ICDDRB: Centre for Health & Population Research | RRC APPLICATION FORM

RESEARCH PROTOCOL
2000 - 032

FOR OFFICE USE ONLY	
Protocol No:	Date received:
RRC Approval: Yes/ No	Date:
ERC Approval: Yes/ No	Date:

Project Title: An open, randomised clinical trial comparing the efficacy and safety of a single dose of ciprofloxacin with erythromycin administered 6-hourly for 3 days in children with cholera.

Theme and key words: Infectious Disease
Cholera, Children, Randomized Clinical Trial, Ciprofloxacin, Single dose, Erythromycin, Antimicrobial Therapy

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Clinical Sciences Division
ICDDR,B., Mohakhali, Dhaka 1212

Co-Principal Investigator(s):

Co-Investigator(s): Dr. Debasish Saha

Student Investigator/Intern: Dr. Anisur Rahman

Collaborating Institute(s): New England Medical Center
Tufts University School of Medicine
Boston, MA. USA.

Population: Inclusion of special groups (*Check all that apply*):

Gender
- ☒ Male
- ☒ Females

Age
- ☐ 0 – 5 years
- ☐ 5 – 9 years
- ☐ 10 – 19 years
- ☐ 20 +
- ☐ > 65

- ☐ Pregnant Women
- ☐ Fetuses
- ☐ Prisoners
- ☐ Destitutes
- ☐ Service providers
- ☐ Cognitively Impaired
- ☐ CSW
- ☒ Others (specify Age 2-15 years)

Project / study Site (*Check all the apply*):
- ☒ Dhaka Hospital
- ☒ Matlab Hospital
- ☐ Matlab DSS area
- ☐ Matlab non-DSS area
- ☐ Dhaka Community
- ☐ Chakaria
- ☐ Abhoynagar
- ☐ Mirsarai
- ☐ Patyia
- ☐ Other areas in Bangladesh _____
- ☐ Outside Bangladesh
  Name of country: _____
- ☐ Multi centre trial
  (Name other countries involved)

Type of Study *(Check all that apply)*:

- ☐ Case Control study
- ☐ Community based trial / intervention
- ☐ Program Project (Umbrella)
- ☐ Secondary Data Analysis
- ☒ Clinical Trial (Hospital/Clinic)
- ☐ Family follow-up study
- ☐ Cross sectional survey
- ☐ Longitudinal Study (cohort or follow-up)
- ☐ Record Review
- ☐ Prophylactic trial
- ☐ Surveillance / monitoring
- ☐ Others

Targeted Population *(Check all that apply)*:

- ☒ No ethnic selection (Bangladeshi)
- ☐ Bangalee
- ☐ Tribal groups
- ☐ Expatriates
- ☐ Immigrants
- ☐ Refugee

Consent Process *(Check all that apply)*:

- ☒ Written
- ☐ Oral
- ☐ None
- ☒ Bengali language
- ☐ English language

Proposed Sample size:

Total sample size: 180 (Evaluable 160 – Dropouts 20) ☐

Sub-group: Ciprofloxacin = 90 (Evaluable 80) ☐ Erythromycin = 90 (80 Evaluable) ☐

_____ ☐ _____ ☐

Determination of Risk: Does the Research Involve *(Check all that apply)*:

- ☐ Human exposure to radioactive agents?
- ☐ Fetal tissue or abortus?
- ☐ Investigational new device? (specify_____)
- ☐ Existing data available from Co-investigator
- ☐ Human exposure to infectious agents?
- ☐ Investigational new drug
- ☐ Existing data available via public archives/source
- ☐ Pathological or diagnostic clinical specimen only
- ☐ Observation of public behavior
- ☒ New treatment regime

Yes/No

☐ ☒ Is the information recorded in such a manner that subjects can be identified from information provided directly or through identifiers linked to the subjects?

☐ ☒ Does the research deal with sensitive aspects of the subject's behavior; sexual behavior, alcohol use or illegal conduct such as drug use?

Could the information recorded about the individual if it became known outside of the research:

☐ ☒ a. place the subject at risk of criminal or civil liability?

☐ ☒ b. damage the subject's financial standing, reputation or employability; social rejection, lead to stigma, divorce etc.

Do you consider this research *(Check one)*:

- ☐ greater than minimal risk
- ☐ no risk
- ☒ no more than minimal risk
- ☐ only part of the diagnostic test

Minimal Risk is "a risk where the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical, psychological examinations or tests. For example, the risk of drawing a small amount of blood from a healthy individual for research purposes is no greater than the risk of doing so as a part of routine physical examination".

'es/No

☒ ☐ Is the proposal funded? Expected to be Funded

If yes, sponsor Name: New England Medical Center, Boston, MA, USA.

☐ ☐ Is the proposal being submitted for funding?

If yes, name of funding agency: Not Applicable

Do any of the participating investigators and/or their immediate families have an equity relationship (e.g. stockholder) with the sponsor of the project or manufacturer and/or owner of the test product or device to be studied or serve as a consultant to any of the above?

IF YES, submit a written statement of disclosure to the Director.

Dates of Proposed Period of Support *(Day, Month, Year - DD/MM/YY)*		Cost Required for the Budget Period ($)			
		a. *Ist Year*	*2nd Year*	*3rd Year*	*Other years*
Beginning date	01-01-2001	109,273	102,811	0	0
End date	31-12-2002	*b.* *Direct Cost :* 178,467		*Total Cost :* 223,084	

Approval of the Project by the Division Director of the Applicant

The above-mentioned project has been discussed and reviewed at the Division level as well by the external reviewers. The protocol has been revised according to the reviewer's comments and is approved.

Prof. George J. Fuchs, M.D. — Name of the Associate Director

Signature

October 09,2000 — Date of Approval

Certification by the Principal Investigator

I certify that the statements herein are true, complete and accurate to the best of my knowledge. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. I agree to accept responsibility for the scientific conduct of the project and to provide the required progress report if a grant is awarded as a result of this application.

Signature of PIs:

Date: 08/10/2000

Name of Contact Person (if applicable)

Dr. Mohammed Abdus Salam

Chief Physician, CRSC, CSD.

Bayer

CLINICAL TRIAL PROTOCOL

Study Identifier: IMPACT No. 10110 / AP 176

Date and Version: 3 July 2000, Version 10

Title: An open, randomised clinical trial comparing the efficacy and safety of a single dose of ciprofloxacin with erythromycin administered 6-hourly for 3 days in children with cholera

Test Drug: Ciprofloxacin oral suspension

CONFIDENTIAL

SIGNATURE PAGE

Dr Mohammed Abdus Salam Study Co-ordinator	30-07-2000 Date
Dr Michael Bennish Study Consultant	Date
Dr W A Khan Principal Investigator (Dhaka site)	Date
Dr Anisur Rahman Principal Investigator (Matlab site)	Date
Dr Wolf-Dieter Sittner Medical Director: Bayer (Singapore) Pte Ltd	Date
Dr R Schall Biostatistician: Quintiles ClinData	Date

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12. 7. 2000

Dr Wolf-Dieter Sittner
Medical Director:
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Dr Michael Bennish Study Consultant	Date
Dr W A Khan Principal Investigator (Dhaka site)	18th July 2000 Date
Dr Anisur Rahman Principal Investigator (Matlab site)	17th July, 2000 Date
Dr Wolf-Dieter Sittner Medical Director: Bayer (Singapore) Pte Ltd	Date
Dr R Schall Biostatistician: Quintiles ClinData	Date

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Study Co-ordinator

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Dr Michael Bennish
Study Consultant

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Principal Investigator (Dhaka site)

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Dr Anisur Rahman
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27 July 2000

Date

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Dr Mohammed Abdus Salam Study Co-ordinator	Date
[signature]	2 AUGUST, 2000
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Dr Wolf-Dieter Sittner Medical Director: Bayer (Singapore) Pte Ltd	Date
Dr R Schall Biostatistician Quintiles ClinData	Date

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GLOSSARY

AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine Transaminase
ASCON	Annual Scientific Conference
AST	Aspartate Transaminase
CI	Confidence Interval
CNS	Central Nervous System
CRF	Case Report Form
ERC	Ethics Review Committee
GCP	Good Clinical Practice
ICDDR,B	International Centre for Diarrhoeal Disease Research, Bangladesh
ITT	Intention-to-treat
MIC	Minimum Inhibitory Concentration
MRI	Magnetic Resonance Imaging
NGOs	Non-governmental Organisations
ORS	Oral Rehydration Solution
PK	Pharmacokinetic
PP	Per-protocol
RRC	Research Review Committee
V. cholerae	Vibrio cholerae
WHO	World Health Organisation

0. Protocol outline

TRIAL OBJECTIVES

The objectives of this study are as follows:

(i) To compare the clinical and bacteriologic efficacy of a single dose of ciprofloxacin oral suspension (20 mg/kg), and erythromycin oral suspension administered every 6 hours for 3 days (12 doses of 12.5 mg/kg) in the treatment of children with clinically severe cholera due to Vibro cholerae (*V. cholerae)* O1 or O139. In particular, the objective of this study is to show that in the treatment of cholera in children caused by *V. cholerae* O1 or O139, the single dose of ciprofloxacin oral suspension is at least as effective as the 12 doses of erythromycin oral suspension administered every 6 hours for 3 days.

(ii) To determine the safety of ciprofloxacin oral suspension (particularly musculoskeletal safety) in comparison to erythromycin oral suspension among paediatric patients with cholera.

(iii) To determine the pharmacokinetics of ciprofloxacin oral suspension in children with dehydrating cholera.

OVERALL DESIGN AND PLAN OF TRIAL

This is a randomised, open, parallel group clinical trial to compare the efficacy and safety of a single dose of ciprofloxacin oral suspension 20 mg/kg with a 3-day course of erythromycin oral suspension administered in a dose of 12.5 mg/kg every 6 hours (12 doses) in the treatment of children, aged 2-15 years with clinically severe cholera due to *V. cholerae* O1 or O139.

Eligible patients will be admitted to the Clinical Study Ward of the Dhaka and Matlab Hospitals of ICDDR,B. Upon admission, their weight (dehydrated weight) and vital signs will be recorded, and a thorough physical examination, including assessment of dehydration (following WHO guidelines), will be made. Patients will then be rehydrated using intravenous Dhaka Solution (133, 13, 98 and 48 mmol/l of sodium, potassium, chloride and bicarbonate, respectively) over 3-4 hours. Thereafter, they will be observed over a 4-hour Observation Period when their hydration will be maintained using the rice-based oral rehydration solution (ORS) (containing 3.5, 2.5, 1.5 and 50 gram/l of sodium chloride, sodium bicarbonate, potassium chloride and rice powder). Dhaka Solution, as used for initial rehydration, will be used for patients whose hydration cannot be maintained by rice-based ORS.

Patients who have a stool output of 20 ml/kg or more during the Observation Period, and who have *V. cholerae* demonstrated in dark-field microscopic examination of their freshly passed stool sample, will be enrolled upon obtaining written informed consent of their parents or guardians. If possible, assent must be obtained from the child. Patients will then be randomly assigned to receive one of the two treatment regimens.

Children will be hospitalised for 5 days, from the initiation of study drug or until resolution of their diarrhoea, whichever will be longer, and they will be asked to return for a follow-up evaluation 10 to 14 days after study entry. Patients are to return for a further follow-up visit at 4 to 6 weeks (Day 28 to Day 42).

Patients who develop joint changes during therapy, or during the follow-up period, must be followed up. Any new objective finding noted on clinical joint or gait assessment will be thoroughly evaluated by the investigator. This evaluation may include diagnostic procedures, such as MRI and/or joint fluid assessments, as appropriate. Patients with joint changes during therapy, or during the follow-up period, should be followed up until:

a) The adverse event has been resolved

or

b) Until further change in the patient's condition is unlikely and a final causality assessment has been made. This may be shorter or longer than 3 months from the time of discharge.

Medical history will be obtained and a thorough physical examination will be performed daily. Vital signs and intake/output records will be maintained as from the initiation of rehydration.

Patients will be closely monitored through bacteriological and laboratory assessments. Blood, urine and stool specimens will be taken at various time points. Stool culture for enteric pathogens will be done before initiation of the study drug, on study Day 3 and at follow-up visits. Rectal swab culture for *V. cholerae* will be done on each day of the study during the hospitalisation period, and at follow-up (10 to 14 days and 4 to 6 weeks). Complete blood count, serum electrolytes and creatinine, total bilirubin, SGPT and alkaline phosphatase will be determined before initiation of study drug and on study Day 5. (If the baseline creatinine is > 200 mcmol/L, creatinine will also be determined 24 hours post-administration of first dose of study medication, and any patient with a creatinine > than 200 mcmol/L will be considered as suffering from renal failure and will be withdrawn from the trial.) If possible, urinalysis will be done before initiation of drug therapy and on Day 5 of the study. Serum concentration of ciprofloxacin will be determined on the first day of the study at various time intervals after the first dose of the study drug.

DOSAGE AND ADMINISTRATION

Ciprofloxacin will be administered orally in suspension formulation as a single dose of 20 mg/kg body weight (maximum dose will be 750 mg). Erythromycin will be administered in a dose of 12.5 mg/kg body weight every 6 hours for 3 days (maximum individual dose of 500 mg; total 12 doses). Study drugs will be administered by using a syringe without a needle to allow for precise dosing. If the child vomits within 30 minutes of administration of study drug, any other treatment may be given. Such patients will be valid for safety analysis, but invalid for the efficacy analysis.

TRIAL POPULATION

Primary diagnosis

Cholera due to *V. cholerae* O1 or O139 of ≤ 24 hours duration.

Selection of patients

A total of 160 evaluable patients (who are infected with *V. cholerae* O1 or *V. cholerae* O139) and who will have completed 5 days of the study, will be required for this study. Inclusion and exclusion criteria of the study will be as follows:

Inclusion criteria

- Age: 2-15 years.
- Gender: Both.
- Duration of illness: ≤ 24 hours.
- Written informed consent for participation in the study from either of the parents, or guardian, and oral assent from children aged ≥ 8 years.
- Severe dehydration according to World Health Organisation (WHO) guidelines[18].
- Positive stool dark-field microscopic examination for *V. cholerae.*

Exclusion criteria

- History of receiving any antimicrobial agent (including study drugs) effective in the treatment of *V. cholerae* within 72 hours of screening.
- Concomitant infection(s) requiring antimicrobial therapy.
- A concomitant illness that may interfere with the evaluation of outcome or safety of the study drugs.
- Patients with known chronic renal insufficiency. [As all cholera patients with moderate to severe dehydration have pre-renal insufficiency on admission, and as it is not possible to detect whether a patient has renal failure until the patient has been hydrated for at least 24 hours, serum creatinine will be checked 24 hours post-administration of first dose of study medication, on Day 5, and at any time as clinically indicated. (If the baseline creatinine is > 200 mcmol/L, any patient with creatinine > than 200 mcmol/L 24 hours post-administration, will be considered as suffering from renal failure and will be withdrawn from the trial.)]
- Patients with known cardiac or hepatic impairment, i.e. SGOT/SGPT or bilirubin > 3 times the upper limit of normal, and patients with a history of central nervous system (CNS) disorders (known risk of experiencing seizures, a history of convulsive disorders or head injury trauma, currently on anti-seizure medication or within two months post-stroke).
- Patients previously enrolled in the study.
- Patients participating in any clinical study within one month prior to study entry.
- Patients' known to have AIDS.
- Patients treated with quinolones in the 14 days prior to the study.
- Patients known to have underlying rheumatological disease, joint problems, etc.

