CENTERS FOR DISEASE CONTROL AND PREVENTION

November 2013

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Contents

Background

Worldwide, antibiotics are used inappropriately to treat diarrhea, and the prevalence of multidrug-resistant bacterial diarrheal pathogens is high. Such issues might be particularly severe in South Asia. In India, studies found 90% of 145 ambulatory adults[1] and 71% of 843 children presenting to outpatient or inpatient settings[2] with acute diarrhea were treated with antibiotics, in conflict with India's national diarrhea management guidelines.[3] In one study among private practitioners in Pakistan, 96% of prescriptions for patients with acute childhood diarrhea included at least one antibiotic.[4] High rates of multidrug resistance have been found in India and Pakistan among many important causes of diarrhea: enterotoxigenic,[5] enterohemorrhagic,[5] and enteroaggregative[6] *E. coli, V. cholerae*,[7] and *Shigella*[8, 9] and *Salmonella*[10, 11] species. Antimicrobial resistance can lead to treatment dilemmas and increased morbidity and mortality among the infected populations. However, due to global markets and the frequency of international travel, antimicrobial resistance among enteric pathogens is problematic not just for the local population. Antimicrobial drug resistance mechanisms, such as CTX-M-15 extended-spectrum beta-lactamase and New Delhi metallo-beta-lactamase-1, which severely limit therapeutic options, emerged in India and subsequently spread worldwide.[12, 13] Additionally, up to 40% of persons traveling from industrialized to developing countries will develop travel-associated diarrhea, accounting for approximately 160 million cases per year.[14, 15]

Because of the challenges inherent in developing new classes of antimicrobial medications, preserving the function of the limited number of existing drugs is critical. Multiple studies have documented that, among children with diarrhea given oral rehydration therapy for diarrhea, adding zinc to the treatment regimen led to decreased antibiotic use.[16, 17] Thus, patients and health care providers can be redirected to non-antimicrobial medications to satisfy the desire to actively treat the illness, to relieve symptoms, and to permit the patient to return to work and other activities sooner. Because many adult patients with diarrhea in Pakistan are believed to be treated with antimicrobial medications,[18] but zinc is not indicated for adult patients with diarrhea, Pepto-Bismol could fill an important niche in reducing inappropriate use of antimicrobial medications.

Studies have found that Pepto-Bismol reduced the duration of gastrointestinal symptoms among university students with diarrhea in Mexico,[19] university students artificially infected with norovirus in the US[20], and children <5 years old with acute diarrhea.[21, 22] However, there are few published data about the effectiveness of Pepto-Bismol in older adults and across diverse etiologies of acute diarrhea. We propose a study of the effectiveness of Pepto-Bismol for acute diarrhea among adult outpatients with acute diarrhea in Pakistan, and an assessment of the types and costs of additional treatments these patients seek during their illness.

Objectives

Primary

1) To assess Pepto-Bismol's impact on use of antimicrobial medications among adult outpatients with acute diarrhea

Secondary

1) To assess Pepto-Bismol's impact on perceived need for antimicrobial medications among adult outpatients with acute diarrhea

2) To assess Pepto-Bismol's impact on additional care-seeking among adult outpatients with acute diarrhea
3) To determine Pepto-Bismol's effectiveness in reducing duration and severity of acute diarrhea among adult outpatients
4) To measure the proportion of adult outpatients presenting with diarrhea for whom private clinicians recommend antibiotics

Methods

Setting: Ambulatory care clinics staffed by licensed allopathic physicians, in low- to middle-income, multi-ethnic urban communities in Pakistan, during the rainy season (July – September). We will recruit general practitioners who treat adults with acute conditions and who typically evaluate ≥30 patients per day during the rainy season. General practitioners will screen patients and manage them per protocol. We will select 10 clinics that operate during typical business hours and 10 clinics that operate in the evening to ensure that patients from a wide range of demographics have the opportunity to enroll. Field work will be conducted by staff from Health-Oriented Preventive Education, a Karachi-based non-governmental organization working on health and education in communities in Pakistan.

