TITLE

Optimization of Mass Drug Administration with existing drug regimens for Lymphatic Filariasis and Onchocerciasis

('DOLF' project, Death to onchocerciasis and lymphatic filariasis)

Sponsored by:
Bill and Melinda Gates Foundation: GH 5342

Principal Investigator:
Gary J. Weil, M.D.

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1. Statement of Compliance

This study will be carried out in accordance with Good Clinical Practice (GCP) as required by the:

- U.S. Code of Federal Regulations applicable to clinical studies (45 CFR 46)
  http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46

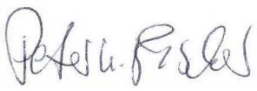
  ICH GCP E6 Completion of Human Subjects Protection Training
  http://grants.nih.gov/grants/guide/notice-files/NOT-OD-0 1-061 .html

- Bill and Melinda Gates Foundation "grant agreement" terms and conditions

2. SIGNATURES

The signature below documents the approval of this protocol and the attachments, and provide the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality and according to local legal and regulatory requirements and to the principles outlined in applicable U.S. federal regulations and ICH guidelines.

Signed: Date: 8 May, 2019



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4. List of Abbreviations

ALB	Albendazole
APOC	African Programme for Onchocherciasis Control
CFR	Code of Federal Regulations
DEC	Diethylcarbamazine
DEC/Alb	Diethylcarbamazine and Albendazole
DOLF	Death to Onchocerciasis and Lymphatic Filariasis
DSMB	Data Safety Monitoring Board
EDTA	Ethylenediaminetetra-acetic Acid
ELF	Elimination of Lymphatic Filariasis
FWA	Federal-Wide Assurance
GPELF	Global Program to Eliminate Lymphatic Filariasis
GCP	Good Clinical Practice
IATA	International Air Transport Association
ICH	International Conference on Harmonisation
ICT	Immunochromatography Test
IRB	Institutional Review Board
Iver	Ivermectin
KK	Kato-Katz
LIBR	Liberia
LF	Lymphatic Filariasis
MDA	Mass Drug Administration
MF	Microfilaria(e)
OCP	Onchocerciasis Control Programme

OHRP	Office of Human Research Protection
Oncho	Onchocerciasis
OSHA	Occupational Safety and Health Administration
PDM	Project Data Manager
PI	Principal Investigator
SAE	Serious Adverse Events
SOP	Standard Operating Procedure
STH	Soil Transmitted Helminth
WHO	World Health Organization
µl	Microlitre

5. Protocol Summary

Title: Optimization of Mass Drug Administration with existing drug regimens for Lymphatic Filariasis and Onchocerciasis

Population: Approximately 5,200 people will participate per year. The study population will include females and males over 5 years of age who live in filariasis endemic areas. Subject selection will not be based on health status.

Number of Sites: Two sites in Liberia

Study Duration: **7 years**

Subject Duration: Participants will be studied only once in cross-sectional surveys. Some subjects may be included in more than one annual population survey, but this is not a longitudinal study.

Objectives:

A. To evaluate different mass drug administration (MDA) regimens for lymphatic filariasis and onchoceriasis as well as its impact on soil transmitted helminthes. MDA is administered by others (e.g., Ministry of Health) and may enhance efforts to control and eliminate these important neglected tropical diseases.
B. We will compare the relative impact and cost effectiveness of annual vs. twice yearly mass drug administration (MDA) for elimination of lymphatic filariasis (LF) and control of onchocerciasis.
C. We will also study the impact of annual vs. semiannual MDA on soil transmitted helminth (STH) infection in the population.
D. ***Following conclusive results on the first objectives that annual MDA is as effective as semiannual MDA for LF, oncho and STH, we will conduct an additional survey to determine long term (7 year) impact of continued MDA on onchocerciasis, LF, and STH in two areas.***

Remarks on the project structure: The Project "Optimization of Mass Drug Administration with existing drug regimens for Lymphatic Filariasis and Onchocerciasis" has 2 major Objectives (Objective 1-Community MDA Trials, Objective 2-Randomized Clinical Trials). Objective 1 will be studied in 4 countries in Africa and 2 countries in South East Asia. Although the overall objectives are similar there are country specific modifications. This protocol was developed for Liberia.

6. KEY ROLES

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7. 2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

8. 2.1 Background Information

Lymphatic filariasis (LF) is a deforming and disabling infectious disease that causes elephantiasis and genital deformity (especially hydroceles). The infection affects some 120 million people in 81 countries in tropical and subtropical regions with well over 1 billion people at risk of acquiring the disease [1]. LF is caused by *Wuchereria bancrofti* and *Brugia* spp. (*B. malayi* and *B.timori*), nematode parasites that are transmitted by mosquitoes. The World Health Organization (WHO) developed a plan for LF elimination that is based on using novel approaches to rapidly map endemic areas and 4 to 6 annual rounds of mass drug administration (MDA) with antifilarial medications [2, 3]. A recent report from WHO reported that more than 1.9 billion doses of MDA were distributed between 2000 and 2007 [4]. Thus, the Global Programme to Eliminate Lymphatic Filariasis (GPELF) is the largest infectious disease intervention program attempted to date based on MDA. MDA has worked better in some areas than others. A recent publication reviewed challenges faced by GPELF [5]. These include (among others) inability to conduct

MDA programs in areas of Africa where *Loa loa* is coendemic because of the unacceptable risk of Serious Adverse Events (SAE's) with Ivermectin in persons with heavy *L. loa* infections, the limited macrofilaricidal activity of current MDA regimens (especially Ivermectin/Albendazole) that necessitate repeated annual rounds of MDA, and the difficulty of achieving high compliance rates for MDA over a period of years. ***It is clear that new dosing schedules for MDA have the potential to greatly improve the number of countries that will successfully eliminate LF by the WHO target date of 2020.***