- Patients with a known hypersensitivity to any of the study drug regimens or related compounds (including fluoroquinolones and macrolides).
- Female patients who are lactating, or are sexually active and using unreliable contraception.
- Patients having a known underlying rheumatological disease, joint problems secondary to trauma or pre-existing conditions known to be associated with arthropathy.
- Patients with conditions precluding the performance of a reliable series of musculoskeletal examinations are to be excluded from trial participation.

Note: Patients will be enrolled at any time of the day, and on any day of the year, subject to fulfilment of enrolment criteria.

CRITERIA FOR TRIAL OBJECTIVES AND SAFETY EVALUATION

Criteria for evaluation of safety

All adverse reactions or unusual events must be described on the adverse event page of the case report form (CRF). This report must include a description of the adverse event including the time of onset and duration, whether or not the study treatment was discontinued, what corrective measures were taken, the outcome of the adverse event, and the relation to study drug. Safety will also be evaluated through careful reporting of laboratory tests of renal, hepatic and haematological functions; and serial examination of the joints performed before, during and after administration of the study drug.

Criteria for evaluation of efficacy

The aims of this study are to investigate the efficacy of a single dose of ciprofloxacin oral suspension for treatment of severe cholera in children due to *V. cholerae* O1 or O139, and to evaluate the safety of the drug in children.

As measures of efficacy, the following outcome measures will be compared:

Primary outcome measures

- Rates of clinical success at test of cure visit.

Secondary outcome measures

- Rates of bacteriologic success at test of cure visit.
- Duration of diarrhoea.
- Rates of clinical relapse.
- Rates of bacteriologic relapse.
- Duration of faecal excretion of *V. cholerae* O1 or *V. cholerae* O139.
- Measurements of six-hourly volume of watery stool will be done for the period in which patients are hospitalised.
- Proportion of patients requiring unscheduled intravenous fluids.
- Frequency of vomiting and its volume.
- Frequency of stool per day.

- Frequency of vomit per day.
- Safety.
- PK-assessment of serum and stool.

Definitions

Response to therapy will be evaluated at test of cure visit (Day 5).

Test of cure (end of Day 5)

The clinical response will be defined as follows:

- **Clinical success:** cessation of watery stool within 48 hours of administration of the study drug without recurrence by Day 5.
- **Clinical failure:** continuation of watery stool for > 48 hours, or initial cessation with recurrence on or before Day 5.

The bacteriological response will be defined as follows:

- **Bacteriological success:** eradication of the infecting *V. cholerae* organism from faecal specimens within 48 hours of initiation of the study drug without its subsequent isolation by Day 5.
- **Bacteriological failure**: isolation of infective *V. cholerae* O1 or O139 from a faecal sample on Days 3, 4 or 5.

Pharmacokinetic criteria

- **Pharmacokinetics:** ciprofloxacin concentrations will be determined for both stool and serum.
  - To determine the pharmacokinetics of ciprofloxacin, blood samples will be taken from each patient during one of four time periods; before drug administration; within 1 hour of first drug administration; 1-2 hours after first drug administration; and 4-12 hours after the first dose. A 1-ml sample will be required at each collection time.
  - Stool will be collected 6-hourly for the first 72 hours of the study (thus 12 stool samples per patient).
  - Concentrations will be determined using the HPLC-method. Concentrations will be determined on both uncentrifuged and centrifuged supernatant samples, to determine how much of the drug is protein bound.
  - Erythromycin concentrations will be determined only in stool, which is the active site of infection.

Description of subject groups for analysis

Pharmacokinetic population

Ciprofloxacin concentrations will be determined in the first 20 patients aged 2-5 years, and in the first 20 patients, aged > 5 years who will enter the study. Ciprofloxacin concentrations will also be determined in all patients who vomit within 30 minutes of receiving their first dose of medication.

Safety analysis population

Patients will be included in the safety analysis if they receive at least one dose of study treatment.

ITT analysis population

Patients will be included in the ITT analysis if they have been diagnosed with cholera due to *V. cholerae* O1 or O139, and if they have received at least one dose of study treatment. Patients regarded as treatment failures (as discussed above) will be included in the ITT analysis.

PP analysis population

Patients will be included in the PP analysis if they satisfy the criteria for a valid course. Patients regarded as treatment failures (continuation of watery stool for > 48 hours) will be included in the PP analysis.

Definition of a valid course

For a course of therapy to be valid for evaluating the efficacy of treatment, the following criteria must be met and documented in the CRF:

- *V. cholerae* O1 or O139 must have been isolated from either the stool or rectal swab culture performed before initiation of the study drug on the day of admission (pre-therapy).
- No other systemic antimicrobial agent must have been administered concomitantly with the study drug unless it is done consequent to declaration of "clinical failure".
- Documented adequate compliance with administration of the single ciprofloxacin dose, or at least 10 doses of the erythromycin medication. Non-compliance will also be considered if two consecutive doses of the study medication are missed by a patient.
- No protocol violations influencing the treatment efficacy.
- The patient must have met the inclusion/exclusion criteria.

STATISTICAL PLAN

Sample size estimation

The primary efficacy variable is the clinical response of the patient. The aim of the study is to show that single-dose therapy with ciprofloxacin oral suspension (test treatment) is at least as effective as the 3-day treatment regimen with erythromycin. The anticipated cure rate for ciprofloxacin is at least 0.85, and for erythromycin at most 0.80. The statistical hypothesis and alternative are:

$H_o : P_T - P_R < -0.15$

$H_a : P_T - P_R \geq -0.15$

Rejection of the hypothesis allows one to conclude that the cure rate P_T for the test treatment is at most 15% less than the cure rate P_R of the reference treatment.

Given these assumptions and hypotheses, a power of 90%, and a two-sided significance level of 5%, a sample size of N = 80 patients per group are required to reject the above hypothesis (Farrington CP, Manning G. Statistics in Medicine 1990: 1447-1454). Assuming an invalidity rate of 10%, a total sample size of 180 patients is required.

Data management

All relevant study data will be entered into a computer using data management software (Clintrial 4.1). Data will be entered twice to ensure accuracy of data entry. Standard Bayer and study specific edit checks will be programmed for the data.

All data discrepancies and queries will be referred to the study centres, and an audit trail of all data corrections and updates will be maintained.

Disposition of patients/Enrolment characteristics

Adherence to the study protocol will be checked and all deviations from the study protocol, including withdrawals, will be documented. The number and frequency of protocol violations and withdrawals will be presented by treatment group. Demographic and baseline characteristics will be summarised by treatment group. Continuous data will be summarised by descriptive statistics (N, mean, median, standard deviation, minimum and maximum, and interquartiles) and categorical data by means of absolute and relative frequencies.

The comparability between the two treatment groups regarding demographic and baseline data will be assessed. Continuous variables will be compared by Student's t-test. Categorical variables will be compared by the chi square test or Fisher's exact test when appropriate.

Efficacy analysis

The efficacy variables (clinical and bacteriological response at test of cure visit) will be listed for all patients. The two treatment groups will be compared by calculating the Mantel-Haenszel point estimate and 95% confidence interval (CI) for the difference in success rates (clinical and bacteriological). For the single dose treatment with ciprofloxacin oral suspension to be declared at least as effective as the 3-day treatment with erythromycin oral suspension the lower bound of the 95% CI for the difference in clinical success rate at test of cure must be ≥ -0.15 (-15%).

The secondary efficacy variables will be listed for each patient, with descriptive statistics for each treatment group. With regard to duration of diarrhoea, the treatments will be compared using the log-rank test, and Kaplan-Meyer curves will be presented. The stool and vomit volumes, proportion of patients requiring unscheduled intravenous fluids, and frequency of vomiting will be compared descriptively.

Safety analysis

All safety variables will be analysed descriptively. Adverse events will be listed with detailed descriptions. Adverse events will be summarised by frequencies, the number of patients and percentage of patients according to body system categories.

The individual laboratory variables will be listed, with summary statistics for each treatment group. The frequencies of abnormal laboratory values will be given for each treatment group. All the other safety variables will be listed and summarised by means of summary statistics or relative and absolute frequencies.

Interim analysis

No interim analysis is planned.

1. Introduction

Cholera remains a major public health problem in Asia, Africa and Latin America. Its continued importance is reflected in the hundreds of thousands of cases, and tens of thousands of deaths that occurred when the seventh pandemic of cholera reached South America in 1991; the tens of thousands of deaths that occurred among Rwandan refugees; and the massive epidemics of cholera that occurred following the appearance of a new serogroup of cholera, *V. cholerae* O139, in Asia in 1993.

In countries where cholera is endemic, rather than epidemic, the majority of cholera morbidity and mortality occurs in children. Infection with *Vibrio cholerae* O1 or O139 is far more likely to cause dehydration than any of the other watery diarrhoeas of childhood, including those caused by enterotoxigenic *E. coli* and rotavirus[1]. If not effectively treated, cholera can lead to severe dehydration, hypovolemic shock, metabolic acidosis and death within a few hours of the onset of disease. The explosive epidemic form of cholera is associated with a very high case-fatality rate, as was demonstrated during the 1994 cholera epidemic among Rwandan refugees in Goma, Zaire when an estimated 20 000 persons died from cholera in a 4-week period[2].

Fluid replacement and antimicrobial therapy are the mainstays of therapy of moderate to severe cholera. Appropriate antimicrobial therapy reduces the volume and the duration of diarrhoea by approximately 50%, and thus shortens the duration of hospitalisation requirement for rehydration fluids. Furthermore, antimicrobials shorten the duration of faecal excretion of *V. cholerae* and thus reduce transmission of infection to others[3-5]. All of these effects make antimicrobial therapy of cholera a cost-effective intervention. Tetracycline, chloramphenicol, doxycycline, furazolidone, trimethoprim-sulfamethoxazole and erythromycin are all effective in the treatment of cholera when given for 3-5 days[3,6-8]. Single dose tetracycline and doxycycline therapies are also effective in the treatment of cholera, although bacterial eradication is slower than with multiple dose therapy. Tetracycline and doxycycline, however, are not recommended for use in children under 8 years of age, and in pregnant and lactating women. Chloramphenicol is a relatively toxic drug and not recommended for routine use in cholera.

Current therapy for cholera in children requires administration of an effective antimicrobial agent for 3 days. In one study, the rates of clinical success with a 1-day and a 3-day course of furazolidone therapy were 48% and 77% respectively. Although the difference was not statistically significant, it is clinically important, and a small sample size may be an explanation for the statistical insignificance[19]. Ciprofloxacin is effective in the treatment of cholera in multiple doses, but we have recently demonstrated that a single dose of ciprofloxacin is more effective than single dose doxycycline therapy of cholera in adults[9].

Treatment of cholera in children has been further complicated by the emergence of multiply resistant strains of *V. cholerae*. Strains resistant to tetracycline (which also implies resistance to doxycycline), furazolidone (the drug that has been most commonly used to treat childhood cholera), and trimethoprim-sulfamethoxazole have been reported from Asia (including Bangladesh), Africa and Latin America[10-17]. Currently, over 90% of the *V. cholerae* O1 isolates at the Treatment Centres of ICDDR, B are resistant to trimethoprim-sulfamethoxazole and furazolidone, and approximately 30% are additionally resistant to tetracycline [Unpublished observations].

Because of the high prevalence of multiply-resistant strains of *V. cholerae* and the lack of alternative agents, erythromycin has become the first-line therapy for cholera in children at the ICDDR,B. Erythromycin is administered in multiple doses for 3 days, and is associated with a high incidence of gastrointestinal adverse events. Because of the problem of resistance, lack of a safe drug for single-dose therapy for cholera in children, and proven efficacy of a single-dose of ciprofloxacin in the treatment of severe cholera in adults, it can be reasonably hoped that single-dose ciprofloxacin therapy may also be effective in the treatment of clinically severe cholera in children. A suspension formulation of the drug, suitable for administration in children, is now available for clinical trials. Although toxicity with this drug is small when used for short courses of therapy, such as would be for treatment of cholera, there remains a reluctance to use the drug in children, particularly due to a concern on the risks for arthropathy. However, in a recent study serious adverse events, including arthropathy, were not observed in any of the 71 children who had received ciprofloxacin suspension for 5 days for treatment of shigellosis[20]. Published reports both from the developing and developed countries indicate that ciprofloxacin is a safe drug for use in children[21-24].

2. Trial objectives

The objectives of this study are:

(i) To compare the clinical and bacteriologic efficacy of a single dose of ciprofloxacin oral suspension (20 mg/kg), and erythromycin oral suspension administered every 6 hours for 3 days (12 doses of 12.5 mg/kg) in the treatment of children with clinically severe cholera due to *V. cholerae* O1 or O139. In particular, the objective of this study is to show that in the treatment of cholera in children caused by *V. cholerae* O1 or O139, the single dose of ciprofloxacin oral suspension is at least as effective as the 12 doses of erythromycin oral suspension administered every 6 hours for 3 days.

(ii) To determine the safety of ciprofloxacin oral suspension (particularly musculoskeletal safety) in comparison to erythromycin oral suspension among paediatric patients with cholera.

(iii) To determine the pharmacokinetics of ciprofloxacin oral suspension in children with dehydrating cholera (blood and stool).

3. Investigators and other trial participants

Study Co-ordinator
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4. Test drug and control agents

4.1 Investigational product(s)

The following investigational products will be used in the study:

Ciprofloxacin group

Active ciprofloxacin oral suspension 5% (5 g ciprofloxacin in 100 ml) for single dose only. Ciprofloxacin will be administered orally in suspension formulation in a dose of 20 mg/kg body weight only once (maximum dose will be 750 mg).

Erythromycin group

Two bottles of 100 ml (200 mg/5 ml) of active erythromycin suspension for doses 1 to 12. Erythromycin will be administered in a dose of 12.5 mg/kg body weight every 6 hours for 3 days (maximum individual dose of 500 mg; total 12 doses).

Ciprofloxacin is manufactured by Bayer AG, Germany. Erythromycin (Paediathrocin manufactured by Abbott) will be bought and provided by Bayer AG.

4.2 Supply, packaging, labelling and storage

The study drugs will be supplied as suspension in light protected, brown glass bottles.

The labelling of ciprofloxacin suspension and erythromycin suspension will be done by Bayer Leverkusen. Each box will be clearly labelled with the following information:

"Study number"
"Bulk Batch No."
"Dosage: 20 mg/kg, once only (ciprofloxacin)
or 12.5 mg/kg 6 hourly for 3 days (erythromycin)"
"Random number"
"Patients initials (to be completed by the investigator)"
"Bottle no."
"Centre no."
"Store below 25°C"
"For clinical trial use only".

The drugs provided by Bayer AG will be used exclusively for the study as specified in the protocol. All drug supplies will be retained by the Research Officer working for the protocol in a safe and secure place at controlled room temperature of < 25°C and protected from light until use. The Research Officer will confirm receipt of the study drugs on the Drug Supply Confirmation Form, a copy of which will be returned to Bayer AG. The Research Officer will also be responsible for dispensing the study medication as specified. The study-ward nurse will be responsible for administering the drug to the patients. The Research Officer will also be responsible for maintaining drug inventory and accountability records. All unused material must be accounted for and returned to Bayer AG at the end of the study.