Design

1. Eligibility. Persons aged 15 – 65 years old presenting with mild to moderate, non-bloody, acute diarrhea (≥3 loose stools/day for <3 days) to participating health care settings will be screened for eligibility. We set the lower age bound at 15 years because, while the study drug is approved for use in children 12 years and older, children younger than 15 years may not be able to complete study tasks reliably. The upper age bound is set at 65 years because diarrheal illness tends to be more severe in older persons. We will include patients for whom the study physicians recommend antimicrobial treatment. Patients who are pregnant, require hospitalization, or who have signs or symptoms of septicemia, a primary complaint of another acute illness, a serious chronic illness, an allergy to aspirin, or who have been exposed to antimicrobial or antidiarrheal medications within 72 hours of enrollment will be excluded. Patients may enroll in only one arm of the study, once during the study period.
2. Groups. Patients will be assigned to one of two treatment groups.
    a. Intervention group. The study drug, Pepto-Bismol (bismuth subsalicylate), will be dosed as chewable tablets each containing 262 mg bismuth subsalicylate. Patients will be instructed to take 2 tablets every 30 – 60 min as needed for diarrhea, but not to exceed 8 doses (16 tablets) per 24 h. Patients may discontinue the medication when stools become formed. Each patient will be given 32 tablets of the study drug.
    b. Control group. Placebo tablets will be visually identical to the study drug but will not contain any bismuth subsalicylate. Patients will be instructed to take 2 tablets every 30 – 60 min as needed for diarrhea, but not to exceed 8 doses (16 tablets) per 24 h. Patients may discontinue the tablets when stools become formed. Each patient will be given 32 placebo tablets.
    c. Instructions and interventions for both groups.
        i. Patients will receive a 48-h supply of the study drug or placebo and instructions about how to use it; oral or intravenous hydration as required; and standard counseling about

supportive care and prevention of diarrhea. The first dose of study medication/placebo will be administered before leaving the physician's office (attachment 6).

ii. Patients will not be given antibiotics upon enrollment.

iii. Patients will be encouraged to seek care from the study physician at any time they feel substantially worse than they did at enrollment, without waiting for additional direction from study staff.

iv. Patients will be asked to submit a stool specimen or rectal swab at the time of enrollment. If the patient is not able to produce a stool specimen at the clinic and does not wish to undergo rectal swabbing, study staff will attempt to collect a stool specimen during the first home visit. The stool/rectal swab will be cultured at Aga Khan University laboratories for standard enteric pathogens, and resulting isolates will be tested for antimicrobial susceptibility. Isolates will be stored for 1 year.

v. At 24 h after taking the initial dose of study drug/placebo. Study staff will visit patient to collect information and assess patient condition. Patients will be instructed to return to the clinic for additional management if they report feeling worse than they did at the time they took the initial dose of study drug/placebo. The physician will evaluate and treat the patient at his/her discretion. The study drug/placebo will be discontinued, but the patient will be followed for the full 5 days.

vi. At 48 h after taking initial dose of study drug/placebo. Study staff will visit patient to collect information and assess patient condition. Patients will be instructed to return to the clinic for additional management if, at 48 h after the first dose of the study drug/placebo, they report feeling the same as or worse than they did at enrollment. The physician will evaluate and treat the patient at his/her discretion. The patient will be instructed to discontinue the study drug/placebo if this has not yet been done. The patient will be followed for the full 5 days.

vii. At 5 days (120 h) after taking initial dose of study drug/placebo. Study staff will visit patient to collect information and assess patient condition. Patients will be instructed to return to the clinic for additional management if, at 120 h after the first dose of the study drug/placebo, they report feeling the same as or worse than they did at enrollment. The physician will evaluate and treat the patient at his/her discretion. The patient will be instructed to discontinue the study drug/placebo if this has not yet been done.

3. Group assignment. Within each provider's practice, eligible patients will be randomly assigned to the study drug or placebo. For each practice, we will generate a random sequence for assigning patients to study group in a 1:1 ratio. A single investigator will pre-label courses of study drug and placebo with the appropriate sequence before the study begins; this individual will maintain the assignment key and will not participate in data collection.
4. Masking. Allocation of the study drug and placebo will be concealed from providers, patients, and investigators until data are analyzed.
5. Sample size.
    a. Endpoint: Antibiotic use in active drug vs. placebo groups
    While accounting for stratified design and assuming 95% confidence, 1:1 enrollment of active drug and placebo patients, negligible drop-out, and antibiotic use among 10% of intervention

patients, we would require 20 providers to enroll 20 patients each (i.e., 10 per treatment group), for a total of 400 patients, to achieve 80% power to detect a 10% difference in antibiotic use between groups (i.e., 20% of control patients use antibiotics) during the 5 days of observation.