Onchocerciasis ("Oncho") is similar in some ways to LF in that it is a vector-borne nematode parasitic disease that causes severe disability. Oncho affects approximately 33 million people, mostly in 30 countries in sub-Saharan Africa (with small foci in Latin America and Yemen) [5]. In contrast to LF, this disease causes blindness and severe skin disease rather than elephantiasis, and it is spread by black flies instead of mosquitoes. *O. volvulus* adult worms live in subcutaneous nodules while the adult worms of the LF parasites live in lymphatic vessels. *O. volvulus* adult worms are larger and less sensitive to available drug treatments than those of the species that cause LF. They also have a longer lifespan (approximately 14 years rather than the estimated 7 years for LF parasites). Several programs and developments have greatly improved the Oncho situation since the 1970's when the Onchocerciasis Control Programme (OCP) in West Africa (green countries in the map) was initiated. OCP relied exclusively on vector control in its early years. However, following the appearance of Ivermectin (Mectizan) on the scene in the late 1980's, OCP transitioned to become a drug distribution program with annual Ivermectin MDA in 11 countries. OCP ended in 2002. This was replaced by the African Programme for Onchocherciasis Control (APOC) which coordinates community directed distribution of Ivermectin MDA in 28 African countries (including the former OCP countries). OCP and APOC have done a good job of reducing parasite infection intensities and Oncho disease rates in many endemic countries. Unfortunately, there is no real end in sight for the APOC approach (apart from a funding endpoint in 2015); while it may be possible to eliminate Oncho in selected areas by MDA with Ivermectin (alone, or combined with vector control), disease control programs in most African countries will require active maintenance for many years to come. While Ivermectin has good activity against the parasite larvae that cause disease in the skin and eye (microfilariae or MF), it does not kill *O. volvulus* adult worms, and they resume production of MF that can lead to transmission of new Oncho cases by black flies after a few months. APOC activities are focused on areas with high infection rates (where disease risks are highest). However, extensive areas in Africa where fewer than 20% of adult men have Oncho nodules detectable by palpation are not receiving interventions for onchocerciasis at this time. These areas are not disease free (Oncho dermatitis can be severe in hypoendemic areas), and they also may serve as a source for reintroduction of the parasite into previously controlled areas after interventions stop. More effective drugs or dosing schedules for MDA against Oncho could shorten the number of years needed to interrupt Oncho transmission in areas that previously had high disease rates. Improved treatments should also make it feasible to extend MDA into areas that are currently not being helped. These changes have the potential to completely change the game to make global elimination of onchocerciasis a feasible goal.

Drugs used for LF MDA are also active against soil transmitted helminths (STH, e.g., *Ascaris*, Hookworm, and *Trichuris*). The estimated numbers of infected individuals (in millions) for *Ascaris*, hookworm and *Trichuris* range from 807-1227, 576-740, and 604-795 respectively [6]. Taken together these worm infections cause more disability adjusted life years than malaria. De-worming campaigns using anthelminthics usually target special groups of the population, such as schoolchildren, and have limited impact on the transmission. Treatment of the total population and semiannual treatments may reduce re-infection considerably and will most likely lead to reduced infection densities and infection prevalences. Suppression of STH is an important ancillary benefit of MDA programs for filarial infections [2]. Increasingly control programs for filariasis and STH are being integrated with programs for other parasitic diseases such as schistosomiasis. For this reason, participants in Foya district will also be tested for schistosomiasis. Results from this survey will help the Liberian Ministry of Health implement schistosomiasis control programs in the study area and in other parts of the country.

Results of Previous Work

The result of the studies conducted under this protocol produced evidence that annual treatment is superior to semiannual treatment for reduction of mf (both LF and oncho), and of STH infection intensities (multiple species).

In Maryland, at the last survey in 2016, O. volvulus microfilaria (mf) prevalence was 11% in the semiannual villages and 17% in the annual villages. Positive ICT for Wb antigen was 13% in the semiannual group and 5% in the annual group. In the semiannual villages, Ascaris spp. prevalence was 40%, hookworm was 17%, and Trichuris was 79%. In the annual group, Ascaris spp. prevalence was 50%, hookworm was 9%, and Trichuris was 7%.

In Lofa County, at the last survey in 2017, O. volvulus mf prevalence was 5% in the semiannual villages and 4% in the annual villages. Positive ICT for Wb antigen was 0% in the semiannual group and 0% in the annual group. Ascaris spp. prevalence was 2%, hookworm was 11%, and Trichuris was 1% in the annual group. In the semiannual group, Ascaris spp. was 2%, hookworm was 10%, and Trichuris was 2%.

9. 2.2 Rationale

This study is based on the assumption that currently used MDA regimens and schedules are not optimal for achieving elimination of LF. These regimens (either annual Alb 400 mg plus DEC 6 mg/kg or Alb 400 mg plus Iver 200 µg/kg for LF) were developed more than 10 years ago [3, 7]. Annual Iver (150 µg/kg) is effective for prevention of blindness, but it is unlikely to lead to elimination in most endemic areas. The highly successful African Programme for Onchocerciasis Control (APOC) is focused on morbidity prevention rather than disease elimination, and this explains its focus on hyperendemic and mesoendemic areas where Oncho blindness and dermatitis are significant public health problems [7]. The relatively small Onchocerciasis Elimination Program for the Americas (OEPA) provides a proof of principal that Oncho can be eliminated in some ecological settings [8]. Computer simulations suggest that Iver MDA may be sufficient to eliminate Oncho in some areas in Africa. However, the very long

duration of MDA and coverage rates required for this outcome [9] suggest that different strategies may be needed to improve chances for elimination in a reasonable period of time.

WHO (WHA 50.29) has targeted lymphatic filariasis for global elimination by the year 2020. GPELF recommends 4 to 6 years of annual MDA [2]. However, the likelihood of this strategy to succeed depends on a number of factors [5]. While some national MDA programs have succeeded, others are struggling to sustain MDA with high coverage rates for 5 to 7 years according to WHO guidelines, and others have not completed mapping or initiated MDA. Annual DEC/Alb may be sufficient to eliminate LF in endemic areas with low to moderate endemicity when high MDA coverage (at least 75%) can be sustained for 5 or more years. However, in a few countries in South East Asia the endemicity is high in some areas and annual DEC/Alb may not be optimal. In addition, the Iver/Alb regimen used for LF in Africa is less active against adult worms than DEC/Alb, and annual Iver/Alb may not be sufficient to eliminate LF in Africa. We assume that more effective and efficient MDA regimens might tip the balance toward LF elimination in areas that are failing or at risk of failing to reach elimination targets with current regimens. Therefore, the goal of Objective 1 is to compare intensive (twice per year, 2X) MDA with conventional annual MDA (1X) to determine whether improved efficacy of the 2X regimens justifies increased resources required for this more intensive treatment. These trials are based on two major *assumptions*:

A. We assume that 2X MDA regimens will reduce the time needed to reach LF elimination targets. 2X MDA should shorten the time it takes to interrupt transmission (preventing infections that would otherwise have to be treated in later years); depending on the drug combination used and parasite species targeted, 2X treatment should also lead to faster clearance of adult worms. Current MDA treatment strategies are based on interrupting transmission for the reproductive life span of the adult worms (estimated to 5-7 years for species that cause LF and 10-15 years for *O. volvulus*). However, these durations may be overly conservative, because they do not factor in the partial macrofilaricidal activity of repeated rounds of treatment. Accelerated MDA programs may improve compliance and reduce costs for social mobilization and training expenses for health personnel. These factors may reduce the time required to reach elimination targets. In addition, more intensive LF elimination programs may be more attractive for public health officials to undertake than programs that require 6 years or longer.