5. Investigational plan

5.1 Overall design and plan of trial

This is a randomised, open, parallel group clinical trial to compare the efficacy and safety of a single dose of ciprofloxacin oral suspension 20 mg/kg with a 3-day course of erythromycin oral suspension administered in a dose of 12.5 mg/kg every 6 hours (12 doses) in the treatment of children, aged 2 to 15 years, with clinically severe cholera due to *V. cholerae* O1 or O139.

The sample size of the study has been determined to include 80 valid patients in each of the two treatment groups, i.e. a total of 160 patients. It is estimated that approximately 180 children, fulfilling eligibility criteria, will be initially enrolled to ensure the desired sample size.

Eligible patients will be admitted to the Clinical Study Ward of the Dhaka and Matlab Hospitals of ICDDR,B. Upon admission, their weight (dehydrated weight) and vital signs will be recorded, and a thorough physical examination including assessment of dehydration (following WHO guidelines) will be made. Patients will then be rehydrated using intravenous Dhaka Solution (133, 13, 98 and 48 mmol/l of sodium, potassium, chloride and bicarbonate respectively) over 3-4 hours. Thereafter, they will be observed over a 4-hour Observation Period when their hydration will be maintained using the rice-based ORS (containing 3.5, 2.5, 1.5 and 50 gram/l of sodium chloride, sodium bicarbonate, potassium chloride and rice powder). Dhaka Solution, as used for initial rehydration, will be used for patients whose hydration cannot be maintained by rice-based ORS.

Patients who have a stool output of 20 ml/kg or more during the Observation Period, and who have *V. cholerae* demonstrated in dark-field microscopic examination of their stool sample, will be enrolled upon obtaining written informed consent of their parents or guardians. If possible, assent must be obtained from the child. Patients will then be randomly assigned to receive one of the two treatment regimens.

Children will be hospitalised for 5 days or until resolution of their diarrhoea whichever is longer, and they will be asked to return for a follow-up evaluation 10 to 14 days after study entry. Patients are to return for a further follow-up visit at 4 to 6 weeks (Day 28 to Day 42).

Patients who develop joint changes during therapy or during the follow-up period will be followed up for a further 3 months from the time of discharge. Any new objective finding noted on clinical joint or gait assessment will be thoroughly evaluated by the investigator. This evaluation may include diagnostic procedures, such as MRI and/or joint fluid assessments, as appropriate. Patients with joint changes during therapy, or during the follow-up period, should be followed up until:

a) The adverse event has been resolved
   or
b) Until further change in the patient's condition is unlikely and a final causality assessment has been made. This may be shorter or longer than 3 months from the time of discharge.

A medical history will be obtained and thorough physical examination will be performed daily. Vital signs and intake/output records will be maintained for each 6-hour period from the time of administration of the first dose of the study drugs.

Patients will be closely monitored through bacteriological and laboratory assessments. Blood, urine and stool specimens will be taken at various time points. Stool culture for enteric pathogens will be done before initiation of the study drug, on study Day 3 and at follow-up visits. Rectal swab culture for *V. cholerae* will be done on each day of the study during the hospitalisation period, and at follow-up (10 to 14 days and 4 to 6 weeks). Complete blood count, serum electrolytes and creatinine, total bilirubin, SGPT and alkaline phosphatase will be determined before initiation of study drug and on study Day 5. (If the baseline creatinine is > 200 mcmol/L, any patient with creatinine > than 200 mcmol/L 24-hour post-administration, will be considered as suffering from renal failure and will be withdrawn from the trial.) Urinalysis will be done before initiation of drug therapy, and on Day 5 of the study. Serum concentration of ciprofloxacin will be determined on the first day of the study at various time intervals after the first dose of the study drug has been administered.

Efficacy of the study drug will be assessed by clinical and bacteriological outcomes. For each patient, the study period will be divided into three phases as follows:

Phase 1: Assessment of eligibility of enrolment in the study.
Phase 2: Hospitalisation period (5 days or until resolution of diarrhoea whichever is longer). Study days will be counted from the time of administration of the first dose of the study drugs, and each 24-hour period will constitute a study day.
Phase 3: Follow-up assessments: the interval between discharge of the patients from the hospital and the follow-up visits scheduled to occur 10 to 14 days after study entry, and 4 to 6 weeks after study entry.

5.2 Selection of subjects

5.2.1 Primary diagnosis

Cholera due to *V. cholerae* O1 or O139 of ≤ 24 hours duration.

5.2.2 Number of subjects

A total of 160 evaluable patients (patients who are infected with *V. cholerae* O1 or *V. cholerae* O139 and who will have completed 5 days of the study) will be required for this study.

5.2.3 Inclusion criteria

- Age: 2-15 years.
- Gender: Both.
- Duration of illness: ≤ 24 hours.
- Written informed consent for participation in the study from either of the parents, or guardian, and oral assent from children aged ≥ 8 years.

- Severe dehydration according to WHO guidelines (WHO guidelines filed in the investigator's file).
- Positive stool dark-field microscopic examination for *V. cholerae.*

5.2.4 Exclusion criteria

- History of receiving any antimicrobial agent (including study drugs) effective in the treatment of *V. cholerae* within 72 hours of screening.
- Concomitant infection(s) requiring antimicrobial therapy.
- A concomitant illness that may interfere with the evaluation of outcome or safety of the study drugs.
- Patients with known chronic renal insufficiency. [As all cholera patients with moderate to severe dehydration have pre-renal insufficiency on admission, and as it is not possible to detect whether a patient has renal failure until the patient has been hydrated for at least 24 hours, serum creatinine will be checked 24-hour post-administration of first dose of study medication, on Day 5, and at any time as clinically indicated. (If the baseline creatinine is > 200 mcmol/L, any patient with creatinine > than 200 mcmol/L 24-hour post-administration, will be considered as suffering from renal failure and will be withdrawn from the trial.)]
- Patients with known cardiac or hepatic impairment, i.e. SGOT/SGPT or bilirubin > 3 times the upper limit of normal, and patients with a history of central nervous system (CNS) disorders (known risk of experiencing seizures, a history of convulsive disorders or head injury trauma, currently on anti-seizure medication or within two months post-stroke).
- Patients previously enrolled in the study.
- Patients participating in any clinical study within one month prior to study entry.
- Patients known to have AIDS.
- Patients treated with quinolones in the 14 days prior to the study.
- Patients known to have underlying rheumatological disease, joint problems, etc.
- Patients with a known hypersensitivity to any of the study drug regimens or related compounds (including fluoroquinolones and macrolides).
- Female patients who are lactating, or are sexually active and using unreliable contraception.
- Patients having a known underlying rheumatological disease, joint problems secondary to trauma or pre-existing conditions known to be associated with arthropathy.
- Patients with conditions precluding the performance of a reliable series of musculoskeletal examinations are to be excluded from trial participation.

Note: Patients will be enrolled at any time of the day, and on any day of the year, subject to fulfilment of enrolment criteria.

5.3 Method of assigning subjects to trial groups and blinding procedure

Patients eligible for participation in this study will be randomly assigned to one of the two treatments.

"Code break cards" will be prepared, and will be retained by the investigator. Once, and only once a patient's eligibility for the study has been confirmed, the investigator will open the code break card with the lowest available number and allocate the patient to the treatment specified in the code break card.

5.4 Planned dosage and duration of treatment

5.4.1 Dosage and administration

Study drugs will be administered by a syringe without a needle to allow for precise dosing. If the child vomits within 30 minutes of administration of study drug, any other treatment may be given. Such patients will be valid for safety analysis, but invalid for the efficacy analysis.

Ciprofloxacin group

Ciprofloxacin will be administered orally in suspension formulation in a dose of 20 mg/kg body weight only once (maximum dose will be 750 mg).

Erythromycin group

Erythromycin will be administered in a dose of 12.5 mg/kg body weight every 6 hours for 3 days (maximum individual dose of 500 mg; total 12 doses).

5.4.2 Duration of treatment

Ciprofloxacin will be administered orally in suspension formulation in a dose of 20 mg/kg body weight only once (maximum dose will be 750 mg). Erythromycin will be administered in a dose of 12.5 mg/kg body weight every 6 hours for 3 days (maximum individual dose of 500 mg; total 12 doses).

5.5 Assessment periods

Efficacy of the study drug will be assessed by clinical and bacteriological outcomes. For each patient, the study period will be divided into three phases as follows:

Phase 1: Assessment of eligibility of enrolment in the study.

Phase 2: Hospitalisation period (5 days or until resolution of diarrhoea whichever is longer). Study days will be counted from the time of administration of the first dose of the study drugs, and each 24-hour period will constitute a study day.

Phase 3: Post-therapy assessments: the interval between discharge of the patients from the hospital and the follow-up visits scheduled to occur 10 to 14 days after study entry, and 4 to 6 weeks after study entry.

5.6 Observations and measurements: assessment for treatment effects

5.6.1 Pre- and during treatment procedures

Only patients who fulfil the inclusion and exclusion criteria, and for whom informed consent has been obtained, will be eligible for enrolment into the study. At the time of enrolment into the study patients will be assessed for the following information, which will be recorded in the CRFs:

Medical history

Information obtained will include history of the current medical illness; current underlying/accompanying diseases; surgical procedures; current medication; previous joint problems and previous use of quinolones; and the date of onset of all underlying/accompanying diseases, if known, at screening.

Demographic details

At screening the following information will be recorded in the CRFs: sex, race and age.

Physical examination

Physical examination will be performed at screening, during the observation period: Day 1, Day 2, Day 3, Day 4, and Day 5; 10 to 14 days follow-up and 4-6 weeks follow-up. A physical examination will include the following:

- Height/length and weight.
- Temperature (axillary).
- Pulse/heart rate.
- Respiratory rate.
- Abdominal signs and symptoms.
- Determination of dehydration status, and rehydration and maintenance of hydration per World Health Organisation guidelines.

Examination of the joints

Clinical examination of joint function

As a part of the physical examination, the ankles, knees, hips, wrists, elbows and shoulders will be examined for pain and tenderness, evidence of inflammation (redness, warmth, and swelling will lead to the exclusion of the patient) and active/passive range of motion. Other symptomatic joints will be examined as well.

Joint examinations will be performed as follows: before initiation of drug therapy daily during hospitalisation; at follow-up 10 to 14 days after study entry; and at 4 to 6 weeks after study entry. Children who develop a joint problem during therapy, or during the follow-up period, should be followed up until:

(a) The adverse event has resolved
or
(b) Until a further change in the patient's condition is unlikely and a final causality assessment has been made. This may be shorter or longer than 3 months from the time of discharge. All efforts will be made to examine the joints during and after completion by the same investigator. All findings will be recorded in the CRFs.

Laboratory assessments

- **Faecal cultures:** stool culture for enteric pathogens (*V.cholerae*, *Salmonella*, *Shigella* and *Campylobacter*) will be done before initiation of the study drug, Day 3 and *Salmonella*, *Shigella* and *Campylobacte* cultures will be done on patients who are symptomatic at the follow-up visits. A rectal swab will be done for isolation of *V. cholerae* O1 and O139 at baseline i.e. on the day of admission and before initiation of the study drug, on each day of hospitalisation, at the time of first follow up visit (10 to 14 days) and at 4 to 6 weeks follow-up.

- **Determination of antimicrobial susceptibility:** this will be done for *V. cholerae* and other enteric pathogens isolated from the specimens collected before initiation of drug therapy. Susceptibility to tetracycline, trimethoprim-sulfamethoxazole, chloramphenicol, erythromycin, furazolidone and ciprofloxacin will be done using the disc-diffusion method. In addition, the minimum inhibitory concentration (MIC) and susceptibility of the study isolates to only ciprofloxacin will be determined by E-test.
- **Microscopic examination of stool:** this will be done before initiation of study drugs and on study Day 4 for semi-quantitative assessment of presence of leukocytes and erythrocytes, as well as demonstration of haematophagous trophozoites of *E. histolytica* and other parasites and their ova.
- **Blood culture:** this will be done only when clinically indicated.
- **Haematology:** haematocrit, total and differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils) white blood cell counts, and platelet count will be done before initiation of the study medication on the day of admission (pre-therapy) and on study Day 5 (post-therapy). This will require drawing of about 0.5 ml of blood from a vein in the elbow of the patients.
- **Blood chemistry:** serum sodium, chloride, potassium, bicarbonate, creatinine, bilirubin, AST, ALT and alkaline phosphatase will be performed before initiation of the study drugs (pre-therapy) on the day of admission and on study Day 5 (post-therapy). This will require collection of about 4.0 ml of blood from a vein in the elbow of the patients on each of these occasions.
- **Pharmacokinetics:** ciprofloxacin concentrations will be determined for both stool and serum.
  - To determine the pharmacokinetics of ciprofloxacin, blood samples will be taken from each patient during one of four time periods; before drug administration; within 1 hour of first drug administration; 1-2 hours after first drug administration; and 4-12 hours after the first dose. A 3-ml blood sample (sufficient to yield 1 ml of plasma) will be drawn at each collection time.
  - Stool will be collected 6-hourly for the first 72 hours of the study (thus 12 stool samples per patient).
  - Concentrations will be determined using the HPLC-method. Concentrations will be determined on both uncentrifuged and centrifuged supernatant samples, to determine how much of the drug is protein bound.
  - Erythromycin concentrations will be determined only in stool, which is the active site of infection.

  The analysis will be conducted by Dr H Stass, Bayer. Samples will be transported to the Bayer laboratory in Germany.

  Instructions for transporting ciprofloxacin blood samples for the PK evaluation are as follows:
    - Protect samples during all steps from direct sunlight.
    - Blood samples should be drawn into NH4-heparin tubes.
    - Blood, adequate to produce 1 ml of plasma should be drawn at each sampling time (e.g. a 3-ml blood sample, sufficient to yield 1 ml of plasma).
    - Up to 2 hours after sampling, the blood should be centrifuged for 10 minutes at 2000 g and +20°C. The plasma must then be separated and transferred into appropriately labelled tubes (glass, polystyrene, or polypropylene).
    - Samples should be stored at about -20°C and shipped on dry ice.
    - Analyses must be performed within 24 months.

- **Urinalysis:** urine specimen will be tested for pH, protein, ketones, blood and glucose. General appearance will be determined, and microscopic examinations will be done for cells, casts and crystals. This will be done before initiation of the study drugs on the day of admission and on Day 5. Any casts or crystals will be described in detail.

Note: A flow chart of required tests and observations is presented in Appendix 12.1.1 and a clinical examination of joint functions is presented in Appendix 12.1.2.