Measurements

1. Primary outcomes
    a. Use of antimicrobial medications by intervention group
        i. At 24 h after enrollment
        ii. At 48 h after enrollment
        iii. At 120 h (5 days) after enrollment
2. Secondary outcomes
    a. Patients' perceived need for antimicrobial medications during first 48 h of observation
    b. Additional care obtained for diarrheal illness during first 48 h and 5 days of observation
        i. Use of antidiarrheal medications
        ii. Visits to other health professionals for diarrhea or complications of diarrhea
        iii. Expenditures on consultations and treatments for diarrheal illness
    c. Disease severity and duration
        i. Time to first formed stool
        ii. Number of stools during first 24/48 h of observation
        iii. Duration of abdominal pain
        iv. Duration of nausea
        v. Time to resolution of illness (any of the following symptoms: diarrhea, nausea, vomiting, abdominal pain)
        vi. Severity of all symptoms of illness
    d. Diarrhea etiologies and antimicrobial susceptibility patterns, with possible sub-group analysis by etiology if sample size permits
    e. Patient experience with the study drug
        i. Satisfaction with resolution of symptoms
        ii. Satisfaction with esthetics of study medication
        iii. Adverse effects
    f. Patient knowledge, attitudes, and practices related to diarrhea, water, hygiene and sanitation
    g. Characteristics and diarrhea treatments experienced by patients ineligible for the randomized, controlled trial
    h. Proportion of adult patients with diarrhea for whom providers recommend antibiotics (during screening)
    i. Additional secondary outcomes may be explored to better understand the data
3. Possible confounders
    a. We will assess demographics, disease severity, and diarrhea management practices of potentially eligible but non-enrolled patients (attachments 1 and 4)

Schedule of study activities

1. Health care providers will be recruited into the study as staff and will be trained in study procedures. Basic information about these providers and their clinics will be collected (attachment 3).
2. On a pre-determined date, all clinics will begin to screen all adolescent and adult patients presenting with diarrhea for eligibility for the study (attachments 2, 4 and 5). We anticipate that each provider will see approximately 8 – 10 adolescent/adult patients with mild or moderate diarrhea each work day. For logistical reasons, we will enroll only the first eligible, consenting patient in each practice each day. We expect that a number of screened patients will be ineligible each day, and that restricting enrollment to the first eligible patient each day will not introduce substantial bias.
    a. The screening questionnaire (attachment 4) will be completed by study staff for each adolescent/adult patient with a presenting complaint of diarrhea, regardless of the ultimate determination about eligibility.
    b. HOPE staff will read the informed consent document (attachment 6) to eligible patients, including children age 15 – 17 years, and will ask each patient for written consent to participate.
        i. A parent or guardian of children aged 15 – 17 years old will be asked for written permission for the child to participate in the study.
3. If the patient is eligible and consents to participate, HOPE study staff will do the following at the time of enrollment:
    a. Complete the clinical record with assistance of physician (attachment 5).
    b. Collect a stool specimen or rectal swab.
    c. Administer the first dose of the study drug/placebo and provide oral rehydration education and supplies (attachment 7).
    d. Ask to accompany the patient to his or her home to simplify locating the home during follow-up.
4. Immediately after enrollment, study staff will:
    a. Transport the patient to his or her home and record the address and directions to the home.
    b. Complete the household questionnaire (attachment 8).
    c. Attempt to collect a stool specimen, if the patient was unable to provide one in the clinic.
5. Between 24 - 28 h, 48 – 52 h, and 120 – 126 h after enrollment, study staff will visit the patient to assess interim symptoms and activities (attachment 9).
    a. At least 24 h in advance, the field worker will arrange a mutually agreeable time and location to re-assess the participant.
        i. If the participant cannot be located during the scheduled follow-up visit, the field worker will attempt to learn where the participant is, and to complete the follow-up assessment within 4 hours of the scheduled meeting.
    b. If patient's condition worsens within 24 h of enrollment, or if condition has not improved by 48 or 120 h after enrollment, study staff will direct participant back to study physician for additional assessment and care. During these visits, physicians will not be asked to modify their recommendations for the study but will instead be asked to treat the patient as they feel necessary. Study staff will record details about the diagnosis and treatment obtained during this consultation (attachment 10).