B. Suppression of STH is an important ancillary benefit of MDA programs for LF [2]. We assume that 2X MDA will be more effective for this purpose than annual MDA. The impact of MDA on STH varies for different parasite species and drug regimens [8, 9]. For example, *Ascaris* and hookworm are more susceptible to Albendazole than *Trichuris*. Persistence of *Ascaris* eggs in soil limits the ability of MDA to reduce *Ascaris* transmission.

DOLF studies in Liberia have provided some of the most complete data on the impact of community MDA regimens for LF and other NTDs. These studies have shown that 3 years of MDA had significant impacts on LF, STH and onchocerciasis prevalence in Liberia and other study sites. However, three years of MDA was not sufficient to meet elimination targets for those infections. An additional survey in the Maryland district will provide further data on the rate of decline of filarial antigenemia prevalence following MDA in Africa and on the effects of additional rounds of MDA on onchocerciasis and on STH prevalence and intensities. Three of these study areas had very high STH prevalence at baseline (two in Liberia and one in DRC), and continuation of measuring the impact MDA through 7 years after initiation will prepare these areas as potential sites for later studies of the efficacy of school-based deworming or other maintenance strategies to prevent the rebound of STH following cessation of MDA for LF.

In the last three years, annual MDA has been administered by the the NTD team of the Ministry of Health (MOH) in Lofa and by MOH/COUNTDOWN in Maryland. At a follow-up visit in 2019 by Liberian DOLF team members, all 16 study villages had received MDA. In Lofa County, MDA was conducted through the MOH alone, and the DOLF team recorded that not all of the 26 study villages in Lofa received MDA in 2018.

The proposed additional survey will provide data on long-term impact of MDA and support endgame research to understand how many rounds of MDA are needed to achieve elimination of LF and oncho and control of STH infections. The elimination targets for LF are <2% prevalence of antigen (assessed with FTS) and <1% prevalence of microfilaria (assessed with thick blood smear). The elimination target for onchocerciasis is <5% microfilaria in the skin (assessed by skin snip). The proposed survey will determine if these targets have been reached, and will answer the question of how many additional rounds of MDA are needed to achieve elimination targets. The answer to this question is critical for global elimination programs and may inform global policies.

10. 2.3 Potential Risks and Benefits / Potential Risks

Immediate risks

11. 2.3.1 Potential Risks

This research includes risks associated with collection of blood by finger prick and of skin snips (superficial skin biopsies collected by corneoscleral biopsy punch).

Likely **Collection of blood and skin snips causes minor pain.**

Less Likely **Collection of blood can cause a bruise, bleeding or infection at the collection site.** To minimize risks, sterile disposable lancets will be used for blood collection. Blood will be collected after disinfecting the skin with alcohol. Subjects will be instructed to apply pressure to finger prick sites to minimize bleeding and hematoma formation. The amount of blood being collected (less than 1 ml) is not enough to cause anemia.

Collection of skin snips can cause a bruise, bleeding or infection at the collection site. To minimize risks, skin snips will be collected after disinfecting the skin with alcohol using a sterile skin snip punch. Skin snip punches will be cleaned and soaked in 4% Mucocit-P for 5 minutes and then rinsed with 70% ethanol between subjects. Subjects will be instructed to apply pressure to skin snip sites for two minutes and to keep these areas clean.

There are no risks associated with collection of stool or urine samples.

Long range risks: None

- *Rationale for the necessity of such risks:* Blood and skin snips are required for diagnosis of filarial infection. Procedures in this project meet the definition of "minimal risk". Stool and urine samples are needed for diagnosis of other STH and schistosomiasis infections.
- *Alternative data gathering procedures that have been considered or will be considered:* None. Blood and skin snips are needed for diagnosing filarial infections (microfilariae) which are the subject of this project.
- *Why the value of the information to be gained outweighs the risks involved.* The potential benefits to individuals, society and science are considerable. The risks are minimal.

12. 2.3.2 Known Potential Benefits

- To subjects:

  The study will screen participants for parasitic infections and refer infected subjects for treatment at their local government health center. We will also provide data on infection rates to district health officials. This information will help the Liberian Ministry of Health to plan public health programs for villages where our study subjects live.

- To society:

  Participation will provide information on the impact of MDA on filarial and STH infections that affect the public health in the community.

3 OBJECTIVES

To conduct population-based field studies to determine the relative cost and efficacy of annual vs. semiannual MDA for control and elimination of onchocerciasis and lymphatic filariasis.

1. We will test the hypothesis that twice annual MDA is superior to annual MDA for eliminating lymphatic filariasis.
2. We will test the hypothesis that twice annual MDA is superior to annual MDA for controlling soil transmitted helminth infections and onchocerciasis.
3. ***Following conclusive results on the first objectives that annual MDA is as effective as semiannual MDA for LF, oncho and STH, we will conduct an additional survey to determine long term (7 year) impact of continued MDA on onchocerciasis, LF, and STH in two areas.***

13. 4 STUDY DESIGN

(Please read this section together with Section 5, ″Study Population″)

The project is comprised of repeated annual cross-sectional surveys in sentinel communities before and after initiation of mass drug administration for LF. MDA (standard regimens recommended by WHO) will be provided by government health officials. Data collection will include demographic data, history of lymphedema, scrotal swelling (hydrocele), acute filarial fever or adenolymphangitis, prior treatment for LF. Information on the presence of onchocercal nodules as well as on onchocercal skin and eye disease will be also recorded. Nodules will be assessed by superficial palpation. Blood samples will be collected from systematically sampled households. Blood will be tested for filarial antigenemia with one or more of the following: the BinaxNow Filariasis card test (also known as ICT), the Alere Filariasis Test Strip, and the TropBio test. Blood will also be tested for onchocerciasis (serology testing). Blood from persons with positive filarial antigen tests will also be tested for microfilaremia (*W. bancrofti* MF in the blood, see Section 6 below for methods). Two skin snips will be examined for microfiladermia (*O. volvulus* MF in the skin, see Section 6 below for methods). Stool examinations will be performed for diagnosis of STH infections and schistosomiasis (*S. mansoni*), and urine will be tested for *S. hematobium*. *Note that not all tests will be performed on all samples (blood, stool and/or urine).*

Safety oversight: Study personnel will monitor subjects for adverse events related to blood collection. No medical monitor or DSMB is needed for this minimal risk, non-intervention study.