<u>Case Management</u>

Clinical evaluation and laboratory studies

Patients will be hospitalised for at least 5 days. The following clinical evaluations will be performed on study patients:

- **Weighing**: before rehydration (dehydrated weight), after rehydration (rehydration weight) and just before administration of the study drug (after the 4-hour observation period; rehydration weight -2), and at 24 hour intervals from the time of administration of the first dose of the study drug during hospitalisation. An electronic weighing scale (Sartorius, accuracy 10 grams) will be used for this purpose.
- **Physical examination**: before rehydration, after rehydration, at the time of administration of the study drug, and then daily during hospitalisation. In addition to evaluation of hydration status, the history and physical examinations will also focus on adverse events including vomiting, gastrointestinal distress, rash, and joint assessment.
- **Vital signs**: axillary temperature, pulse and respiratory rates, and blood pressure will be recorded before rehydration, after rehydration, just before administration of study drug, and then every 6 hours during the study.
- **Quantitation of stool, urine and vomit volume**: this will be done for the rehydration and the observation periods, and then for each 6 hour period during the study.
- **Rehydration guidelines**: children admitted with severe dehydration according to the WHO guidelines will be given 100 ml/kg of Dhaka Solution over 3-4 hours. After initial rehydration, children will be evaluated and appropriate treatment plan will be used for continuation of further fluid therapy. Fluids given to maintain hydration should be based on the amount of ongoing stool losses as well as the child's willingness to drink. Fluid therapy will continue until diarrhoea stops. If signs of dehydration reappear, fluid appropriate to the degree of dehydration will be administered and the study protocol will continue to be followed.
- **Feeding**: appropriate feeds for age will be provided.
- **Procedures to be followed in the case of pathological changes of the joint:** a radiological examination of the affected joint and the contra-lateral joint (i.e. normal joint opposite the affected joint) will be performed. Efforts will also be made to perform ultrasonographic and magnetic resonance imaging (MRI) examination of the affected and the contra-lateral joints and/or joint fluid assessments, as appropriate.

Laboratory evaluation

For evaluation of bacteriologic response to the treatment regimen, stool or rectal swab culture will be done on each day of the study for isolation and identification of *V cholerae* O1 or O139. Stool culture for enteric pathogens will be done before initiation of study drug, on Day 3 and follow-up visits.

Reporting treatment failures

If the study treatment is judged to have clinically failed, patients will be treated at the investigator's discretion.

5.6.2 Follow-up procedures

Follow-up 10 to 14 days after study entry

At the follow-up visit the following will be done:

- Physical examination, including weight and height or length.
- A rectal swab or stool sample culture for the isolation of *V cholerae*.
- *Salmonella*, *Shigella* and *Campylobacte* cultures will be done on patients who are symptomatic at the follow-up visits.
- A detailed examination of gait and joints, to include ankles, knees, hips, shoulders, wrists and elbows and also any other symptomatic joint.

Follow-up 4 to 6 weeks after study entry

- Recording of adverse events.
- A rectal swab or stool sample culture for the isolation of *V cholerae*.
- *Salmonella*, *Shigella* and *Campylobacte* cultures will be done on patients who are symptomatic at the follow-up visits.
- A detailed examination of gait and joints, to include ankles, knees hips, shoulders, wrists and elbows, and also any other symptomatic joint.

Long-term follow-up

Patients who develop joint changes during therapy or during the follow-up period should be followed up until:

(a) The averse event has resolved
or
(b) Until a further change in the patient's condition is unlikely and a final causality assessment has been made. This may be shorter or longer than 3 months from the time of discharge.

Any new objective finding noted on clinical joint or gait assessment will be thoroughly evaluated by the investigator. This evaluation may include diagnostic procedures, such as an MRI and/or joint fluid assessments, as appropriate.

5.7 Subject's compliance

The oral study drugs will be administered in the Study Ward of the Clinical Research Centre of ICDDR,B. by study nurses. The prescription chart and the drug inventory log will provide documentation of preparation and administration of the study treatment. Patients randomised to the erythromycin arm must take at least 10 doses of erythromycin medication. Patients assigned to the ciprofloxacin arm must take the single dose of ciprofloxacin in order to be considered compliant with the protocol. Non-compliance will also be considered if two consecutive doses of the study medication are missed by a patient.

5.8 Concomitant therapy

All concomitant medication will be recorded in the case report form. Information recorded will be the name of the drug(s), individual, daily and total dose (or range of doses) received, and dates of administration.

5.8.1 Medication not allowed

Concomitant treatment with warfarin (or products containing coumarin derivatives), theophylline, non-steroidal anti-inflammatory drugs or cyclosporin will be avoided, except when such therapy is indicated and appropriate monitoring as well as laboratory investigations have been done. Concomitant treatment with glibenclamide and probenicid should also be avoided.

Concomitant treatment with oral/parenteral antimicrobial agents must be avoided. Patients who receive concomitant antimicrobials will be considered protocol violators and will be invalid for analysis of efficacy. However, should concomitant antibiotic therapy be initiated for the primary illness on the basis of clinical necessity, although unlikely, the patient will be assessed as a treatment failure.

Treatment with iron, sucralfate or antacids and highly buffered drugs containing magnesium, aluminium or calcium reduce the absorption of ciprofloxacin and should be avoided.

5.8.2 Medication allowed

Paracetamol may be used for control of fever, although this will be unlikely in association with cholera. The proportion of patients who may require paracetamol in the two treatment groups will be compared during analysis.

Ciprofloxacin should be administered either 1 to 2 hours before or at least 4 hours after administration of antacids, iron, sucralfate and highly buffered drugs containing magnesium, aluminium or calcium.

5.9 Removal of subjects from trial

It is the responsibility of the investigator to maintain the patients in the study. However, a patient may be withdrawn prematurely from the study for any of the reasons mentioned below. The reasons must be documented in the CRFs:

- Lack of clinical efficacy:
  In the event no response to treatment (significant remission of clinical signs and symptoms) is observed, or if the clinical condition of the patient deteriorates within 48 hours of initiation of the study drugs, the study drug will be stopped and such patients will be treated with an effective alternative drug as described under Section 5.6.1, Reporting treatment failures.
- Significant adverse events and clinical deterioration:
  In the event of a significant adverse event or deterioration in the clinical condition which would preclude further participation in the study, for example:
  - Serious toxic or allergic reaction.
  - Intercurrent diseases.
  - Aggravation of a concomitant disease.
  - Serious laboratory abnormality.
- Withdrawal of consent.
- Protocol violations.
- If the child vomits within 30 minutes of administration of study drug, any other treatment may be given and the patient will be withdrawn from the trial.

Procedures at premature termination of treatment

If a patient's clinical condition shows no sign of improvement or deteriorates 48 hours after initiation of the study drug, or if a patient develops a serious adverse event or allergic reaction, or if a superinfection develops, or if both the admission stool and rectal swab culture fail to grow *V. cholerae*, the study drug will be stopped and appropriate management will be instituted. However, before institution of any other antimicrobial agent such patients will be clinically evaluated and appropriate laboratory tests, including cultures, will be performed to ensure that the information required to evaluate the discontinued study drug therapy will be available and recorded on the CRFs. Patients who receive at least one dose of the study drug will be evaluated for safety. Every effort will be made to follow-up such patients, including patients who are dropped from the study for any reason. Trained health workers will be sent to locate patients who fail to show up for the follow-up assessments at their homes. Parents will be encouraged to comply with the follow up visit.

Follow-up procedures for patients prematurely withdrawn from the study

All patients who receive the study drug should be followed-up for 10 to 14 days after study entry. This should be done even if no adverse events or abnormal laboratory values are evident during hospitalisation. As indicated above, patients who develop any adverse event will be closely observed until the effect is reversed, or until a further change in the patient's condition is unlikely, and after a final causality assessment has been made. If a patient discontinues participation in the study for any reason, a final evaluation will be made at the time of discontinuation or as soon as possible thereafter. The results of the final assessment, and the reasons for discontinuation of study drug, will be recorded in the CRF. In the event of premature termination of study due to an adverse event, the procedure as described in Section 5.3 will be followed. Study patients presenting with adverse events, including clinically relevant laboratory

test abnormalities, will be followed-up by the investigator. Assessments must be made of the seriousness, intensity and relation to the administration of the trial medication.

5.10 Criteria for evaluation of trial objectives and safety

5.10.1 Description of subject groups for analysis

Safety analysis population

Patients will be included in the safety analysis if they receive at least one dose of study treatment.

ITT analysis population

Patients will be included in the ITT analysis if they have been diagnosed with cholera due to *V. cholerae* O1 or O139 and have received at least one dose of study treatment. Patients regarded as treatment failures, as discussed above, will be included in the ITT analysis.

PP analysis population

Patients will be included in the PP analysis if they satisfy the criteria for a valid course. Patients regarded as treatment failures (continuation of watery stool for > 48 hours) will be included in the PP analysis.

Definition of a valid course

For a course of therapy to be valid for evaluating the efficacy of treatment, the following criteria must be met and documented in the CRF:

- *V. cholerae* O1 or O139 must have been isolated from either the stool or rectal swab culture performed before initiation of the study drug on the day of admission (pre-therapy).
- No other systemic antimicrobial agent must have been administered concomitantly with the study drug unless it is done consequent to declaration of "clinical failure".
- Documented adequate compliance with administration of the single ciprofloxacin dose, or at least 10 doses of the erythromycin medication. Non-compliance will also be considered if two consecutive doses of the study medication are missed by a patient.
- No protocol violations influencing the treatment efficacy.
- The patient must have met the inclusion/exclusion criteria.
- Efficacy data from the test of cure visit is available, unless there has been an earlier treatment failure.

Pharmacokinetic population

Ciprofloxacin concentrations will be determined in the first 20 patients aged 2-5 years, and in the first 20 patients aged > 5 years who enter the study. Ciprofloxacin concentrations will also be determined in all patients who vomit within 30 minutes of receiving their first dose of medication.

5.10.2 Trial objectives

The aims of this study are to investigate the efficacy of a single dose of ciprofloxacin oral suspension in comparison to erythromycin oral suspension for treatment of severe cholera in children due to *V. cholerae* O1 or O139, and to evaluate the safety (particularly musculoskeletal safety) of the drug.

Criteria for Evaluation of Study Objectives

As measures of effectiveness, the primary and secondary outcome measures will be compared.

Primary outcome measures

- Rates of clinical success at test of cure visit.

Secondary outcome measures

- Rates of bacteriologic success at test of cure visit.
- Duration of diarrhoea.
- Rates of clinical relapse.
- Rates of bacteriological relapse.
- Duration of faecal excretion of *V. cholerae* O1 or *V. cholerae* O139.
- Measurements of six-hourly volume of watery stool will be done for the period in which patients are hospitalised.
- Proportion of patients requiring unscheduled intravenous fluids.
- Frequency of vomiting and its volume
- Frequency of stool per day.
- Frequency of vomit per day.
- Safety.

Ciprofloxacin concentrations will be determined for both stool and serum. Stool will be collected in six-hourly for the first 72 hour of the study (thus 12 stool samples per patient). Blood samples will be taken from each patient during one of four time periods; before drug administration; within 1 hour of first drug administration; 1-2 hours after first drug administration; and 4-12 hours after the first dose. A 1-ml sample will be required at each time window.

Definitions

Response to therapy will be evaluated at test of cure visit (Day 5).

Test of cure (End of Day 5)

The clinical response will be defined as:

- **Clinical success:** cessation of watery stool within 48 hours of administration of the study drug without recurrence by Day 5.
- **Clinical failure:** continuation of watery stool for > 48 hours, or initial cessation with recurrence on or before Day 5.

The bacteriological response will be defined as:

- **Bacteriological success:** eradication of the infecting *V. cholerae* organism from faecal specimens within 48 hours of initiation of the study drug without its subsequent isolation by Day 5.
- **Bacteriological failure**: isolation of infective *V. cholerae* O1 or O139 from a faecal sample on Days 3, 4 or 5.

5.10.3 Safety

All patients who receive at least one dose of the study drug will be evaluated for safety. All adverse reactions or unusual events must be described on the AE page of the CRF. This report must include a description of the adverse event including the time of onset, duration, whether or not the study treatment was discontinued, what corrective measures were taken, the outcome of the adverse event, and the relation to the study drug. Safety will also be evaluated through careful reporting of laboratory tests of renal, hepatic and haematological functions and serial examination of the joints performed before, during and after administration of the study drug.

6. Warning / precautions

General

Please refer respectively to the ciprofloxacin suspension and erythromycin package inserts for warnings/precautions presented in Appendix 12.6.

Hypersensitivity and known adverse drug reactions to the investigational products and/or the class of products

Fluoroquinolone antibiotics such as ciprofloxacin are generally well tolerated and very rarely associated with serious or life-threatening adverse reactions (i.e. reactions possibly or probably related to drug therapy). Indeed, most of the adverse reactions associated with ciprofloxacin are mild and only infrequently discontinuation of treatment (i.e. < 2% of patients) is required. The reported adverse effects include metabolic/nutritional disorders (elevation of serum creatinine, BUN, hepatic enzymes, LDH, alkaline phosphatase), digestive disorders (nausea, vomiting and diarrhoea); skin and skin appendages (rash mainly), musculoskeletal (articular pains, myalgia, tendinopathy) and CNS disorders (headache, convulsive seizures and dizziness). Additional adverse effects include punctuate skin haemorrhage, haemorrhage bullae, vasculitis, Steven's-Johnson's Syndrome, interstitial nephritis and hepatitis. Effects on blood and blood constituents can occur and the most commonly seen are eosinophilia, leukopenia, leukocytosis and anaemia. Further information is given in the Investigator's Brochure.

Precautions for use

As with other quinolones, ciprofloxacin should be used with caution in patients with known or suspected CNS disorders such as severe cerebral arteriosclerosis, epilepsy and other factors that predispose to seizures. Serious and occasional fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving quinolone therapy. Such serious events require immediate emergency treatment as clinically indicated. Severe hypersensitivity reactions characterised by rash, fever, eosinophilia, jaundice and hepatic necrosis with fatal outcome have also been reported extremely rarely in patients receiving ciprofloxacin along with other drugs. As the possibility that these reactions were related to ciprofloxacin cannot be excluded, the drug should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity. Pseudomembranous colitis has been reported with nearly all antibacterial agents including ciprofloxacin, and thus it will be important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of antibacterial agents. As with other broad- spectrum antimicrobial agents, prolonged use of ciprofloxacin may result in overgrowth of non-susceptible organisms. Repeated evaluation of the patient's condition and microbial susceptibility testing is essential. If superinfection occurs during therapy appropriate measures should be taken.

Drug interactions

As with other quinolones, concurrent administration of ciprofloxacin with theophylline may lead to elevated serum concentrations of theophylline and prolongation of its elimination half-life with increased risk of theophylline-related adverse reactions. If concomitant use cannot be avoided, serum levels of theophylline should be monitored and dosage adjustments made as appropriate. Some quinolones, including ciprofloxacin, may interfere with the metabolism of

caffeine leading to reduced clearance of caffeine and prolongation of its plasma half-life. Quinolones have been reported to enhance the effects of the oral anti-coagulant warfarin or its derivatives. When these products are administered concomitantly, prothrombin time or other suitable coagulation tests should be closely monitored. Some quinolones, including ciprofloxacin, have been associated with a transient rise in serum creatinine in patients receiving cyclosporine concomitantly. Probenecid interferes with renal tubular secretion of ciprofloxacin and increases its serum concentration. As alkalisation of urine is associated with ciprofloxacin crystal formation, urine-alkalising agents should be avoided while receiving the drug. However, as children in Bangladesh rarely use the above-mentioned medicines, it is not planned to enrol any patient taking these medicines into this study.