Data management and quality control

Data will be recorded by study personnel on paper questionnaires. These will be delivered on a daily basis to the data manager, who will evaluate them for missing information and errors and will work with enumerators and the local study coordinator immediately to resolve any issues. Paper questionnaires will be stored in a secure cabinet at the HOPE offices. Data will be entered into a Microsoft Access database by trained personnel. Ten percent of questionnaires will be randomly selected for comparison against the electronic database; if more than 1% of fields differ, all questionnaires will be checked against the database and the database corrected as needed.

At the conclusion of report-writing, paper questionnaires will be destroyed.

Ethics

Informed consent

Eligible patients will be invited to participate in the study. Study staff will read a consent form (attachment 2, Flesch-Kincaid Reading Level 7.6) to interested patients, who will be asked to sign the form if they agree to participate. Participants age 15 – 17 years will be asked to sign the consent form; a parent or guardian will also be asked for written consent for the child to participate. Before the study begins, the statement of informed consent will be translated into Urdu and any additional dialects our formative research determines will be needed (see Protocol 6425), and back-translated into English to ensure preservation of meaning.

Risk/Benefit

Risk. The risks associated with participating in this study are minimal. The study will include only patients with mild to moderate acute diarrhea, which typically resolves within 2 – 5 days without treatment. Although clinicians in Pakistan appear to frequently recommend antibiotics for adults with diarrhea,[18] the World Health Organization states that antibiotics may be ineffective or harmful when used to treat diarrhea, and they should not be given routinely.[23] The World Health Organization does recommend considering antibiotic treatment among patients with cholera and severe dehydration, and among patients with dysentery.[23] However, there are few data demonstrating benefits following treatment of uncomplicated patients with dysentery, particularly in the context of rigorous medical follow-up. Although we will ask participants to refrain from using antibiotics to treat their diarrhea, we will include only participants with uncomplicated acute diarrhea, and we will assess them every 24 h for the first 48 h after enrollment. If they experience clinical deterioration during the first 24 h, they will be assessed by their physician and treated as required. They will also be assessed and treated without limitation by their physician if they do not experience improvement in their diarrhea during the first 48 h after enrollment. The risk to participants in this context is therefore minimal.

Randomly selected participants will receive a 48-h course of Pepto-Bismol (bismuth subsalicylate). Pepto-Bismol has been used as a treatment for diarrhea in the United States for nearly 100 years and has a strong safety record.[24] In the United States, it is available over-the-counter, and the Federal Drug Administration has approved its use among persons >12 years old. Adverse effects are typically mild and may include temporary darkening of stool and tongue, metallic taste in mouth, and

constipation. In Pakistan, a similar medication called Bismol is available without a prescription; it contains 265 mg of bismuth subsalicylate per tablet.[25]

Benefit. There are several possible benefits to participating in the study. Study staff will assess patients' illness severity upon enrollment, daily for the ensuing 48 h, and at 5 days after enrollment. Patients will be referred for additional medical evaluation and care as needed. The provider consultation fee for the initial diarrhea visit will be waived for all participants (i.e., eligible patients who consent to participate in the study). Participants will receive counseling about appropriate hydration and diarrhea prevention and will be given sachets of oral rehydration solution to use at home as needed. While oral rehydration is universally recognized as the cornerstone of acute diarrhea management, anecdotal reports suggest that it is not always provided to adult diarrhea patients in Pakistan. Participants receiving the active study drug may also experience faster resolution of their symptoms than if they received standard care.[19] Finally, participants will receive a small meal as a supplement to their nutrition and in appreciation for their time.

Use of a placebo

A placebo is necessary to understand both the clinical and behavioral effects of the study drug on patients. Data about the clinical effects of the study drug among adults infected with a broad array of diarrheal pathogens are limited. Data about the behavioral effects of receiving the study drug among a population accustomed to aggressive use of antimicrobial medications for diarrhea do not yet appear to exist. Thus, disentangling the effects of the study drug from the effects of a placebo is vital to develop effective and cost-effective programs to improve management of diarrhea, and to improve quality of life for patients with diarrhea.