Time to collect specimens: Most participants in the community will only be studied once (demographic data, blood, skin snips, stool and urine samples). Thus, the **duration** of subject participation will be one day.

Parameters and criteria for assessing the impact of MDA:

Blood tests for *Wuchereria bancrofti* infection: The Binax Now Filariasis card test, the Alere Filariasis Test Strip, and the TropBio antigen test (with MF testing of antigen positive subjects). We are using

these tests as measures of LF endemicity. The antigen tests detect antigen released from living adult filarial worms potentially capable of resuming MF production in the future. The filarial antigen tests are much more sensitive for infection in treated subjects than tests for microfilaremia. However, antigen tests may remain positive for years after treatment has cleared microfilaremia. The antigen tests will be performed on blood from individual residents 5 years of age and older. This will be done by sampling populations in sentinel sites (villages) to produce N of 400-500 per site. There will be several sentinel sites for each treatment zone (annual vs. twice annual MDA). The sample size number per sentinel site is close to the overall minimum target sample size of 335 needed to show that the filarial antigen rates are less than 2% (with 95% confidence and 80% power, assuming an expected rate of 0.5%, which is an LF elimination target). While all subjects will be tested with the Binax Now Filariasis card test, not all blood samples will be tested with the Alere Filariasis Test Strip and the TropBio antigen test. The purpose of parallel antigen testing of a subset of blood samples is to compare the performance of these three filarial antigen tests.

Subjects with positive filarial antigen tests will be tested for microfilaremia with 60 µl night thick blood smears collected by finger prick at night. Night blood samples are needed for microfilaria detection, because the parasites only circulate in peripheral blood at night.

Onchocerca volvulus infection- nodule palpation, skin snips and oncho serology: We are using these tests as measures of onchocerciasis endemicity. Due to the presence of deep nodules which cannot be assessed by superficial palpation, nodule data provide only an inaccurate estimate of endemicity. However, this method is used for rapid mapping of onchocerciasis and will be included. The assessment of MF in the skin is a more reliable measure of endemicity in areas with no community directed treatment using ivermectin. After treatment the presence of MF gives valuable information about the MF available for transmission. Two skin snips from skin over the iliac crest will be taken from subjects the same subjects who are tested for filariasis as described above. Blood collected for *W. bancrofti* antigen detection (see above) will be also used for onchocerciasis serology.

Stool examination for infection with STH and schistosomiasis. We will examine stool samples of the study population mentioned above for the presence and the density of STH eggs and *S. mansoni* eggs. We will use the FLOTAC and Kato-Katz (KK) methods to examine a single stool sample from each subject. These methods have excellent sensitivity and will provide accurate data on both the prevalence and intensity of infection. We will use community egg loads as a main indicator which combines both prevalence and density of infection and we target 95% reduction for each species. The Liberian MOH has agreed to provide Praziquantel to communities shown by our study to have high rates of schistosomiasis.

Urine examination for infection with *Schistosoma hematobium* We will examine urine samples by microscopy for the presence and the density of *S. hematobium* eggs. The Liberian MOH has agreed to provide Praziquantel to communities shown by our study to have high rates of schistosomiasis.

Continuation Activities (2019)

With 4 years of annual cross-sectional surveys conducted by DOLF researcher and completed in both Maryland (last survey in 2016) and Lofa (last survey in 2017), we plan to conduct an additional one-time cross-sectional survey in the Harper site in Maryland district in 2019 and in Lofa (Foya & Kolahun Districts) in 2020 to measure the long-term impact of MDA on W. bancrofti (lymphatic filariasis), O. volvulus (onchocerciasis) and on STH infection parameters following these cumulative 7-9 rounds of MDA. Since the last DOLF surveys, there have been a total of 3 annual rounds of MDA in both areas.

The study will recruit 2,500 participants in the Maryland area villages and 3,200 in the Lofa area villages. The proposed activities will comprise of identical survey methods as previously conducted surveys in both study areas. The survey includes:

- ***Stool sample collection with Kato Katz analysis for STH infections,***
- ***Blood collection by finger prick during the day with analysis by FTS and thick blood smear for detection of W. bancrofti antigen and microfilaria (respectively) in the blood (TropBio antigen test and Binax Now card tests will not be used as they were found to be inferior to the Alere Test Strip (FTS))***
- ***Skin snips for detection of O. volvulus microfilaria in the skin***

As a final note, we will not provide MDA as part of this research, but we will share our findings to the MOH and others to support their decision-making for MDA continuation or cessation. We will publish the findings to support global policy decision making.

STUDY POPULATIONS

Description of human subject involvement in research:

We will perform repeated annual cross-sectional surveys in study communities. Eligibility: This project will study people who live in communities that are endemic or have been endemic at the beginning of the study for lymphatic filariasis (LF) and onchocerciasis (oncho). The LF endemicity rate (MF rate) should at the study begin should be about 10% and there should have been no MDA in area immediately prior to study begin. The prevalence of oncho is secondary, but should be at least 5% nodule rate or 10% skin MF. ***Eligibility criteria will remain the same in the continuation surveys in both areas.***

Gender, minority and child inclusion: Males and females will be included in population-based village studies without regard to race, religion, or ethnic group. There is no reason to exclude pregnant women from population-based studies. There is also no reason to exclude children from the studies, and they are included. Exclusion of children less than 5 years of age from community studies is justified because prevalence rates for filariasis tend to be very low in young children and because of difficulties associated with collecting clinical specimens from this population.

14. 6 STUDY PROCEDURES / LABORATORY EVALUATIONS

Study procedures include collection of blood/skin biopsies and testing for microfilaremia, filarial antigenemia, filarial antibodies, microfiladermia and onchocercal nodules. We will perform stool examination to detect STH infections. We will examine urine samples to detect *S. hematobium* infections.

All parasitology tests will be performed in Liberia (*W. bancrofti* MF smears, antigen tests, *O. volvulus* MF detection, antibody tests, stool and urine examinations). The TropBio antigen test (ELISA) will be performed at Washington University (St. Louis, USA) in a laboratory that has facilities and experience needed for this assay.