Magnesium hydroxide or aluminium hydroxide-containing antacids may interfere with the absorption of oral ciprofloxacin resulting in reduced serum and urine concentration. Therefore, ciprofloxacin should be administered either 1-2 hours before. or at least 4 hours after administration of these preparations if their use can not be stopped. It is not anticipated that antacids will be administered to any child enrolled in this study.

Carcinogenesis, mutagenesis and impairment of fertility

Long term carcinogenicity studies in mice and rats have been performed. No carcinogenic or teratogenic effects of ciprofloxacin were noted in these species after daily oral administration of the drug for up to 2 years. Reproduction studies performed in mice, rats and rabbits using parenteral and oral administration did not reveal any evidence of teratogenicity, impairment of fertility, or impairment of peri-/post-natal development.

Overdose

If a dose greater than the prescribed study dose (20 mg/kg body weight of ciprofloxacin as a single dose, or 12.5 mg/kg individual dose of erythromycin) is inadvertently given to any patient, patients will be carefully observed. Observation will include monitoring of respiratory and cardiovascular functions, and appropriate treatment will be provided whenever indicated. Only a small amount of ciprofloxacin (< 10%) is removed from the body after haemodialysis or peritoneal dialysis. The entire history of the incident, and every action taken, should be carefully recorded. When appropriate, blood and urine samples should be obtained for determination of drug concentration. Such a situation will be considered a **Serious Adverse Event** and the appropriate documentation will have to be completed.

7. Ethical aspects and good clinical practice compliance

7.1 Good clinical practice

All clinical work conducted under this protocol is subject to Good Clinical Practice (GCP) rules, and this may include inspection by Bayer staff or representative, government authorities and/or Ethical Review Committee of ICDDR,B at any time. The investigator must agree to these inspections. The investigator must adhere to the above principles in addition to any applicable local regulations.

7.2 Informed consent and subject information

Informed Consent must be obtained from parents/guardians of each of the participating children in the study after of the aims, methods, anticipated benefits and potential hazards of the study has been explained to them. The investigator must also explain that the patients are completely free to refuse to enter the study or to withdraw from it at any time. This informed consent must be obtained in the presence of a witness and his/her signature together with the date must be obtained. If possible, assent must be obtained from the child.

Informed consent

Parents or guardians must provide informed consent for participation of their children in the study before enrolment. The investigators will explain the purpose and procedures of the study, tests to be administered, potential or possible hazards, and that patients may be withdrawn from the study at any time without compromising their treatment. Parents of patients to be included in the pharmacokinetic subset will have to give consent to this procedure specifically.

If it is not possible to obtain written consent because of the inability of the parents or guardians to read or write, they may indicate their consent by putting their thumb impression on the consent form, provided this is done after explaining the purpose and procedures of the study. Consent must be obtained in presence of a witness who will also put his/her signature on the consent form. A copy of the signed consent form will be given to the parents or guardians. The date of obtaining informed consent will be documented on the patient's hospital records.

Instructions to the parents/guardians

As children will be hospitalised, no specific instructions for drug ingestion will be provided. However, if discharged from the hospital before the end of the study, parents or guardians will be urged to bring back their children to the hospital for further assessments as outlined in this protocol. Parents or legal guardian will be instructed to report any unexpected adverse events or changes to the investigators immediately upon their occurrence. They will be cautioned that antacids must not be administered together with the study drug, and that in the event of a need antacids may be given 1-2 hours before or at least 4 hours after administration of the study drug. However, the use of antacids in this study is not anticipated.

7.3 Monitoring by the sponsor

7.3.1 Monitoring

All clinical work conducted under this protocol is subject to Good Clinical Practice (GCP) rules, and this may include inspection by the study monitor and/or Ethical Review Committee of ICDDR,B at any time. The investigators agree to the inspection of study-related records by the study monitor and/or Ethical Review Committee of ICDDR,B. The investigator must adhere to the following principles in addition to any applicable local regulations.

7.3.2 Investigational product control

Appropriate case report forms (CRFs) will be developed for recording of study data. Data of medical history, physical examination, laboratory values, and X-ray findings will be transcribed from printouts or patient files (source data) onto the CRF. All raw data including patient's files, laboratory results and radiographs will be considered as "source data", and will be retained in a secure place.

7.4 Documentation

Correspondence (e.g. with sponsors, Ethics Committee) relating to this clinical study will be kept in appropriate file folders. This includes appropriate records of telephone conversations, Email, faxes, and letter correspondence. Records of patients, source documents, CRFs, and drug inventory pertaining to the study must be kept on file. Records must be retained for a period of 15 years. Bayer must be notified at the end of the 15-year period before data can be moved or destroyed. Bayer will clarify if storage needs to be retained in accordance with the longer ICH retention data requirements at that time. If an investigator retires, moves or withdraws from an investigation, the responsibility for maintaining the records may be transferred to another person (sponsor, or other investigator) who will accept the responsibility, in concurrence with the Director of the Clinical Sciences Division, ICDDR,B.

The data specified in the protocol will be recorded in the CRF. Data should be clearly legible and recorded in black ballpoint pen. Where data are corrected, the original entry should be crossed out completely with a single line and completely rewritten. The person who amends the entry should initial and date the correction. The CRFs must be kept in order and up-to-date so that they always reflect the latest observations on the subjects enrolled in the study. CRFs must be completed legibly for each subject enrolled in the study and signed-off by the investigator. This should be done as soon as possible after completion of therapy. A monitor will review and collect the CRF.

Source documents must be maintained for all patients enrolled in the study. The source data is deemed to be the medium on which a parameter is originally recorded, e.g. case history notes. This source data must be made available to the Clinical Research Scientist or auditor for source data verification.

Personnel log detailing all staff involved in the study, will be kept in the Investigator file. This will contain an example of each individual's handwriting, what tasks they are permitted to carry out, and their job titles.

The investigator should maintain the individual subject files separate from the CRFs. The files should include visit dates of each subject, records of vital signs, medical history or examinations administered, laboratory results, concomitant treatment, any adverse event encountered and other notes deemed appropriate. This constitutes "source data". All entries on the CRFs must be backed up by source data.

Each subject's file should have attached to it the original signed Informed Consent. When the study treatment is completed, the Informed Consent should be kept on file with a copy of the completed CRF in the appropriate file folder provided, or a note made indicating where the records can be located. All records should be kept in conformance to applicable national laws, regulations and ICH requirements.

All original laboratory reports should be available for review in each subject's file. It is important that the original reports are available for review because of the possibility of inaccuracies or errors in transcribing data from original records to the CRF.

The investigator must agree to allow the Regulatory Authority representatives or members of the Local Ethics Committee (RRC &ERC) and Bayer representatives direct access to any trial related documents.

7.5 Premature termination of trial / closure of centre

If for any reasons the sponsor and the investigator together feel that this study should be terminated prior to its completion, an appropriate schedule and conditions for such termination will be instituted.

Reasons for premature termination of study:

- If a serious adverse event probably related to the drug administration occurs or if a significant change in the benefit-risk ratio for patients occurs, where continuation of the study would put the patients at undue risk.
- If the use of the study drug or one of its dosages becomes "no longer justifiable".

A premature termination of the study should be based on mutual agreement between investigator and sponsor.

In addition, Bayer may decide to close a centre prematurely for the following reasons:

- If there is clear evidence that the centre is unable to recruit at a reasonable rate as agreed at the outset of the study. As far as possible this should occur after mutual consultation.
- In case of obvious non-compliance with the protocol.

In the event of a study being discontinued prematurely, all study materials (completed, partially completed, and empty CRFs, study medication, etc.) must be returned to Bayer.

8. Adverse events

8.1 Adverse event monitoring

Each subject must be carefully monitored for adverse events. This includes clinical laboratory test variables. An assessment must be made of the seriousness, intensity and relation to the administration of the trial medication. In the event of an adverse event, the investigator will decide if the study will be continued or terminated for the patient. If treatment is required for management of a patient developing an adverse event, such treatment will be directed at the most prominent symptom. In the event of a serious adverse event, the study medication will be stopped, the patient will receive appropriate treatment, and the patients will be closely observed until reversal of the event and the patient has stabilised.

8.2 Adverse event definitions

Adverse event (AE)

Any adverse event associated with the use of a drug in humans, whether or not considered drug related, includes the following: an adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from an overdose whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action.

Serious adverse event

Includes an adverse event occurring at any dose that results in any of the following outcomes: death, a life-threatening drug experience, inpatient hospitalisation or prolongation of existing hospitalisation, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered serious adverse drug events when, based upon appropriate medical judgement, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dycrasias or convulsions that do not result in inpatient hospitalisation, or the development of drug dependency or drug abuse.

Life threatening means that the patient was, in the view of the investigator, at immediate risk of death from the reaction as it occurred. This does not include an AE that, had it occurred in a more serious form, might have caused death.

Disability means a substantial disruption of a person's ability to conduct normal life's functions.

In cases of overdose only events consequent to an overdose are reportable.

Unlisted (unexpected) adverse event

Any adverse drug experience, the specificity or severity of, which is not consistent with the current Investigators' Brochure (or Package Insert for marketed products).

Relation to investigational product

The assessment of the relationship of an adverse event to the administration of study drug (none, unlikely (remote), possible, probable, not assessable) is a clinical decision based on all available information at the time of the completion of the case report form.

None - includes: (1) the existence of a clear alternative explanation (e.g. mechanical bleeding at surgical site); or (2) non-plausibility (e.g., the patient is struck by an automobile at least where there is no indication that the drug caused disorientation that may have led to the event; cancer developing a few days after drug administration).

Unlikely (remote) - a clinical event, including lab abnormality, with an improbable time sequence to drug administration and in which other drugs, chemicals or underlying disease provide plausible explanation.

Possible - a clinical event, including laboratory abnormality, with a reasonable time sequence to administration of the drug, which could also be explained by concurrent disease* or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

Probable - a clinical event including lab abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease* or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge).

Not assessable - a report of an AE which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

* Concurrent disease includes concomitant, intercurrent and underlying disease/condition. Concomitant disease - any other illness the subject may have at the time of entering the clinical trial. Intercurrent disease - any other illness the subject may develop during the clinical trial. Underlying disease - the illness which is the indication for study drug therapy.

Factors to be considered include:

- **The temporal sequence from drug administration** (The event should occur after the drug is given. The length of time from drug exposure to event should be evaluated in the clinical context of the event.)
- **Recovery on discontinuation (dechallenge), recurrence on reintroduction (rechallenge)** (Subject's response after drug discontinuation (dechallenge) or subjects response after drug re-introduction (rechallenge) should be considered in the view of the usual clinical course of the event in question.)
- **Underlying, concomitant, intercurrent diseases** (Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.)

- **Concomitant medication or treatment** (The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them may be recognised to cause the event in question.)
- **Known response pattern for this class of drug** (Clinical/preclinical.)
- **Exposure to physical and/or mental stresses** (The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.)
- **The pharmacology and pharmacokinetics of the test drug** (The pharmacokinetic properties (absorption, distribution, metabolism and excretion) of the test drug (s) the subject is taking, coupled with the individual subject 's pharmacodynamics should be considered.)

Intensity (severity) of the event

The following classification should be used:
Mild: usually transient in nature and generally not interfering with normal activities.
Moderate: sufficiently discomforting to interfere with normal activities.
Severe: prevents normal activities.

8.3 Adverse event documentation

All adverse events occurring during the trial and follow-up period must be fully recorded in the subject's case record.

Documentation must be supported by an entry in the subject's file. Laboratory test abnormalities considered to be clinically relevant, e.g., causing the subject to drop out of the trial, requiring treatment, causing apparent clinical manifestations, or if the investigator believes the event to be relevant, should be reported as an adverse event. Each event should be described in detail along with start and stop dates, intensity, relationship to investigational product, action taken and outcome.

8.4 Reporting of serious adverse events

Serious adverse events are not anticipated with either of the study drugs. However, if a study patient reports a serious adverse event, the study drug will be stopped, the event will be appropriately treated, and the adverse event form of the CRF will be completed. Information related to serious adverse events must also be recorded on the Serious Adverse Drug Experience Report Form separate from the information in the CRF. Bayer AG, the study monitor, and the Ethical Review Committee of the ICDDR,B must be notified of an adverse event occurrence within 24 hours by the investigators.

The Serious Adverse Event Report must be sent directly to the **AE Management Team in Germany, Fax No: +49 202 368 228.**

The Local Drug Safety Monitor's details are as follows:

Dr Wolf-Dieter Sittner
Bayer (Singapore) Pte Ltd
9 Benoi Sector
Singapore 629844
Telephone: (65) 261 3389 (Gladys X 571)
Facsimile: (65) 266 4866
E-mail: wolfdieter.sittner.ws@bayer-ag.de

Adverse events and serious adverse events occurring during the trial are to be followed up until resolved or until no change in the patient's condition is expected. Adverse events or serious adverse events noted during the follow-up phase (Week 4 - 6) are to be reported and followed up as applicable.

9. Statistics

9.1 Sample size estimation

The primary efficacy variable is the clinical response of the patient. The aim of the study is to show that single-dose therapy with ciprofloxacin oral suspension (test treatment) is at least as effective as the 3-day treatment regimen with erythromycin. The anticipated cure rate for ciprofloxacin is at least 0.85, and for erythromycin at most 0.80. The statistical hypothesis and alternative are:

$H_0 : P_T - P_R < -0.15$

$H_a : P_T - P_R \geq -0.15$

Rejection of the hypothesis allows one to conclude that the cure rate P_T for the test treatment is at most 15% less than the cure rate P_R of the reference treatment.

Given these assumptions and hypotheses, a power of 90%, and a two-sided significance level of 5%, a sample size of N = 80 patients per group are required to reject the above hypothesis (Farrington CP, Manning G. Statistics in Medicine 1990: 1447-1454). Assuming an invalidity rate of 10%, a total sample size of 180 patients is required.

Pharmacokinetics

The first 20 patients aged 2 to 5 years and the first 20 patients, aged > 5 years who enter the study will be evaluated for PK.

9.2 Data management

All relevant study data will be entered into a computer using data management software (Clintrial 4.1). Data will be entered twice to ensure accuracy of data entry. Standard Bayer and study specific edit checks will be programmed for the data.

All data discrepancies and queries will be referred to the study centres, and an audit trail of all data corrections and updates will be maintained.

9.3 Disposition of patients / Enrolment characteristics

Adherence to the study protocol will be checked and all deviations from the study protocol, including withdrawals, will be documented. The number and frequency of protocol violations and withdrawals will be presented by treatment group. Demographic and baseline characteristics will be summarised by treatment group. Continuous data will be summarised by descriptive statistics (N, mean, median, standard deviation, minimum and maximum, and interquartiles) and categorical data by means of absolute and relative frequencies.

The comparability between the two treatment groups regarding demographic and baseline data will be assessed. Continuous variables will be compared by Student's t test. Categorical variables will be compared by the chi square test or Fisher's exact test when appropriate.

9.4 Efficacy analysis

The efficacy variables (clinical and bacteriological response at test of cure visit) will be listed for all patients. The two treatment groups will be compared by calculating the Mantel-Haenszel point estimate and 95% confidence interval for the difference in success rates (clinical and bacteriological). For the single dose treatment with ciprofloxacin oral suspension to be declared at least as effective as the 3-day treatment with erythromycin oral suspension the lower bound of the 95% CI for the difference in clinical success rate at test of cure must be ≥ -0.15 (-15%).

