from the study will be a better understanding of the relative importance of MARVs and non-toxigenic vibrios as a cause of diarrhea and the mode of transmission. This information will lead to improved understanding of this form of diarrheal illness and the need for appropriate antibiotic therapy.

8. The study requires use of Matlab Field Station records and patient serum and stool.

CONSENT FORM

COLLECTION OF STOOL AND SERA FROM CHOLERA

IN-HOSPITAL PATIENTS

Doctors at the Cholera Hospital have recently noted that the germ causing cholera is not sensitive to the normal antibiotics used. If you have this form of cholera, despite our current therapy, you will have to stay in hospital longer and will experience prolonged illness.

While we are planning to search for a new antibiotic therapy in the near future, we need to gather some basic information on this disease so that a proper alternative treatment regimen can be devised. We will be providing you with full care for your illness in the hospital but would like to collect stool specimens by rectal catheter at 12-hour intervals for 2 days and daily until your illness goes away. This will cause you some inconvenience but no danger, and it will provide information important in our search for new treatment.

Furthermore, some of the cholera organisms which have recently been found in Matlab do not cause diarrhea by mechanisms that we understand. We would like to examine your body's response to this disease by drawing a sample of your blood now, and again in 2 weeks so that we can measure the immunity that you have acquired.

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You may decide whether or not you wish to allow us to collect these specimens and you should inform us whether you give your consent to volunteer yourself or your child. If you would prefer not to participate, you will nonetheless receive full treatment for your disease. If you participate, we can provide you assurance that when you leave the hospital, your body will be free of further cholera organisms.

For the purposes of this study, you will not be identified individually or by name. You may withdraw from the study at any time.

পায়খানা ও রক্ত পরীক্ষার জন্য
সম্মতি পত্র

হাসপাতালের ডাক্তারেরা (পরীক্ষা করে) দেখেছেন যে বর্তমানে প্রচলিত ঔষধ দিয়ে কোনকোন ক্ষেত্রে কালাজ্বর জীবাণু প্রতিরোধ করা সম্ভব নয়। যদি আপনার ঐ ধরনের কালাজ্বর হয়ে থাকে, তবে হাসপাতালে চিকিৎসাধীন থাকা সত্ত্বেও আপনি দীর্ঘদিন রোগে ভুগবেন।

অদূর ভবিষ্যতে যখন আমরা এ রোগের নতুন কোন চিকিৎসা পদ্ধতি আরম্ভ করব, তখন কিছু তথ্যের প্রয়োজন হবে। আমরা সেজন্য 'প্লাস্টিক কৌটার' দিয়ে সংগ্রহ: পর পর দু'দিন ও অসুখ চলাকালীন সময় দিয়ে একবার পায়খানা নেব। এতে আপনার কিছু কিছু অসুবিধা হতে পারে। কিন্তু আপনার শরীরের কোন ক্ষতি হবে না।

অসলের ক্ষেত্রে কোন কালাজ্বর রোগের জীবাণু কারো ডায়রিয়াও হয় না। আমরা আপনার শরীরে এ রোগের প্রতিক্রিয়া দেখার জন্য এখন অল্প রক্ত নেব। দু'সপ্তাহ পরে আপনার শরীরে রোগ প্রতিরোধক অবস্থা দেখার জন্য আবার রক্ত নেব।

আমাদের কাজে অংশগ্রহণ করা আপনার ইচ্ছার উপর নির্ভর করে, তবে অংশগ্রহণ করলে আমরা আমাদের রোগ নির্মূল করার চেষ্টা করব। আপনি যদি অংশগ্রহণ নাও করেন তবুও ~~নিজ~~ হাসপাতালের চিকিৎসার কোন ক্ষতি হবে না।

আপনার নাম ও ঠিকানা গোপন রাখা হবে। আপনি যে কোন সময় আপনার নাম প্রত্যাহার করতে পারেন।

CONSENT FORM

(Verbal consent form to be read to subjects at interview for family study.)

Doctors at the ICDDR,B recently treated a member of your family for diarrhea. We are trying to learn whether other members of your family may have the same germ or be ill with diarrhea as well. We would like to obtain a stool specimen now and several times over the next several weeks to see if you might have the same germ. If you are ill, we will provide you with appropriate treatment. You can ask any questions you want and are not required to take part in this study. Information collected will not be given to anyone except you and the doctor will combine it with information from other patients so that you will not be identified individually.

অনুমতি পত্র

বর্তমানে ডাক্তারেরা আপনার পরিবারের একজন লোকের চিকিৎসা করেছেন। আমরা আপনার পরিবারের অন্য লোকের ও সেই ধরনের রোগজীবাণু আছে কি না পরীক্ষা করে দেখার জন্য পরিবারের লোকদের এখন একবার পায়খানা নেব। পরবর্তী কয়েক সপ্তাহে আমাদের প্রয়োজনানুসারে কয়েকবার পায়খানা নেব। যদি কেহ অসুস্থ হয়ে থাকে তবে, উপযুক্ত চিকিৎসার ব্যবস্থা করব।

আপনার নিকট থেকে যে সব তথ্য নেয়া হবে তা গোপন রাখা হবে। এ কাজে অংশগ্রহণ আপনার ইচ্ছার উপর নির্ভর করে। আপনি যে কোন সময়ে আপনার নাম প্রত্যাহার করতে পারেন।