15. 6.1 Laboratory Evaluations

The **rationale** for performing these tests is described in some detail in Section 4 (study design) above. Briefly, the study calls for collection of blood that will be tested for microfilaremia (60 µl thick blood smear), filarial antigenemia and antibodies (300 microliters), performance of skin snips (two superficial biopsies of about 2 mg skin each) for onchocerciasis testing, collection of stool (at least 1g of stool) for detection of parasite eggs. , and collection of urine (10 ml) for detecting S. hematobium eggs. Not all tests will be performed on all samples (blood, stool and/or urine).

Test methods:

Filarial antigen testing: The ICT card test (Binax Filariasis Now test [Alere, Portland, ME) will be performed according to manufacturer's instructions. Briefly, the subject's finger is cleaned with an alcohol wipe, dried with sterile cotton, and stuck with a sterile lancet. Finger blood is collected with a 100 µl capillary tube and placed on a sample pad on the card. The card is closed, and the result is read at 10 minutes.

The Alere Filariasis Test Strip will be performed according to the manufacturer's instructions. Finger prick blood is placed on the strip and the test is read at 10 minutes. This test uses the same reagents as the Binax Filariasis Now card test, and laboratory evaluations have shown that it may be superior to the card test, which is widely used for filariasis testing. This evaluation will determine whether the new strip test should replace the card test. The TropBio antigen test (a commercial ELISA assay) will be performed according to the manufacturer's instructions.

***W. bancrofti* microfilaria (MF) detection:** MF tests will be performed for subjects with positive filarial antigen tests. Three-line thick smears are prepared with a measured 60 µl quantity of finger prick blood collected between 8 pm and 2 am. Slides are fixed, stained with Giemsa, and examined by microscopy with a 10x objective (higher magnification for suspicious objects). The species of MF will be determined by morphological criteria.

***O. volvulus* microfilaria (MF) detection:** Two skin snips will be taken from the buttocks using Holth corneoscleral punches. Biopsies will be individually place in a well of a microtiter plate and incubated in

100 µl phosphate buffer at ambient temperature. Wells will be check for emerging MF after 30 min and after overnight incubation. After the incubation skin snips will be weighted [10].

Onchocerciasis serology: Small amounts of blood (<100 µl) from a subset of individuals may be tested for onchocerciasis infection markers (antibodies or antigens). Testing stool for ova of soil transmitted helminths**.** Stool will be collected in 25 ml containers and preserved in formalin (final concentration 5%). One gram of stool will be examined using the, mini-FLOTAC, and KK methods [11]. These tests are widely used for detecting and quantifying helminth eggs.

Testing urine for S*chistosoma hematobium* eggs. Urine will be collected in 40 ml containers and preserved in formalin (final concentration 5%). Ten ml of urinary sediment will be examined by microscopy to detect parasite eggs.

16. 6.2 Instructions for Specimen Preparation, Handling, and Storage

Finger prick blood will be collected in Eppendorf or microtainer tubes with EDTA anticoagulant and diagnostic tests will be performed within 48h following collection. ICT cards will be read in day light 10 minutes after finishing the procedure as required for the current test. Persons with positive antigen tests will be tested for blood microfilaremia by thick smear examination (60 µl). Blood samples will be stored at RT or 4°C (if available) and not in the direct sunlight.

Skin snips will be placed in separate wells of labeled microtiter plates immediately after collection, phosphate buffer will be added and wells will be covered with tape. Plates will be stored at ambient temperature (25-32°C) protected from direct sunlight. After incubation skin snips and emerged MF may be preserved by adding a drop of 10% formalin.

Stool samples will be preserved with formalin (final concentration 5%) and stored at RT until examination for helminth eggs. Samples will be labeled with barcode numbers that can be linked to unique identifiers (ID numbers).

Urine samples will also be preserved with 5% formalin for later microscopic examination.

Safety: Project personnel will treat all human blood, skin, urine, and stool specimens as if they were infectious, and we will comply with OSHA safety regulations (29CFR part 1910, 1030). **Field personnel will wear gloves, and laboratory personnel will wear gloves and lab coats for protection while working with blood, skin biopsies, urine, or stool samples.**

17. 6.3 Specimen Shipment

Some preserved stool samples and questionable blood smears or skin biopsies (with buffer) will be tested in parallel in the reference laboratory at Washington University in St. Louis for quality control. In addition, serum samples will be tested with the TropBio ELISA at Washington University, as mentioned above. Shipment will comply with Liberia rules and with IATA regulations.

18. 7 STATISTICAL CONSIDERATIONS

19. 7.1 Study Outcome Measures

The following variables will be treated as binary variables: Microfilaremia, antigenemia, microfiladermia, onchocercal nodules, stool parasites (*Ascaris*, Hookworm, and *Trichuris*) and *Schistosoma mansoni and S. haematobium* where applicable microfilaremia counts will also be recorded as MF/60 µl smear, microfiladermia counts as MF/mg skin (and MF/skin snip), nodules as nodules per person. Urine eggs will be recorded as eggs/ml of urine, and stool egg counts will be recorded as eggs/gram of feces.

20. 7.2 Sample Size Considerations

Except as otherwise noted, all sample sizes in this protocol were calculated using a binomial power calculator (using alpha = .05, two-tailed tests, and power = .80). These sample sizes were chosen to provide confidence that measured prevalence rates will be below specified limits based on assumptions regarding true prevalence rates. The sample size analysis considered various contingencies to assess robustness of the sample size estimates (see Appendix).

Note: Sample size considerations for community surveys for demonstrating that prevalence rates are below pre-defined targets for antigenemia, microfilaremia, microfiladermia, schistosomiasis, and STH infections are provided in Section 4, above, and this is not repeated here.

21. 7.3 Participant Enrollment and Follow-Up

This project aims to enroll at least 3,200 subjects per year in Foya District and 2,000 subjects per year in Maryland County. Study areas will have cluster surveys of approximately 400-500 people per 4 sentinel site (4 sites each in the annual and semiannual MDA areas). The community/household surveys are cross-sectional with no follow-up planned.

22. 7.4 Analysis Plan

The following outcome variables will be collected and treated as binary variables: Microfilaremia, microfiladermia, filarial antigenemia and antibody, and stool/urine parasites (separate analyses for *Ascaris*, *Trichuris,* schistosomes, and Hookworm). Microfilaria counts (recorded as MF/60 µl blood), microfiladermia counts as MF/mg skin, nodules as nodules per person, and stool egg counts for each species (recorded as eggs/gram of feces or eggs/ml urine) will be taken as count variables.