The secondary efficacy variables will be listed for each patient, with descriptive statistics for each treatment group. With regard to duration of diarrhoea, the treatments will be compared using the log-rank test, and Kaplan-Meyer curves will be presented, if appropriate, otherwise the data will be analysed descriptively using median duration. The stool and vomit volumes, proportion of patients requiring unscheduled intravenous fluids, and frequency of vomiting will be compared descriptively.

9.5 Safety analysis

All safety variables will be analysed descriptively. Adverse events will be listed with detailed descriptions. Adverse events will be summarised by frequencies, the number of patients and percentage of patients according to body system categories.

The individual laboratory variables will be listed, with summary statistics for each treatment group. The frequencies of abnormal laboratory values will be given for each treatment group. All the other safety variables will be listed and summarised by means of summary statistics or relative and absolute frequencies.

9.6. Pharmacokinetic analysis

Ciprofloxacin concentrations will be determined in the first 20 patients, aged 2-5 years, and in the first 20 patients, aged > 5 years who will enter the study. Ciprofloxacin concentrations will also be determined in all patients who vomit within 30 minutes of receiving their first dose of medication.

Ciprofloxacin concentrations will be determined on both stool and serum. Stool will be collected in six-hourly for the first 72 hour of the study (thus 12 stool samples per patient). Concentrations will be determined using a HPLC-method. Concentrations will be determined on both uncentrifuged and centrifuged supernatant samples, to determine how much of the drug will be protein bound.

A population pharmacokinetic model will be used to determine pharmacokinetics in blood. Blood samples will be taken from each patient during one of four time periods; before drug administration; within 1 hour of first drug administration; 1-2 hours after first drug administration; and 4-12 hours after the first dose. A 1-ml sample will be required at each time window.

Erythromycin concentrations will be determined only in stool, which is the active site of infection. Erythromycin concentrations will also be done on six-hour aliquots, and determinations will be done using a bioassay method.

9.7 Interim analysis

No interim analysis is planned.

10. Use of data and publication

All data derived from the study will be the property of Bayer. The study will be the subject of a Medical Research Report compiled by or by order of Bayer. Bayer may disclose derived data from the study to any of its subsidiary firms, to other investigators and national or foreign drug authorities.

The investigator will be free to publish or present the results of the study. However, the investigator will provide a draft manuscript at least 30 days before submitting for publication and Bayer will have 15 days to comment on the manuscript. If the sponsor informs NEMCH that the manuscript or disclosure contains confidential information, the principal investigator must delete such information and the principal investigator and the sponsor will use their best efforts to provide scientifically meaningful equivalent information for use in such disclosure.

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12. Appendices

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12.1 Trial flow chart

12.1.1 Trial flow chart

Appendix 12.1.1
Flow chart for study activities

Assessments	Time										
	Initial Screening	Rehydration Period*	After Rehydration Period**	Observation Period	D-1	D-2	D-3	D-4	D-5	10 to 14 Days Follow-up (after study entry)	4 to 6 Weeks Follow-up (after study entry)
Inclusion/exclusion criteria	X										
Medical history[1]	X										
Demographics[2]	X										
Physical examination[3]	X			X	X	X	X	X	X	X	X
Intake/output (stool, urine, vomitus)		X		X	X	X	X	X	X		
Examination of joint[4]	X				X	X	X	X	X	X	X
Faecal cultures[5]	X						X			X	X
Rectal swab[6]	X				X	X	X	X	X	X	X
Antimicrobial cultures[7]	X										
Susceptibility testing and MIC[8]	X										
Microscopic examination of stool[9]	X							X			
Haematology[10]	X								X		
Clinical chemistry[11]	X								X		
Urinalysis[12]	X								X		
Pharmacokinetics (stool and serum)					X	X	X				
Start of study medication[13]					X						
Clinical response[14]									X		
Bacteriological response[15]									X		
Adverse events		◄									►

Note: [1] = Current illnesses and underlying diseases and medication, surgical procedures, previous joint problems, previous use of quinolones and, if known, date of onset of underlying diseases.

[2] = Sex, race, age.

[3] = Weight, temperature, pulse/heart rate, respiratory rate, abdominal signs and symptoms, determination of hydration status and rehydration according to WHO guidelines.

[4] = Ankles, knees, hips, wrists, elbows and shoulders for pain and inflammation.

[5] = Stool culture for enteric pathogens (*V.cholerae*, *Salmonella*, *Shigella* and *Campylobacter*).

[6] = For the isolation of *V.cholerae 01 and 0139*.

[7] = For *V.cholerae* and other enteric pathogens isolated from the specimens collected before initiation of drug therapy. Susceptibility to tetracycline, trimethoprim-sulfamethoxazole, chloramphenicol, erythromycin, furazolidone and ciprofloxacin.

[8] = For tetracycline, trimethoprim-sulfamethoxazole, chloramphenicol, erythromycin, furazolidone and ciprofloxacin.

[9] = For semi-quantitative assessment of presence of leukocytes and erythrocytes, and demonstration of haematophagous trophozoites of *E. histolytica* and other parasites.

[10] = Haematocrit, total and differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils) white blood cell counts, and platelet count.

[11] = Serum sodium, chloride, potassium, bicarbonate, creatinine, bilirubin, AST, ALT and alkaline phosphatase. (If the baseline creatinine is > 200 mcmol/L, any patient with creatinine > than 200 mcmol/L 24-hour post-administration, will be considered as suffering from renal failure and will be withdrawn from the trial.)

[12] = pH, protein, ketones, blood and glucose; microscopic examinations will be done for cells, casts and crystals.

[13] = After 4-hour observation period. Study days will be counted from the time of administration of the first dose of the study drugs, and each 24-hour period will constitute a study day.

[14] = Clinical response includes the following: Weight, History and physical examination, Vital signs, Fluid therapy, Quantitation of stool volume, Feeding, X-ray and MRI.

Weight: Before rehydration (dehydrated weight), after rehydration (rehydration weight) and just before administration of the study drug (after the 4-hour observation period), and at 24 hour intervals from the time of administration of the first dose of the study drug during hospitalisation.

Physical examination: before rehydration, after rehydration, at the time of administration of the study drug, and then daily during hospitalisation. Physical examinations will also focus on adverse events including vomiting, gastrointestinal distress, rash, and joint assessment.

Vital signs: pulse and respiratory rates, and blood pressure will be recorded before rehydration, after rehydration, just before administration of study drug, and then every 6 hours during the study.

Quantitation of stool volume: Also for each 6-hour period during the study.

* = Rehydration guidelines according to WHO guidelines. Children admitted with severe dehydration according to the WHO guidelines will be given 100 ml/kg of Dhaka Solution over 3-4 hours. After initial rehydration, children will be evaluated and appropriate treatment plan will be used for continuation of further fluid therapy.
Fluids given to maintain hydration should be based on the amount of ongoing stool losses as well as the child's willingness to drink. Fluid therapy will continue until diarrhoea stops. If signs of dehydration reappear, fluid appropriate to the degree of dehydration will be administered and the study protocol will continue to be followed.

** = Appropriate feeds for age will be provided.
Radiological examination of the affected joints and, as appropriate, ultrasonographic and magnetic resonance imaging (MRI) examination of the affected joints and/or joint fluid assessments will be performed.

15 = For evaluation of bacteriological response to the treatment regimen, stool or rectal swab culture will be done on each day of the study for isolation and identification of *V cholerae* O1 or O139.

12.1.2 Clinical examination of joint function

Appendix 12.1.2

CLINICAL EXAMINATION OF JOINT FUNCTION

JOINT EXAMINATION: Normal ☐
Abnormal ☐ (If abnormal, please specify (mark an "x" in the appropriate block)

	Knee		Hip		Shoulder		Ankle		Wrist		Elbow	
	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
Redness												
Warmth												
Swelling												
Pain												
Tenderness												

RANGE OF MOTION: Normal ☐
Abnormal ☐ (If abnormal, please specify (mark an "x" in the appropriate block)

	Knee		Hip		Shoulder		Ankle		Wrist		Elbow	
	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
Abduction												
Adduction												
Extension												
Flexion												
Internal rotation												
External rotation												
Hyperextension												
Lateral flexion												
Plantar flexion												
Dorsiflexion												
Gait: Stance phase												
Gait: Swing phase												

12.2 Patient information sheet and consent form

The patient information sheet and consent form will be developed as a separate document and will be submitted to EC with the protocol.

12.3 Declaration of Helsinki

DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Recommendations guiding physicians
in biomedical research involving human subjects

Adopted by the 18th World Medical Assembly
Helsinki, Finland, June 1964
and amended by the
29th World Medical Assembly, Tokyo, Japan, October 1975
35th World Medical Assembly, Venice, Italy, October 1983
41st World Medical Assembly, Hong Kong, September 1989
and the
48th General Assembly,
Somerset West, Republic of South Africa, October 1996

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research, which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognised between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research, which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.
2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.
3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject had given his or her consent.
4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.
6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimise the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.
8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.
9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely given informed consent, preferably in writing.
10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.
11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity

makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

Whenever the minor child is in fact able to give consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE
(Clinical research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, re-establishing health or alleviating suffering.
2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.
3. In any medical study, every patient - including those of a control group, if any - should be assured of the best-proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.
4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.
5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I,2).
6. The Physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS
(Non-clinical biomedical research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
2. The subject should be a volunteer - either healthy persons or patients for whom the experimental design is not related to the patients' illness.
3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.
4. In research on man, the interest of science and society should never take precedence over considerations related to the well being of the subject.

12.4 ICH GCP guideline

See study file for a copy of the ICH GCP guideline.

12.5 Package inserts: ciprofloxacin and erythromycin

Please refer to the Investigator's file for details regarding package inserts.

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CLINICAL TRIAL PROTOCOL AMENDMENT

Study Identifier:	IMPACT No. 10110 / AP 176
Date and Version No. of Study Protocol:	03rd July 2000, Version No. 10
Title:	An open, randomised clinical trial comparing the efficacy and safety of a single dose of ciprofloxacin with erythromycin administered 6-hourly for 3 days in children with cholera
Test Drug:	BAY q 3939, Ciprofloxacin oral suspension,
Amendment Number:	02
Amendment Version no and date:	Version 2, 22nd December, 2000
Applicable Country(s):	Bangladesh only

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Study Co-ordinator

07 January 2001
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Dr Michael Bennish
Study Consultant

5 JANUARY, 2001
Date

Dr W A Khan
Principal Investigator (Dhaka site)

07 JANUARY. 2001
Date

Dr Hafizur Rahman Chowdhury
Principal Investigator (Matlab site)

7 JANUARY, 2001
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Dr Hafizur Rahman Chowdhury
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Dr Wolf-Dieter Sittner
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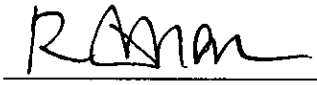

5 JANUARY 2001

Dr R Schall
Biostatistician:
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Reason for Amendment :

As requested by the Research Review Committee (RRC) of International Centre For Diarrhoeal Disease Research, Bangladesh (ICDDR,B) to clearly specify the strategy for collection of blood samples from patients (Pharmacokinetics).

List of Changes to Protocol AP176 (Version 10)

1. Strategy for collection of blood sample from patients (Pharmacokinetics)

1.1 Pharmacokinetics criteria, (Protocol Outline, page 10)

Before Revision:

- **Pharmacokinetics:** ciprofloxacin concentrations will be determined for both stool and serum.
    - To determine the pharmacokinetics of ciprofloxacin, **blood samples will be taken** from each patient during one of four time periods; before drug administration; within 1 hour of first drug administration; 1-2 hours after first drug administration; and 4-12 hours after the first dose. **A 1-ml sample will be required at each collection time.**
    - Stool will be collected 6-hourly for the first 72 hours of the study (thus 12 stool samples per patient).
    - Concentrations will be determined using the HPLC-method. **Concentrations will be determined on both uncentrifuged and centrifuged supernatant samples, to determine how much of the drug is protein bound.**
    - Erythromycin concentrations will be determined only in stool, which is the active site of infection.

After Revision:

- **Pharmacokinetics:** ciprofloxacin concentrations will be determined for both stool and serum.
    - To determine the pharmacokinetics of ciprofloxacin, **3.0 ml of blood will be taken from each patient during one of the following four time periods;**
      1. before drug administration,
      2. within 1 hour of first drug administration,
      3. 1-2 hours after first drug administration and
      4. 4-12 hours after the first dose.
    - Stool will be collected 6-hourly for the first 72 hours of the study (thus 12 stool samples per patient).
    - Concentrations will be determined using the HPLC-method.
    - Erythromycin concentrations will be determined only in stool, which is the active site of infection.

1.2 Laboratory Assessments, (Section 5.6.1, page 27)

Before Revision:

- **Pharmacokinetics:** ciprofloxacin concentrations will be determined for both stool and serum.
  - To determine the pharmacokinetics of ciprofloxacin, **blood samples will be taken** from each patient during one of four time periods; before drug administration; within 1 hour of first drug administration; 1-2 hours after first drug administration; and 4-12 hours after the first dose. **A 3-ml blood sample (sufficient to yield 1 ml of plasma) will be drawn at each collection time.**
  - Stool will be collected 6-hourly for the first 72 hours of the study (thus 12 stool samples per patient).
  - Concentrations will be determined using the HPLC-method. **Concentrations will be determined on both uncentrifuged and centrifuged supernatant samples, to determine how much of the drug is protein bound.**
  - Erythromycin concentrations will be determined only in stool, which is the active site of infection.

After Revision:

- **Pharmacokinetics:** ciprofloxacin concentrations will be determined for both stool and serum.
  - To determine the pharmacokinetics of ciprofloxacin, **3.0 ml of blood will be taken from each patient during one of the following four time periods;**
    1. before drug administration,
    2. within 1 hour of first drug administration,
    3. 1-2 hours after first drug administration and
    4. 4-12 hours after the first dose.
  - Stool will be collected 6-hourly for the first 72 hours of the study (thus 12 stool samples per patient).
  - Concentrations will be determined using the HPLC-method.
  - Erythromycin concentrations will be determined only in stool, which is the active site of infection.