Inclusion of children

Children suffer from higher rates of diarrheal disease and tend to seek medical attention for a greater proportion of their diarrheal illnesses than do adults. Therefore, interventions to manage diarrhea among children may have much greater reach in this population than among adults and the risks and benefits of such interventions among children should be studied. Because the study medication has been approved by the US FDA for use in, and in several countries is marketed to, children age 12 years and older, it is relevant to include children in this particular study. Including children will also expand the pool of eligible study participants, thereby increasing efficiency and decreasing the costs of conducting the study.

Confidentiality

Patients will be assigned a unique study identification number upon enrollment in the study. This number will be used to link baseline, household, follow-up, and clinical information. The link between patient identifiers and the study identification number will be stored in a locked cabinet at the HOPE office. During data entry, patient identifiers will be removed and only the study identification number will be recorded. After completion of the data analysis and communication of findings to the participants, the linking information will be destroyed. Reports will contain only de-identified, summary information.

Justice

This study is intended to assess the health impact and acceptability of bismuth subsalicylate in a low-income setting with very high rates of diarrhea. Bismuth subsalicylate is currently available for purchase at low cost in Pakistan, so people in this community could immediately apply any positive findings.

Institutional review

This protocol will be reviewed by the Institutional Review Boards of HOPE and the Centers for Disease Control and Prevention.

Reporting

Results of the study will be summarized and distributed to all participating providers, who may wish to incorporate the findings in their practices. The aggregate results of this study will be presented to the community through educational programs developed by HOPE. Finally, results will be summarized and submitted for publication in a peer-reviewed journal.

Conflict of interest

Procter & Gamble states that their purpose is to improve the lives of the world's consumers,[26] and Procter & Gamble is interested in knowing whether their products and services are effective in this capacity. Because it is a public, for-profit company, Procter & Gamble must develop products that consumers find useful enough to purchase regularly. Thus, this protocol will help the company understand more fully how its products further their mission to improve lives, while it may also help the company develop new marketing angles for their products.

Adverse events

While we do not anticipate any adverse events to result from study activities (completion of a few brief questionnaires during a 5-day period, exposure to up to 16 doses of Pepto-Bismol or placebo tablets), adverse events will be reported in a timely manner to HOPE (Dr. Mubina Agboatwalla, 92-214-53-9393), CDC (Dr. Anna Bowen, 404-639-4636), and to the Pakistani and US IRBs in accordance with institutional procedures. Adverse events may include, but are not limited to, anaphylaxis, hospitalization, or death. We will routinely record patient experiences with the study drug/placebo tablets and symptoms of their diarrheal illness (attachment 7), but such reports will not be considered adverse events.

Investigators

CDC

Anna Bowen, MD, MPH. Principal investigator. Conceived of study. Responsible for securing funding, drafting protocol, assisting with logistics of field implementation, analyzing study, and leading report writing.

Tracy Ayers, MS. Responsible for assisting with statistical aspects of protocol development, assisting with statistical analysis of study, and critically reviewing manuscript.

HOPE

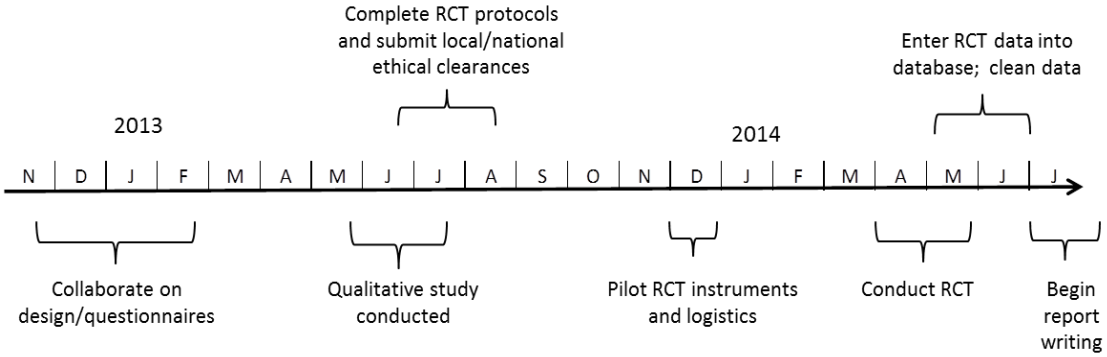
Mubina Agboatwalla, MBBS. Responsible for providing input into protocol, overseeing field implementation, coordinating referral services for patients experiencing adverse events, and assisting with report writing.

Sohail Hussein, BS. Responsible for overseeing data management and quality control.