Data will also be collected for demographic characteristics and covariates including age, gender, and history of lymphedema, scrotal swelling (hydrocele), and prior treatment for LF. For demographic characteristics variables, descriptive statistics will be examined for the individuals who participate in the trials by sentinel site (village) and over years of observation. Frequency will

be tabulated for categorical variables. Descriptive statistics (mean, median, range and standard deviation) will be obtained for continuous variables.

Impact of MDA on study outcome measures

1. Testing the primary hypothesis

The primary hypothesis is that twice annual MDA is superior to annual MDA for eliminating LF. The binary outcome variables used to test this hypothesis include microfilaremia and antigenemia. The model which is being used will fit a linear trend over time within each village. The mean slope across villages within each treatment group will then allow estimates of time to target levels for control (microfilaremia < .5% and antigenemia < 2%) for a selection of baseline prevalences. To illustrate the analysis strategy, we use antigenemia as an example.

The antigenemia prevalence will be expressed as the filarial antigenemia rate (proportion of examined individuals with filarial parasite antigenemia detected with the Binax Now Filariasis card test. If Alere stops selling the card test, we may need to switch to their antigen strip test as the primary antigen test in later years of the project. To estimate the effect of MDA on antigenemia prevalence, we will tabulate mean rates of antigenemia across the four sentinel sites from each treatment zone (annual vs. twice annual MDA) over years of observation including the baseline. A generalized linear mixed model (GLMM) with a logistic link function will be used to account for the correlation of observations clustered within the same household from the same sentinel site. The model to estimate the difference in the odds of antigenemia includes treatment regimen and year of observation, and interaction between treatment regimen and year of observation. Some covariates that will be adjusted for in the analysis include sentinel sites, history of lymphedema, scrotal swelling (hydrocele) and prior treatment for LF as well as demographic variables of interest. Modeling will be performed with use of PROC GLIMMIX in SAS 9.2. CONTRAST statements will be used to test the significance of the log odds of antigenemia between the two treatment regimens at each year of observation. The difference of slope of rate decrease between the two regimens over the years of observations will also be tested with CONTRAST statements in PROC GLIMMIX. The resulting estimates will be converted to odds ratios with 95% confidence interval calculated from the robust estimator of variance. The other binary outcome variables (e.g., microfilaremia and microfiladermia) will be analyzed with the same technique.

With microfilaria (per 60 µl of blood) measured as counts, we will display mean counts of microfilaria across the four sentinel sites from each treatment zone (annual vs. twice annual MDA) over years of observation including the baseline. To accommodate zero counts in modeling, we will use Geometric mean intensity (GMI) of circulating microfilaria. GMI is calculated as antilog $[(\Sigma \log(x+1))/n] - 1$, where x is the number of microfilaria per 60 mm^3 of blood and n is number of subjects. A generalized linear mixed model (GLMM) (implemented in PROC GLIMMIX) will be used to account for correlation of observations resulted from clustering. CONTRAST statements will be used to test the significance of differences in GMI of antigenemia between the two treatment

regimens at each year of observation. The resulting estimates of GMI will be presented with 95% confidence interval. All statistical tests will be two-sided at a significance level of 0.05, but one-sided p-value will be reported according to the hypothesis. Similar analytic models will be done for community Mf loads, community *O. volvulus* Mf load, and for community egg loads for each of three intestinal worm species.

The cost analysis comparing the two treatment regimens will be conducted by Ann Goldman of the George Washington University School of Public Health and Health Services. The model will also allow cost effectiveness analysis when combined with the efficacy analysis.

2. Testing secondary hypothesis

The secondary hypothesis is that twice annual MDA is superior to annual MDA for controlling STH and onchocerciasis in the Foya district. The primary endpoint for assessing the impact of MDA on STH infections is community egg load (average stool egg count per species).The primary endpoint for onchocerciasis will be Mf prevalence by skin snip. We will also compare community Mf loads for onchocerciasis. The analysis strategy for these end points is the same for microfilaria count in testing the primary hypothesis.

Adverse event

Since this is a minimal risk and nonintervention study, adverse events are not expected to be an issue. However, subjects will be monitored for adverse events related to blood collection. Proportion of subjects with an adverse event will be tabulated with 95% confidence interval for each sentinel site at each year of observation.

Treatment coverage rate

Treatment coverage rate of the eligible population will be reported from the repeated cross-sectional surveys for the sentinel sites (villages) during different rounds of treatment. Differences in treatment coverage rates will be evaluated between the two treatment regimens (annual vs. twice annual MDA) over time with the use of Chi-square test.

23. 8 SUBJECT CONFIDENTIALITY

Subject confidentiality will be strictly held in trust by the participating investigators and staff. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participating subjects. This project does not include genetic testing. The study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any third party without prior written approval of the Principal Investigator. The study monitor or sponsor representatives may inspect all documents and records required to be maintained by the Investigator.

Data privacy control:

1- Every individual included in the study will have an ID number (unique identifier) that can be used to identify Locality ID, House ID, and Person ID.

2- Every sample collected in the field will be labeled with barcode stickers linked to ID number.

3- The Laboratory will test and report results using sample numbers, not names or ID.

4- Person names and identifying information will be directly entered into an Android Smartphone, and the information will be backed up daily from Smartphones to a laptop. The data from the Smartphones will be uploaded as it is collected to a central database on a secure Microsoft Azure cloud server under an account that is covered by a business service agreement between the Washington University in St. Louis School of Medicine and Microsoft to be HIPAA compliant. Information that includes names will be kept in a separate database that will be password protected and accessed only by the Liberian Project Data Manager (PDM) the DOLF PI (Dr. Weil), the Objective 1 PI (Dr. Fischer), country PI (Dr. Bolay), or DOLF Project Manager. This dataset will only be used during the data cleaning process to answer any discrepancies between serial/sample numbers and ID numbers. Names will be removed from the standard project database as the identifying data is not necessary for analysis.

5- The Data Management Team will be responsible for ensuring that no one in the project can link the sample IDs with the person IDs and that no one can use the names database except the PDM and others listed in #4 above. Person ID's will not be released for use in other projects.

6- The data server will keep a log file/data audit trail that will indicate the time/date and identify for every access to the data files. No one outside the Data Management Group will be able to modify any data on the server, and unauthorized persons will not be able to access any of the data files.

7- Each computer, Smartphone, or smart telephone with project data will have a separate password. The PDM is responsible for controlling these permissions, and she/he is the only one that can change this. Also, each database will have an access system with user names and passwords that will control the level of access and permissions for each user. The DOLF Project Manager will be responsible for managing access to the Microsoft Azure database.