1.3 Secondary Outcome Measures, (Section 5.10.2, page 33)

Before Revision:

Ciprofloxacin concentrations will be determined for both stool and serum. Stool will be collected in six-hourly for the first 72 hour of the study (thus 12 stool samples per patient). **Blood samples will be taken** from each patient during one of four time periods; before drug administration; within 1 hour of first drug administration; 1-2 hours after first drug administration; and 4-12 hours after the first dose. **A 1-ml sample will be required at each time window.**

After Revision:

Ciprofloxacin concentrations will be determined for both stool and serum. Stool will be collected in six-hourly for the first 72 hour of the study (thus 12 stool samples per patient). **3.0 ml of blood will be taken from each patient during one of the following four time periods;**

1. **before drug administration,**
2. **within 1 hour of first drug administration,**
3. **1-2 hours after first drug administration and**
4. **4-12 hours after the first dose.**

1.4 Pharmacokinetic Analysis, (Section 9.6, page 45)

Before Revision:

A population pharmacokinetic model will be used to determine pharmacokinetics in blood. **Blood samples will be taken** from each patient during one of four time periods; before drug administration; within 1 hour of first drug administration; 1-2 hours after first drug administration; and 4-12 hours after the first dose. **A 1-ml sample will be required at each time window.**

After Revision:

A population pharmacokinetic model will be used to determine pharmacokinetics in blood. **3.0 ml of blood will be taken from each patient during one of the following four time periods;**

1. **before drug administration,**
2. **within 1 hour of first drug administration,**
3. **1-2 hours after first drug administration and**
4. **4-12 hours after the first dose.**

1.5 Trial Flow Chart, (Section 12.1.1, page 52)

Before Revision:

Appendix 12.1.1
Flow chart for study activities

Assessments	Time										
	Initial Screening	Rehydration Period*	After Rehydration Period**	Observation Period	D-1	D-2	D-3	D-4	D-5	10 to 14 Days Follow-up (after study entry)	4 to 6 Weeks Follow-up (after study entry)
Inclusion/exclusion criteria	X										
Medical history[1]	X										
Demographics[2]	X										
Physical examination[3]	X			X	X	X	X	X	X	X	X
Intake/output (stool, urine, vomitus)		X		X	X	X	X	X	X		
Examination of joint[4]	X				X	X	X	X	X	X	X
Faecal cultures[5]	X						X			X	X
Rectal swab[6]	X				X	X	X	X	X	X	X
Antimicrobial cultures[7]	X										
Susceptibility testing and MIC[8]	X										
Microscopic examination of stool[9]	X							X			
Haematology[10]	X								X		
Clinical chemistry[11]	X								X		
Urinalysis[12]	X								X		
Pharmacokinetics (stool and serum)					X	X	X				
Start of study medication[13]					X						
Clinical response[14]									X		
Bacteriological response[15]									X		
Adverse events		◄									►

After Revision:

Appendix 12.1.1
Flow chart for study activities

Assessments	Time										
	Initial Screening	Rehydration Period*	After Rehydration Period**	Observation Period	D-1	D-2	D-3	D-4	D-5	10 to 14 Days Follow-up (after study entry)	4 to 6 Weeks Follow-up (after study entry)
Inclusion/exclusion criteria	X										
Medical history[1]	X										
Demographics[2]	X										
Physical examination[3]	X			X	X	X	X	X	X	X	X
Intake/output (stool, urine, vomitus)		X		X	X	X	X	X	X		
Examination of joint[4]	X				X	X	X	X	X	X	X
Faecal cultures[5]	X						X			X	X
Rectal swab[6]	X				X	X	X	X	X	X	X
Antimicrobial cultures[7]	X										
Susceptibility testing and MIC[8]	X										
Microscopic examination of stool[9]	X							X			
Haematology[10]	X								X		
Clinical chemistry[11]	X								X		
Urinalysis[12]	X								X		
Pharmacokinetics (stool)					X	X	X				
Pharmacokinetics (serum)					X						
Start of study medication[13]					X						
Clinical response[14]									X		
Bacteriological response[15]									X		
Adverse events		◄									►

Bayer

CLINICAL TRIAL PROTOCOL AMENDMENT

Study Identifier:	IMPACT No. 10110 / AP 176
Date and Version No. of Study Protocol:	03rd July 2000, Version No. 10
Title:	An open, randomised clinical trial comparing the efficacy and safety of a single dose of ciprofloxacin with erythromycin administrered 6-hourly for 3 days in children with cholera
Test Drug:	BAY q 3939, Ciprofloxacin oral suspension,
Amendment Number:	01
Amendment Version no and date:	Version 3, 21st September, 2000
Applicable Country(s):	Bangladesh only

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Reason for Amendment :

Dr Anisur Rahman will be absent from Matlab for at least one year during the conduct of this trial pursuing further studies in Sweden. Dr Hafizur Rahman Chowdhury has been identified by the study team to replace for Dr Anisur Rahman as the new Principal Investigator of Matlab site.

List of Changes to Protocol AP176 (Version 10)

1. Change of Principal Investigator at Matlab site

1.1 Investigators and other trial participants, (Section 3, page 18)

Before Revision:
Principal investigator (Matlab site)
Dr Anisur Rahman
Senior Medical Officer
Matlab Health Research Programme (MHRP)
ICDDR, B
GPO Box 128
Dhaka-1000
Bangladesh
Telephone: 0841-3299 (Ext. 03) - ICDDR,B / 084268005 (Mobile)

After Revision:
Principal investigator (Matlab site)
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Senior Physician In-Charge
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Telephone: 08426-8004 - ICDDR,B Matlab
Facsimile: 08426-8001
Email: hafiz@icddrb.org

2. Obtaining a child assent and her/his acceptance of participation in this study

2.1 Trial Population, (Protocol Outline, page 8 and Section 5.2.3 Inclusion Criteria, page 22)

Before Revision:
Inclusion Criteria

- Age: 2-15 years.
- Gender: Both.
- Duration of illness: ≤ 24 hours.
- Written informed consent for participation in the study from either of the parents, or guardian, and ***oral assent from children aged ≥ 8 years.***
- Severe dehydration according to World Health Organisation (WHO) guidelines[18].
- Positive stool dark-field microscopic examination for *V. cholerae*.

After Revision:
Inclusion Criteria

- Age: 2-15 years.
- Gender: Both.
- Duration of illness: ≤ 24 hours.
- Written informed consent for participation in the study from either of the parents, or guardian, and **if possible, assent of the child should be obtained.**
- Severe dehydration according to World Health Organization (WHO) guidelines[18].
- Positive stool dark-field microscopic examination for *V. cholerae*.

International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B.), Dhaka, Bangladesh
Voluntary Consent Form

Title of the research project: An open, randomized clinical trial comparing the efficacy and safety of a single dose of ciprofloxacin with erythromycin administered 6-hourly for 3 days in children with cholera.

Short title: Study of the efficacy and safety of single-dose ciprofloxacin therapy for childhood cholera due to V. cholerae O1 or O139.

Principal Investigator: Dr. Wasif Ali Khan, and Dr. Hafizur Rahman Chowdhury

Before recruiting into the study, the study subject must be informed about the objectives, procedures, and potential benefits and risks involved in the study; details of all procedures and their risks, utility, duration, frequencies, and severity should also be informed. All questions of the subject must be answered to her/his satisfaction, indicating that the participation is purely voluntary. For children, consents must be obtained from their parents or legal guardians and where capable assent of the child should be obtained with signature or thumb printing and personally date on this form indicating her/his acceptance of participation.

Patient Information Sheet

We suspect that your child is suffering from cholera, a diarrhoeal disease caused by infection of the intestine by a germ called *Vibrio cholerae*. Treatment of cholera requires correction of water and salts losses from the body, continued feeding, and killing of cholera germs with an effective antibiotic drug. Antibiotics are usually given for 3 days. It has been possible to treat cholera in adults using a single dose of ciprofloxacin, and we are conducting a research study to examine if that is also possible in children. Treatment of childhood cholera would be much simpler and cheaper if a single dose of ciprofloxacin is found effective.

We request for your permission to enroll your child in this study. By doing so, in addition to receiving the standard good care of this hospital, your child will be able to contribute to the society by improving our knowledge about treatment of this important disease of Bangladesh. If you agree to our proposal for enrollment of your child in this study, we would like to inform you that:

1. We would admit your child to a research ward of this hospital for full 5 days or longer if required for her/his treatment. She/he would be required to come to the hospital for assessment of her/his condition 10-14 days and 4-6 weeks after discharged. We would bear all costs related to your child's hospital stay, food, laboratory tests, and treatment in this hospital, and would also support transport cost to bring her/him for the follow-up visits.

2. We would ask you questions about your child's diarrhoea and other health problems, and examine her/him several times on the day of admission, at least once a day during her/his hospitalization, and at follow up visits.

3. We would collect a small amount of child's stool on admission to study, every morning during her/his hospitalization, and at follow up visits. We would also collect 4.5 ml (little less than one teaspoonful) of blood from a vein on her/his elbow, and a urine specimen on admission to study and hospital day 5. Results of these laboratory tests would be used in the treatment of your child as well as research purposes. If your child receives ciprofloxacin, we would similarly collect another 3.0 ml (little over ½ teaspoonful) of

blood during one of the following four time periods; (1) before drug administration; (2) within 1 hour of first drug administration; (3) 1-2 hours after first drug administration; and (4) 4-12 hours after the first dose to determine the concentration of the drug in blood. Thus, we would collect a total of 12.0 ml (Just over two teaspoonful) of blood over 5-day period by a total of 3 venipunctures. Other than mild momentary pain, and rare possibilities of skin discolouration around the needle prick and infection, drawing of this amount of blood will not cause other problem to your child. We will take precautions to prevent these problems. To determine the concentration of drug in stool, we would collect specimen of his/her stool at various time of the study.

4. Purely by chance, your child would receive either a single 20mg/Kg dose of ciprofloxacin oral suspension, or erythromycin in a dose of 12.5mg/Kg every 6 hours for a total of 3 days (Total of 12 doses). Erythromycin is the drug currently used in the same manner to treat cholera in children at this hospital, and we are testing if a single dose of ciprofloxacin also effective. We would recruit a total of 160 children in this study.

5. Like most antibiotics, the drugs to be used in this study have some adverse effects. Vomiting and diarrhoea are among the common adverse effects of both of the study drugs. The other side effects of ciprofloxacin include skin rashes, headache, and sleeplessness. In young animals it may also cause serious joint problems that usually gets better after stopping the drug, but this problem was not seen when children were treated with this drug for 5 days. Children in this study will receive only one dose of ciprofloxacin. The most common side effects of erythromycin include abdominal discomfort, loss of appetite, and vomiting. We would monitor adverse effects including joint problems during hospitalization of your child and at follow-up visits. In the event of a joint problem, we would perform X-rays of your child's affected joints, and may also perform ultrasonographic examination and a special investigation called magnetic resonance imaging (MRI) to assess the joint(s). These procedures are painless, and the chance of risks from them is very low; these tests would be repeated at three (3) months from the time of last visit.

6. If you do not agree to our proposal, we will not be enrolling your child in the study. In that case your child would receive standard care of this hospital. You may withdraw your consent at any time of the study without affecting her/his further treatment at this hospital.

7. We would inform you in a timely manner if information becomes available that might be relevant to your child's willingness to continue participation. You are free to ask questions to the investigators, and other doctors and the nurses of this hospital involved in your child's care. The investigators of this study may withdraw your child from the study if that is considered the best.

8. The medical information and results of the laboratory tests of your child will be recorded, and stored in a secure place. This information would be used for treatment of your child and assessment of effectiveness and safety of the study drugs. Name and address of the study children would not be used in publishing study results. None other than the investigators and monitor of this study, and the Ethical Review Committee of this Centre would be able to see the records, which would be stored for 15 years. If you want, we would provide you result of any or all tests performed on your child as they become available.

9. Bayer AG, producer of the drug, would compensate for any adverse event that occurs to your child as a result of administration of ciprofloxacin suspension.

CONSENT FORM
Study No. IMPACT NO. 10110/ AP 176

Patient: _____ Hospital No. _____

1. I hereby wish to consent for my child's participation in the ciprofloxacin study as set out above and as explained to me by the investigators.

2. I have been adequately informed by the investigators the purpose, and all known adverse effects of the drugs to be used in the treatment of my child under this study.

3. My questions have been answered completely and to my satisfaction, and I have been given a copy of the "Patient Information Sheet". I also understand that if I have any further question(s), I would be able to freely contact any investigator of this study as indicated below:

Study Site	Investigator's Name	Telephone No (Office)		Telephone No (Residence)
		PABX	Extension	
Dhaka Hospital	Dr. Wasif Ali Khan	8811751-60	2314	323388, 323844
	Dr. Debasish Saha	8811751-60	2314	7110183
	Mohammed Abdus Salam	8811751-60	2302	9129030
Matlab Hospital	Dr. Hafizur Rahman Chowdhury	084268	005	
	Dr. Anisur Rahman (Junior, Nick name Anu)	084268	005	

Written Consent: ☐ Yes ☐ No

Witness verbal consent (for illiterate): ☐ Yes ☐ No

_____ _____ _____
Parent/Legal Guardian Signature, or Left Thumb Impression Date

Assent of patient (where capable): ☐ Yes ☐ No

_____ _____ _____
Patient (if capable) Signature, or Left Thumb Impression Date

_____ _____ _____
Investigator Signature Date

_____ _____ _____
Witness Signature Date

Original: Investigator
Copy: Parents/Legal Guardian of the Patient

আন্তর্জাতিক উদরাময় গবেষণা কেন্দ্র, বাংলাদেশ (আই,সি,ডি,ডি,আর,বি), ঢাকা, বাংলাদেশ
স্বেচ্ছা সম্মতি-পত্র

গবেষণা প্রকল্পের নামঃ এ্যান ওপেন, র‍্যানডোমাইজড ক্লিনিক্যাল ট্রায়েল কমপেয়ারিং দি এফিকেসি এ্যান্ড সেফটি অফ এ সিঙ্গেল ডোজ অফ সিপ্রোফ্লোক্সাসিন উইথ ইরিথ্রোমাইসিন এ্যাডমিনিস্টারড ৩-আওয়ারলি ফর থ্রি ডেজ ইন চিল্ড্রেন উইথ কলেরা।

গবেষণার নামের সংক্ষিপ্ত বাংলা তর্জমাঃ ভিব্রিও কলেরি ও১ এবং ও১৩৯ সংক্রমনে সৃষ্ট শিশুদের কলেরা চিকিৎসায় এক-মাত্রার সিপ্রোফ্লোক্সাসিনের কার্যকারিতা ও নিরাপত্তা নির্ণয়।

প্রধান গবেষকঃ ডাঃ ওয়াসিফ আলী খান এবং ডাঃ হাফিজুর রহমান চৌধুরী।

গবেষণায় অন্তর্ভূক্তির আগে রুগীকে অবশ্যই এ গবেষণার উদ্দেশ্য, পদ্ধতি, এবং এ গবেষণায় অংশ গ্রহনের ফলে রুগীর সম্ভাব্য লাভ ও ক্ষতি সম্বন্ধে জানাতে হবে, এবং গবেষণায় ব্যবহৃত প্রতিটি পদ্ধতির প্রয়োজনীয়তা, তাদের থেকে সৃষ্ট বিপদের সম্ভাবনা, মেয়াদ ও মাত্রা ইত্যাদি সহ বিস্তারিত জানাতে হবে। রুগীর প্রতিটি প্রশ্নের সন্তোষজনক উত্তর দিতে হবে, এবং এও জানাতে হবে যে গবেষণায় অংশগ্রহন করা বা না করা সম্পূর্নভাবে তার ইচ্ছাধীন। শিশুদের ক্ষেত্রে তাদের বাবা-মা অথবা অভিভাবকের সম্মতি অবশ্যই নিতে হবে। এবং যেক্ষেত্রে সম্ভব সেক্ষেত্রে তারিখ এবং শিশুর স্বাক্ষর অথবা বৃদ্ধাঙ্গুলির ছাপ সহ গবেষণায় তার অন্তর্ভুক্তির সম্মতি নিতে হবে।