P&G

Adam Pitz, PhD, Jose Brum, MD and Quantitative Sciences Organization. Responsible for assisting with design of study, securing funding, and critically reviewing manuscript.

Timeline



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414 **Attachment 1: Patient flow through eligibility assessment**

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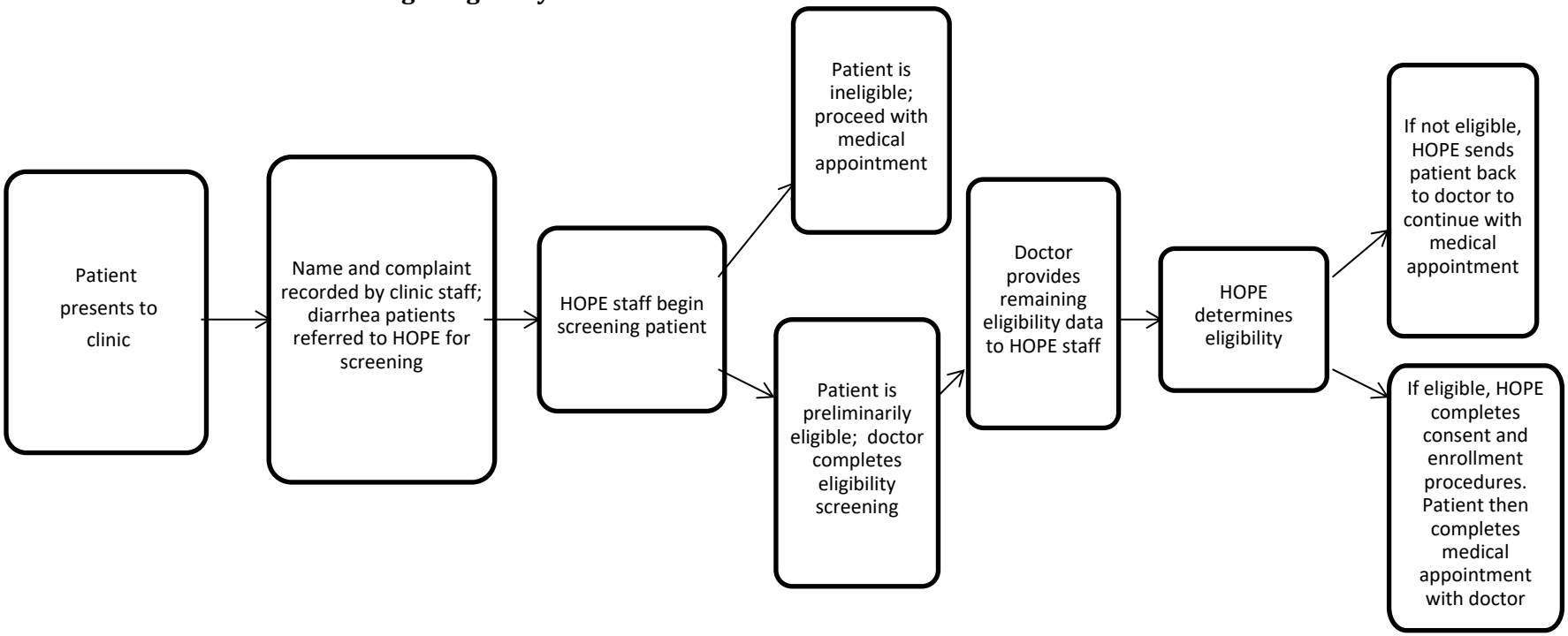

Attachment 2: Consent for participation

Dear sir or madam,

Many people in Pakistan and other places become sick with diarrhea each year, and we are doing a research study to understand how to take better care of them.

We would like to ask you to join this study. If you decide to join, we will pay the consultation fee to your doctor today. Your doctor will tell you about how to take care of your illness, and will give you some ORS, or oral rehydration solution, to take home. The doctor will also give you some tablets for free. Half of the people who join the study will get tablets that might help you feel better faster when you have diarrhea. This medicine is similar to Bismol and it has been used to help people with diarrhea in many parts of the world for decades. The other people in the study will get tablets that look the same, but they don't have any medicine in them. The kind of tablet you get will be decided by chance-- for example, by flipping a coin. We will also ask you to give us some stool. We will test it for germs that might be making you sick. We will tell your doctor the results so he or she can be sure you got the right treatments, but you might be feeling better before the tests are done.