24. 8.1 Future Use of Stored Specimens

Residual specimens (serum, blood smears) will be maintained after the study is completed for future research on infectious diseases. Samples will be stripped of unique identifiers and stored in endemic country laboratories or in the PI's laboratory at Washington University. Sequencing will be performed with DNA isolated from a small number of stool or blood samples to detect and characterize worm parasite DNA (blood or stool) and bacterial DNA (stool). The samples will be deidentified prior to any sequencing procedures. In addition, all human DNA sequences will

be filtered out prior to bioinformatic analysis and no genetic testing of humans will be performed.

25. 9 INFORMED CONSENT PROCESS

We will follow procedures outlined in the DHHS Regulation on Informed Consent 45 CFR Part 46 - Subpart A, 46.116 (http://www. hhs.gov/ohrp/humansubjects/guidance/45cfr46. htm#46. 116).

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continuing throughout the individual's study participation. Study physicians will read the consent script (with potential risks and benefits) in a locally understood language to subjects and their families and leave a copy of this with each family. The consent document will be reviewed and approved by project IRB's prior to initiation of the study. Study physicians will discuss risks and possible benefits of participation in this study with subjects and their families. Study physicians will explain the purpose of the study to subjects and answer any questions that may arise. The subjects may withdraw consent at any time throughout the course of the study. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

26. 9.1 Informed Consent/Assent Process (in Case of a Minor or Others Unable to Consent for Themselves.

Inclusion of minor children in community surveys will require consent from at least one parent plus assent of the child.

Human studies for this project are pending at FWA registered institutional review boards at Washington University (Dr. Fischer) and at IRB of the University of Liberia, Monrovia (Dr. Bolay); no human studies will be conducted prior to approval by both IRBs.

Participants will be re-consented with a revised informed consent document that includes a summary of progress on disease elimination (data findings) to date as well as a description of the survey procedures (similar to the previously used informed consent).

27. 10 LITERATURE REFERENCES

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28. Annex 1: Protocol for the Survey on resumption of mass treatment for parasitic infections in Foya District following the recent Ebola outbreak

Background

In March 2014 all DOLF study related work was suspended after cases of Ebola were reported in and around our research site at Foya District. Since then, no government MDA has taken place in this area, which turned out to be the early epicenter of the Ebola outbreak in Liberia. Now the Ebola outbreak is under control in Liberia. There have been no new reported cases in the country since the end of February according to Mar 11, 2015 WHO situation report. This means that important public health campaigns like MDA can resume. However, given these communities' difficult experience with the outbreak, their trust in the national health system may be strained or damaged in way that could negatively impact MDA programs for parasitic infections.

Objective

Before the government restarts its MDA program, it is important for us to know how communities will respond to these drug distribution programs. We need to understand communities' feelings and opinions toward these programs following the recent Ebola outbreak.

Study Design

This is a cross sectional, questionnaire study. The questionnaire will be administred to community leaders in 21 of the 32 DOLF MDA community survey study villages. Due to time constraints, we are using a purposive sample of at least two adult influential community leaders (ex. village chief, religious leader, teacher) and at least one community directed distributor per village. The questionnaire includes questions on demographics, community feelings toward MDA, and about Ebola's effect on personal and community life. Several open ended questions have been included to elicit rich qualitative data. Reponses to the survey will be audio recorded

Analysis Plan

The main outcomes of interest from the questionnaire of community leaders in Foya are whether or not village leaders think their communities are ready to participate in MDA and/or continue participation in the community surveys. Frequency of categorical responses will be aggregated for each village and as a whole for all of the villages and used together with qualitative data to describe overall feelings in these communities toward mass treatment programs for parasitic infections in Foya.

Subject Confidentiality

Participant's names will not be recorded in the survey. Audio recordings and other information will be kept confidential and only made available to project researchers. Group results from this survey will be reported without the names or identifying information of participants. Data stored on password protected laptops or paper copies will be kept with researchers and stored in locked rooms, until they can be saved on secure Washington University servers. Data will not be shared with third parties without permission from the PI (Gary Weil).

Informed Consent

Informed consent is a process that is initiated prior to the individual′s agreeing to participate in the study and continuing throughout the individual′s study participation. Researchers will read the consent script (with potential risks and benefits) in a locally understood language to subjects and leave a copy of this with each participant. The consent document will be reviewed and approved by project IRB′s prior to initiation of the study. Researchers will explain the purpose of the study to subjects and answer any questions that may arise. The subjects may withdraw consent at any time throughout the course of the study. Only adults 18 years or older will be included in this study.
(See the *Informed Consent Script to Be Read for Questionnaire of Community Leaders in Foya District* included in Supplements/Appendices)

29. SUPPLEMENTS / APPENDICES

A. Standard Operating Procedure (SOP) Summary of Laboratory Work

Project laboratories will receive, process, and archive biological samples. They will perform assays and report results to the Data Management Team and Project scientists. The Laboratory will perform the following procedures and assays.

Blood samples: The laboratory will use finger blood samples to perform several tests.

Microfilaria testing (*W. bancrofti*): Thick blood smears (60 µl in 3 parallel lines of 20 µl each) will be stained with Giemsa and examined with a microscope for MF.

Microfilaria testing (*O. volvulus*): Two skin biopsies will be incubated in an isotonic buffer and emerging MF will be detected using a microscope.

Filarial antigen tests: Binax Now Filariasis card tests using finger prick blood (100 µL) will be performed in the laboratory according to the kit protocol and read at 10 minutes for *W. bancrofti*. The Alere Filariasis Test Strip, and TropBio ELISA tests will be performed according to the manufacturer's instructions for *W. bancrofti* . Tests for onchocerciasis are to be determined.

Stool examinations for STH: Stool will be collected in 25 ml containers and preserved in formalin (final concentration 5%). One gram of stool will be examined using the FLOTAC and KK methods [10]. This method provides a sensitive means of detecting and quantifying helminth and *Schistosoma* eggs.

Urine examinations for *Schistosoma hematobium*: Urine will be collected in 40 ml containers and preserved in formalin (final concentration 5%). The sediment from 10 ml of urine will be examined by microscopy.

Specimen archive: The Laboratory will be responsible for maintenance of archived samples (serum, preserved stool and urine samples, etc.) collected during the DOLF project.

QC activities: DOLF investigators will visit study sites to review procedures and results. We will also keep in close contact by email, telephone, and during visits by collaborating scientists from disease-endemic countries to the USA. All samples will be tested in the endemic country laboratories. Some preserved stool samples and questionable blood smears will be tested in parallel in the reference laboratory at Washington University.