রুগীর বাবা-মা/ অভিভাবকের জন্য তথ্যঃ

আমরা মনে করি আপনার শিশুর কলেরা হয়েছে, যা ভিব্রিও কলেরি নামের রোগজীবানুর সংক্রমনে ঘটে থাকে। কলেরার চিকিৎসায় রুগীর শরীরের পানি ও লবনের ঘাটতি পূরন, স্বাভাবিক খাবার, ও রোগজীবানু ধ্বংস করার জন্যে কার্যকর এ্যান্টিবায়োটিক ঔষধ তিন দিন প্রয়োগ করতে হয়। প্রাপ্ত-বয়স্কদের কলেরার চিকিৎসা সিপ্রোফ্লোক্সাসিন নামক এ্যান্টিবায়োটিক এক-মাত্রায় ব্যবহারেও সম্ভব এবং আমরা গবেষণা করে দেখতে চাই শিশুদের কলেরা চিকিৎসাও এক-মাত্রার সিপ্রোফ্লোক্সাসিন দিয়ে সম্ভব কি না। এক-মাত্রায় সিপ্রোফ্লোক্সাসিন কার্যকর প্রমানিত হলে শিশুদের কলেরা চিকিৎসা পদ্ধতি অনেক সহজ হবে এবং চিকিৎসার খরচও কমবে।

আমরা এই গবেষণায় আপনার শিশুর অন্তর্ভূক্তির অনুরোধ জনাচ্ছি। গবেষণায় অংশগ্রহন করলে আপনার শিশু এ হাসপাতালের প্রচলিত সুচিকিৎসা পাবার পাশাপাশি বাংলাদেশের এই গুরুত্বপূর্ন রোগের চিকিৎসায় আমাদের জ্ঞান বৃদ্ধির মাধ্যমে সমাজের উপকারেও অবদান রাখতে পারে। আপনি যদি এই গবেষণায় আপনার শিশুর অংশগ্রহনের আমাজের প্রস্তাবে সম্মত হন, তাহলে আমরাঃ

(১) আপনার শিশুকে গবেষণার প্রয়োজনে পূর্ন পাঁচ (৫) দিনের জন্য অথবা চিকিৎসার প্রয়োজনে আরো বেশী দিনের জন্য এ হাসপাতালের গবেষণা প্রকোষ্ঠে ভর্ত্তি করবো, এবং শিশুর অবস্থা পর্যালোচনা করার জন্য হাসপাতাল থেকে ছুটির ১০-১৪ দিন এবং ৪-৬ সপ্তাহ পর তাকে প্রায় ১ ঘন্টা সময়ের জন্য হাসপাতালে আনতে বলব। আমরা আপনার শিশুর চিকিৎসার সার্বিক ব্যয় যেমন হাসপাতালে ভর্ত্তি, ঔষধ ও পথ্য, ল্যাবরেটরী পরীক্ষা, এবং ছুটির ১০-১৪ দিন এবং ৪-৬ সপ্তাহ পর তাকে হাসপাতালে আনার যাতায়াত খরচ বহন করবো।

(২) আপনার শিশুর ডায়ারিয়া ও অন্যান্য স্বাস্থ্য সমস্যা সম্বন্ধে আপনাকে কিছু প্রশ্ন করবো, এবং ভর্ত্তিব দিন কয়েক বার, হাসপাতালে ভর্ত্তি থাকাকালীন দৈনিক অন্ততঃ একবার, এবং ছুটির পর হাসপাতালে এলে শিশুর সম্পূর্ন শারীরিক পরীক্ষা করবো।

(৩) গবেষণায় ভর্ত্তির দিন, হাসপাতালে ভর্ত্তি থাকাকালীন প্রতিদিন, ও ছুটির ১০-১৪ দিন এবং ৪-৬ সপ্তাহ পর হাসপাতালে এলে আমরা শিশুর মলের সামান্য নমুনা বিভিন্ন পরীক্ষার জন্যে সংগ্রহ করবো। শিশুর চিকিৎসা ও গবেষণার প্রয়োজনে হাসপাতালে ভর্ত্তির দিন ও ভর্ত্তির ৫ম দিন তার বাহুর শিরা হতে ৪.৫ মিঃলিঃ (১ চা-চামচেরও কম) পরিমান রক্ত এবং সামান্য পরিমানে মূত্রের নমুনা বিভিন্ন পরীক্ষার জন্যে সংগ্রহ করবো। আপনার শিশুকে সিপ্রোফ্লোক্সাসিন দিয়ে চিকিৎসা করা হলে রক্তে ঔষধের পরিমান নির্নয়ের জন্য ঔষধের প্রথম মাত্রা প্রয়োগের সামান্য আগে অথবা ঔষধ প্রয়োগের ১.০ ঘন্টা, ১.০-১.৫ ঘন্টা অথবা ৪.০-১২.০ ঘন্টা

পর, এর যে কোন এক সময়ে, আরোও ৩.০ মিঃলিঃ (১/২ চা-চামচেরও কম) রক্ত একই নিয়মে সংগ্রহ করবো। পাঁচ দিনের মধ্যে তিনবারে সর্বমোট ১২.০মিঃলিঃ (দুই চা'চামচের সামান্য বেশী) রক্ত সংগ্রহের সময় সূঁচের আঘাত-জনিত তাৎক্ষনিক সামান্য ব্যাথা, রক্ত সংগ্রহের জায়গার আশেপাশের ত্বকের রংয়ের সাময়িক পরিবর্তন, এবং রোগ-জীবাণুর সংক্রমনের ক্ষীণ সম্ভাবনা ছাড়া কারনে শিশুর আর অন্য কোন ক্ষতির সম্ভাবনা নেই। আমরা চেষ্টা করবো যাতে শিশুর এসব সমস্যাও না হয়। ঔষধের পরিমান নির্নয়ের জন্যে শিশু গবেষণায় ভর্ত্তি থাকাকালীন বিভিন্ন সময় তার মলের নমুনাও সংগ্রহ করা হবে।

(৪) সম্পূর্ন ভাগ্যনির্ভর হয়ে আপনার শিশু তার শরীরের প্রতি কিলোগ্রাম ওজনের জন্যে ২০ মিঃগ্রাঃ হারে শুধুমাত্র এক-মাত্রা মুখে খাবার তরল সিপ্রোফ্লোক্সাসিন অথবা ১২.৫ মিঃগ্রাঃ হারে ৬ ঘন্টা পরপর ৩ দিন (১২ মাত্রা) মুখে খাবার তরল এরিথ্রোমাইসিন ঔষধ পাবে। বর্ত্তমানে এ হাসপাতালে এরিথ্রোমাইসিন দিয়ে একই নিয়মে শিশুদের কলেরার চিকিৎসা করা হয় এবং আমরা দেখতে চাই এক-মাত্রার সিপ্রোফ্লোক্সাসিনও কার্যকর কিনা। আমরা এই গবেষণায় সর্বমোট ১৬০ জন শিশুকে অর্ন্তভূক্ত করবো।

(৫) বেশী ভাগ এ্যান্টিবায়োটিক ঔষধের মতো এ গবেষণায় ব্যবহৃত ঔষধ দুটিরও কিছু পার্শ্ব-প্রতিক্রিয়া আছে। বমি ও ডায়ারিয়া এ গবেষণায় ব্যবহৃত ঔষধ দুটির সাধারন পার্শ্ব-প্রতিক্রিয়ার মধ্যে অন্যতম। সিপ্রোফ্লোক্সাসিনের অন্যান্য পার্শ্ব-প্রতিক্রিয়ার মধ্যে আছে ত্বকের ফুস্কুরি, মাথাব্যথা ও অনিদ্রা। সিপ্রোফ্লোক্সাসিন অপ্রাপ্ত-বয়স্ক পশুদের গিটের মারাত্মক প্রদাহ সৃষ্টি করতে পারে তবে ঔষধ সেবন বন্ধ করে দিলে তা সাধারনতঃ ভালো হয়ে যায়, তবে মানব শিশুর ক্ষেত্রে এই ঔষধ ৫ দিন ব্যবহার করেও এধরনের সমস্যা হতে দেখা যায়নি। এ গবেষণায় শিশুদেরকে সিপ্রোফ্লোক্সাসিনের শুধু মাত্র একটি মাত্রা দেওয়া হবে। এরিথ্রোমাইসিনের সচরাচর পার্শ্ব-প্রতিক্রিয়ার মধ্যে রয়েছে পেটের অস্বস্তিঃ, খাবার অরুচি, এবং বমি। আমরা হাসপাতালে ভর্ত্তি থাকাকালীন প্রতিদিন, এবং ছুটির পর হাসপাতালে এলে শিশুর গিটের সমস্যা বা অন্য কোন পার্শ্ব-প্রতিক্রিয়া হচ্ছে কি না সেদিকে বিশেষ লক্ষ্য রাখবো। গিটের সমস্যা দেখা দিলে আমরা অবস্থা পরীক্ষার জন্য গিটের এক্সরে করবো, এবং প্রয়োজন হলে আলট্রা-সনোগ্রাফি ও ম্যাগনেটিক রেজোন্যান্স ইমেজিং (এম, আর, আই) নামের বিশেষ পরীক্ষাও করবো। এসব পরীক্ষা ব্যথামুক্ত এবং এসব পরীক্ষার কারনে শিশুর অন্য কোন ক্ষতির সম্ভাবনাও খুবই কম। এই পরীক্ষাগুলো শিশুর হাসপাতাল থেকে ছুটির তিন (৩) মাস পরে পুনরায় করতে হবে।

(৬) এ গবেষণায় আপনার শিশুর অর্ন্তভূক্তির আমাদের প্রস্তাবে রাজী না হলে আমরা তাকে গবেষণায় অর্ন্তভূক্ত করবো না। সেক্ষেত্রে আপনার শিশু এ হাসপাতালের প্রচলিত সুচিকিৎসা পাবে। গবেষণায় শিশুর অর্ন্তভূক্তির পরেও যে কোন সময়ে আপনি আপনার সম্মতি প্রত্যাহার করতে পারবেন, এবং সেক্ষেত্রেও এ হাসপাতালে শিশুর পরবর্ত্তী চিকিৎসার কোন তারতম্য হবে না।

(৭) আপনি এ গবেষণার গবেষক অথবা আপনার শিশুর চিকিৎসায় জড়িত অন্য কোন ডাক্তার যা নার্সকে আপনার শিশুর ব্যাপারে প্রশ্ন করতে পারবেন। গবেষকরা আপনার শিশুর স্বার্থে তাকে গবেষণা থেকে প্রত্যাহার করতে পারবেন।

(৮) আপনার শিশুর স্বাস্থ্য-সম্পর্কীয় তথ্য এবং ল্যাবরেটরী পরীক্ষার ফলাফল লিপিবদ্ধ করে নিরাপদ হেফাজতে রাখা হবে। এসব তথ্য শিশুর চিকিৎসা ও গবেষণায় প্রয়োজনে ব্যবহার করা হবে, তবে গবেষণার ফলাফল প্রকাশের সময় কোথাও অংশগ্রহনকারী শিশুদের নাম বা ঠিকানা উল্লেখ করা হবে না। এ গবেষণার গবেষক, গবেষণা তদারককারী, এবং এই কেন্দ্রের "এথিক্যাল রিভিউ কমিটি (নীতিশাস্ত্র পর্যালোচনা কমিটি)" ছাড়া এসব তথ্য আর কেউই দেখতে পারবেন না। এসব তথ্য আমাদেরকে পনের (১৫) বছরের জন্যে সংরক্ষণ করতে হবে। আপনি চাইলে এবং আমাদের জানা সাপেক্ষে, আপনার শিশুর ব্যাপারে সংগৃহীত যে কোন বা সকল তথ্য এবং/অথবা পরীক্ষার ফলাফল আমরা আপনাকে জানাবো।

(৯) সিপ্রোফ্লোক্সাসিন প্রয়োগের কারনে আপনার শিশুর কোন সমস্যা হলে এই ঔষধের প্রস্তুতকারী, বায়ার এজি, আপনাকে উপযুক্ত ক্ষতিপূরন দেবে।

সম্মতি-পত্র।

গবেষণা নম্বর : ইম্প্যাক্ট নং ১০১১০/ এপি১৭৬

Study number: IMPACT No. 10110/AP 176

রুগীর নামঃ _____ হাসপাতাল নিবন্ধন নম্বরঃ _____

(১) আমি উপরে লিখিত এবং গবেষকদের বর্ণিত তথ্যের ভিত্তিতে স্বেচ্ছায় আমার শিশুকে এই গবেষণায় অর্ন্তভূক্তির অনুমতি দিচ্ছি।

(২) গবেষকরা আমাকে এ গবেষণার উদ্দেশ্য ও পদ্ধতি, এবং গবেষণায় ব্যবহৃত ঔষধ ও তাদের সকল পার্শ্ব-প্রতিক্রিয়া সম্বন্ধে বিস্তারিত জানিয়েছেন।

(৩) আমার সকল প্রশ্নের সম্পূর্ন ও সন্তোষজনক উত্তর দেওয়া হয়েছে, এবং আমাকে "রুগীর জন্যে তথ্য" এর অনুলিপিও দেওয়া হয়েছে। আমাকে এও জানানো হয়েছে যে পরবর্ত্তীতেও আমি ডাঃ ওয়াসিফ, ডাঃ দেবাশীষ অথবা ডাঃ সালামকে (ঢাকা হাসপাতালের জন্য) / ডাঃ হাফিজুর রহমান চৌধুরী অথবা ডাঃ আনিসুর রহমান (মতলব হাসপাতালের জন্য) এর সাথে নীচের ঠিকানায় যোগাযোগ করতে, এবং আমার শিশু এবং ও গবেষণার ব্যাপারে প্রশ্ন করতে পারবো।

গবেষণা কেন্দ্র	গবেষকের নাম	টেলিফোন নম্বর (অফিস)		টেলিফোন নম্বর (বাসা)
		পি,এ,বি,এক্স	সম্প্রসারন	
ঢাকা হাসপাতাল	ডাঃ ওয়াসিফ আলী খান	৮৮১১৭৫১-৬০	২৩১৪	৩২৩৩৮৮ ও ৩২৩৮৪৪
	ডাঃ দেবাশীষ সাহা	৮৮১১৭৫১-৬০	২৩১৪	৭১১০১৮৩
	ডাঃ মোহাম্মদ আবদুস সালাম	৮৮১১৭৫১-৬০	২৩০২	৯১২৯০৩০
মতলব হাসপাতাল	ডাঃ হাফিজুর রহমান চৌধুরী	০৮৪২৬৪০০৫		
	ডাঃ আনিসুর রহমান	০৮৪২৬৮০০৫		

লিখিত সম্মতি: ☐ হ্যাঁ ☐ না সাক্ষীর উপস্থিতিতে মৌখিক সম্মতি: ☐ হ্যাঁ ☐ না

নামঃ পিতা/মাতা/অভিভাবক	স্বাক্ষর/টিপসই	তারিখ

শিশুর মৌখিক সম্মতি (যে ক্ষেত্রে প্রযোজ্য): ☐ হ্যাঁ ☐ না

নামঃ রুগী	স্বাক্ষর/টিপসই	তারিখ
নামঃ গবেষক	স্বাক্ষর	তারিখ
নামঃ সাক্ষী	স্বাক্ষর	তারিখ

মূল কপিঃ গবেষকের জন্যে
অনুলিপিঃ পিতা-মাতা/অভিভাবকের জন্যে