After you are finished with the doctor, we will go with you to your house and give you some snacks for energy while you are sick. We will pay for the trip back to your house today. We will come back to your house each day for 2 days, and also after 5 days, to see how you are feeling. Each visit will take about 15 minutes. We ask that you keep track of how often you pass stools during this time so we can understand how the medicine is working. What we learn can help other people with diarrhea in the future. There are very few risks involved in the study, but the tablets might make your stool and tongue look very dark or black for a few days. This does not harm you and it goes away by itself. You do not need to pay anything to join the study.

We will label every survey with a code number rather than your name, and all of the surveys will be kept private. Your name will not be used in any report.

You may choose whether or not to join the study. You may skip any questions you do not wish to answer, and you may stop participating in the study at any time.

The results of the study will help us understand how to help improve people's health. After the study is finished, we will share the results with people and doctors in your community.

Health-Oriented Preventive Education, or HOPE, the United States Centers for Disease Control and Prevention, the Procter & Gamble Company, and your physician are working together on this study. If you have any questions about this study or about your rights as a participant, you may contact Dr. Mubina Agboatwalla at 92-333-213-1960. If you feel harmed or have questions about your rights as a study participant, you may contact the HOPE IRB at 02-13-224-3889.

Agreement to participate

Would you like to join the study *(circle one)*? Yes No

We may want to contact you again in the future for a related or follow-up study. Do you want us to contact you in the future for a related or follow-up study? Yes No

Name_____ Signature_____ Date (dd/mm/yy)_____

For parent/guardian of participants 15 – 17 years old

I agree to allow my child to participate in this study. Yes No

Signature of parent/guardian _____Date (dd/mm/yy)_____

Attachment 3: Script for distributing ORS and study drug/placebo

Read:

When we have diarrhea, our bodies lose more water than usual. When we lose too much water, or get dehydrated, our bodies can't work normally. When you are dehydrated, you usually have a dry mouth, feel thirsty and urinate less often, and you might get dizzy or light-headed. We can usually replace the water we lose during diarrhea by drinking. If the doctor told you that you are dehydrated, you will need to drink more than usual for another day or two, plus drink about a cup of fluid every time you have a loose stool. If your stomach is upset or you have been vomiting, it is easier to drink small amounts, but you will need to do this more often. For example, instead of drinking 2 cups all at once, you may have less vomiting if you drink ¼ cup every 5-10 minutes for an hour.

Some drinks work better than others. Coffee, juice, soda, and strong tea do not usually work very well to prevent or cure dehydration. Clear fluids, like water or weak tea or soup, work better. Oral rehydration solutions work especially well. I will give you some ORS sachets to take home. Have you used ORS before? [Explain how to prepare ORS and give 2 sachets.]

Now I will give you the study tablets. Here are 2 to take right now. You can chew them. [Break seal on bottle and give 2 tablets.] For the next 2 days, that is, 48 hours from now, you should take 2 tablets every hour as long as you are having symptoms of diarrhea. You can take up to 16 tablets during the next 24 hours (or in other words, until this time tomorrow). You can do the same thing during the next 24 hours. Do not take more than 16 tablets per day. These instructions are on the bottle to help remind you. [Give participant the bottle and show him/her the directions. Check whether the patient can explain to you how to take the tablets.] Do you have any questions about how to take the tablets?

As we discussed before, these tablets might cause your stool and even your tongue to look dark grey or black. This won't hurt you, and it will go away by itself after a few days.

I would like you to try to keep track of when you pass stools during the study, so for 5 days. When I visit you tomorrow, I will ask how many times you passed stool, when this happened, and whether it was diarrhea or normal stool. This might not be easy, but please try to remember. Some people like to keep track by making a tally on a piece of paper, or by adding 1 dry bean to a pile each time a stool is passed.

It is very important that I visit you 24 hours from now to see how you are doing. I hope that you will be feeling better. However, if your diarrhea is worse then, I will help you return to this clinic. If you are feeling much worse at any time before I visit you, please come back to this clinic for more care.

Now I would like to help you get back home, and give you a small meal if you are able to eat now. We would also like to offer you a free test of your stool, which you could provide in a stool cup in the privacy of your own home. Do you have any questions? [Arrange to go to participant's home, collect household information and stool specimen, and provide incentives.]