B. Standard Operating Procedures Summary (SOP) for Data Collection and Field Work

Field work will be done by trained physicians and paramedical personnel who will be trained for data and blood collection.

All field team members will be trained by staff physicians with assistance from other project personnel:

1. All field epidemiology personnel (physicians, technicians and field workers) will be trained in GCP topics for research involving human subjects.
2. Field and laboratory personnel will also be trained regarding proper procedures for collecting blood, preparing blood smears, performing card serological tests, skin snips, and labeling specimens (barcode stickers).
3. Field data will be entered in the field using questionnaires on Smartphones. Finger-prick blood and skin biopsies will be collected by physicians or trained technicians for laboratory studies. All samples will be labeled in the field with barcode stickers.
4. Technicians will be responsible for transferring all blood and skin samples to the Laboratory immediately after field trips (same night of collection).
5. Stool and urine samples will be collected by the field epidemiological personnel during the survey or on the next day.

C. Informed Consent Script to Be Read in Population-Based Field Surveys

Project title: **Optimization of chemotherapy for control and elimination of onchocerciasis and lymphatic filariasis**

Project Director: **Dr. F. Bolay (country Principal Investigator)**

Sponsored by: **Bill and Melinda Gates Foundation (USA)**

1. Invitation: You (and your family members) are being invited to participate in a project to test the impact of a public health program on parasite infections (river blindness and lymphatic filariasis and intestinal worm infections) that are common in this area.

2. Purpose: The purpose of this project is to assess the continued effects of mass drug administration on filariasis and other worm infections in Liberia. This project is being conducted by the Liberia Institute for Biomedical Research (LIBR) in cooperation with scientists at Washington University in St. Louis USA.

We came to this area several years ago to do a similar study. We found that four years of the drug administration decreased the amount of river blindness and lymphatic filariasis in your area and we found out that once a year treatment is enough to reduce the infections. Now villages in your area have had three more years of the mass drug administration, we want to test you for the infections and find out if the number of infections in your area has gone down even more.

3. Procedures: Your finger will be cleaned with alcohol, and a few drops of blood will be collected by finger prick. We will keep blood samples collected now to do other research studies of infectious diseases in the future. We will also palpate your pelvic region for worm nodules and take two small skin samples (skin snips). We will also collect information (such as name, age, and address or house location. The screening procedure will take a few minutes of your time for collecting information and the blood and skin samples. We will also collect stool and urine samples to test for other worm infections

4. Risks: There are no significant risks. Collection of blood (a few drops by finger prick) and skin (less than the size of a grain of rice) samples causes minor pain and occasionally a small bruise. You will be asked to keep pressure with cotton on your finger for 2 minutes to stop bleeding. The small amount of blood and the small piece of skin being collected will not harm your health.

5. Number of participants and duration of the project: Approximately 5,700 people will participate in the project (3,200 people from Foya district and 2,500 people from the Maryland area) per year; the tests will be given once in each area.

6. Benefits: Participation in this health project will benefit you and your family by providing a free screening test for early detection of parasitic worm infections. If you or any of your family members are found to have worm infections, you will be referred to your local health center for treatment. The project will also help the Ministry of Health by providing information on the effects of their mass drug

administration program on filariasis and other worm infections in your community. The test we are going to do will find out if you have the infections, but we are not providing additional treatment or a cure.

7. Confidentiality: Results of any abnormal blood, stool or urine tests will be provided to you and also to local health authorities. All project records may be reviewed by the sponsors of the program. Otherwise, any information linked to your name will be strictly confidential.

8. Questions: You are free to ask any question regarding this health study now. If questions arise later, please contact Dr. Bolay, who can be reached by telephone **Tel. +2316516302 / +2316516803/ +231886513040 or Email: director.libr@gmail.com**

9. Participation is voluntary: Participation by you and your family members in this public health assessment project is entirely voluntary. Children should not be forced to participate against their will. Refusal to participate will not penalize you in any way, and you are free to withdraw at any time.

Note: Program personnel must mark each computer record to verify that they have read this script to all participants and answered any questions. A copy of this information form should be left in each house included in the program.

C. Informed Consent Script to Be Read for Questionnaire of Community Leaders in Foya District

For the survey on resumption of mass treatment for parasitic infections in Foya district following the recent Ebola outbreak

Invitation: Because you are considered to be a leader in this community, you are being invited to participate in a survey to help understand the best way to resume mass treatment for parasitic infections following the recent Ebola epidemic. This program was started in 2012 to measure how these treatments improve the health of people in your village.

Purpose: The purpose of this questionnaire is to learn how your community feels about the mass treatment program that started in 2012 and their willingness to take the medicines when this public health program resumes in the near future. We would like to understand whether any actions or special education is needed to reassure your community about the purpose and value of this free drug distribution program. The project is being conducted by the Liberia Institute for Biomedical Research (LIBR) together with scientists at Washington University in Saint Louis, USA.

Procedures: During the questionnaire you will be asked questions about yourself, your community, mass drug administration programs, and Ebola. Your responses will be audio recorded. The questionnaire will take between 10-15 minutes. You may choose not to answer any question at any time. Your name will not be collected in the questionnaire.

Risks: There are no significant risks. Some of the questions may be uncomfortable or difficult for you to answer. You are not required to answer any question and may choose not to answer or stop the questionnaire at any time.

Number of participants and duration of the project: Approximately 100 adults will participate in the project. We will talk to 4 to 5 people per village in about twenty villages in Foya district over the course of 7 days.

Benefits: This information will benefit the Ministry of Health by providing information about how communities will respond to disease control programs that were interrupted by the Ebola epidemic. There is no direct benefit to you for participating in this survey. However by sharing your opinion you can help improve how mass drug administration programs operate in your community.

Confidentiality: Your name will not be recorded as part of the survey. Audio recordings and other information will be kept confidential and only made available to project researchers. Group results from this survey will be reported and (and perhaps published) without the names or identifying information of participants

Participation is voluntary: Your participation in this survey is entirely voluntary. Refusal to participate will not penalize you in any way, and you are free to withdraw at any time.

Consent: Your participation in this survey (answering our questions) will indicate that you have consented to join the survey.

Questions: You are free to ask any question regarding this questionnaire now. If questions arise later, please contact Dr. Bolay, who can be reached by telephone **Tel. +2316516302 / +2316516803/ +231886513040 or Email:** mailto: director.libr@gmail.com

Note: Program personnel must mark each computer record to verify that they have read this script to all participants and answered any questions. A copy of this information form should be left with each participant.