

“Community Based Safety and Efficacy Study of 2-drug (Diethylcarbamazine and Albendazole) versus 3-drug (Ivermectin, Diethylcarbamazine and Albendazole) Therapy for Lymphatic Filariasis in Indonesia”

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Type: Community Based Mass Drug Administration

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INVESTIGATOR AGREEMENT

“Community Based Safety Study of 2-drug (Diethylcarbamazine and Albendazole) versus 3-drug (Ivermectin, Diethylcarbamazine and Albendazole) Therapy for Lymphatic Filariasis in Indonesia”

DOLF_IDA_Indonesia: v5.0 24 May 2017

I have read the protocol, including the appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined and make a reasonable effort to complete the study within the time designated.

I will provide all study personnel, participating in the study under my supervision copies of the protocol and access to all study related information provided by the DOLF project. I will discuss with them to ensure they are full informed about the study drug(s) and the study procedures.

Project Principle Investigator: _____

Name/Title (Print/Type)

Signed: _____ **Date:** _____

NOTE: Both the Project PI and local PI should have signed investigator agreements on file.

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Local Principle Investigator: _____

Signed: _____ **Date:** _____

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LIST OF ABBREVIATIONS

GENERAL PROJECT ABBREVIATIONS

AE	Adverse Event/Adverse Experience
AEERF	Adverse Event Evaluation and Report Form
AFC	Anti-Filariasis Campaign
Ag	antigenemia
ALB	Albendazole
CDD	Community Drug Distributor
CRF/eCRF	Case Report Form also referred to as eCRF (electronic case report form)
CRO	Contract Research Organization
DA	Two Drug Therapy (diethylcarbamazine and albendazole)
DEC	Diethylcarbamazine
DOLF	Death for Onchocerciasis and Lymphatic Filariasis
DOT	Directly Observed Treatment
DSMB, DSRB or DMC	Data and Safety Monitoring Board also called Data Safety Review Board or Data Monitoring Committee
EC	Ethics Committee (may also be called IRB or Institutional Review Board)
EDC	Electronic Data Capture
FTS	Filariasis Test Strip
GCP	Good Clinical Practice
GPELF	Global Programme to Eliminate Lymphatic Filariasis
GPS	Global Positioning System
ICF	Informed Consent Form
ICH	International Conference on Harmonization

IDA	Triple Drug Therapy (Ivermectin, Diethylcarbamazine, and Albendazole)
IMA	IMA World Health
IRB	Institutional Review Board (may also be called EC)
IVM	Ivermectin
KAP	Knowledge, Attitude and Practices
LF	Lymphatic Filariasis
MDA	Mass Drug Administration
MF	Microfilaria(e)
Mg	Milligram
NTD	Neglected Tropical Diseases
NLM	National Library of Medicine
PHM	Public Health Midwife
PI	Principal Investigator
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
STH	Soil transmitted helminthes
TAS	Transmission Assessment Surveys
UNID	Unique Study Identification Numbers
UR	University of Ruhuna
USAID	United States Agency for International Development
WHO	World Health Organization

COUNTRY SPECIFIC ABBREVIATIONS

UI	Universitas Indonesia
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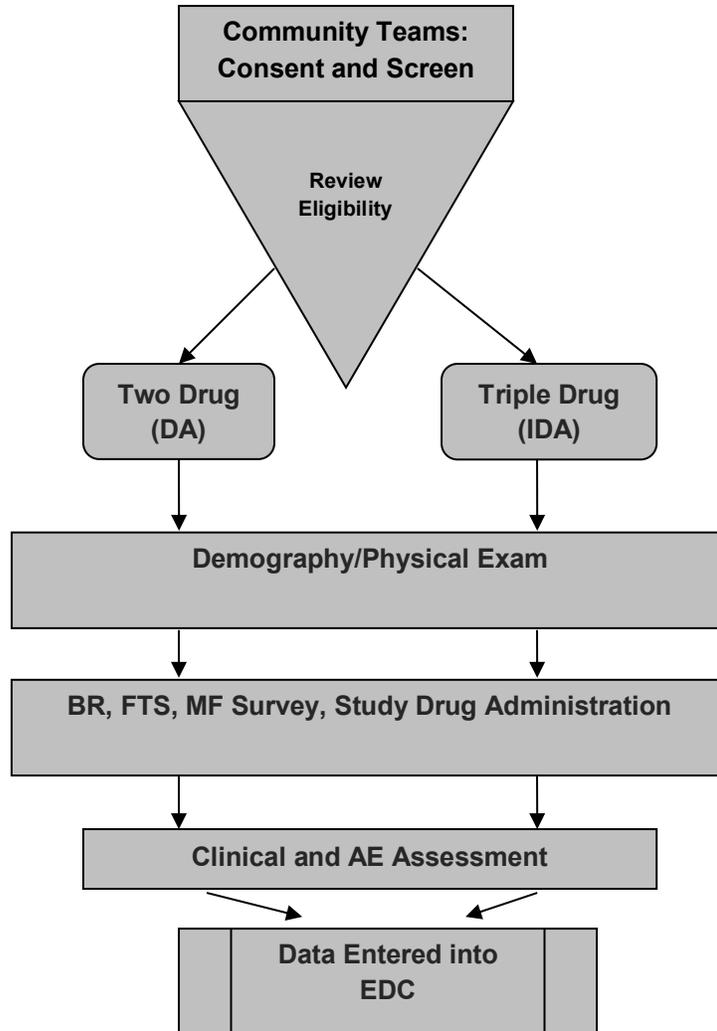
1 PROTOCOL SUMMARY

Study Title:	Community Based Safety Study of 2-drug (Diethylcarbamazine and Albendazole) versus 3-drug (Ivermectin, Diethylcarbamazine and Albendazole) Therapy for Lymphatic Filariasis in Indonesia
Type of Study:	Mass Drug Administration
Population:	IDA/ Triple Drug Arm: participants more than or equal to 5 years of age DA/ Dual Drug Arm (DA): participants more than or equal to 5 years of age
Number of Treated Areas:	Treated areas include Flores (Flores Timur District, Ojandetun village, <i>B. timori</i> MF prevalence 8.6%) and Sumba (Sumba Barat Daya District, Karang Inda, Kahale, and Rada Malando villages, <i>B. timori</i> MF prevalence 6.5%) islands that are mainly endemic for <i>B. timori</i> .
Duration of Participant Participation	Single treatment with daily adverse event follow-up thru Day 7, then a long-term follow-up visit at 1 year. Hospital-based participants will be observed in hospital for the first 48 hours. Some participants may also be selected for follow-up at 1 month for stool collection, or follow-up at 2-4 months for an acceptability survey.
Study Drugs	Ivermectin (3 mg tablets) <i>*not included in two drug arm treatment</i> Diethylcarbamazine (100 mg tablets) Albendazole (400 mg tablets)
Primary Objectives:	Determine the safety profile of triple-drug therapy by measuring frequency, type, and severity of adverse events following triple drug therapy (IVM+DEC+ALB) compared to the standard two drug treatment (DEC+ALB) in infected and uninfected individuals in a community Compare the efficacy of IDA (3 drug therapy) to DA (2 drug therapy) administered in communities for clearance of MF and filarial antibody for <i>Brugia timori</i> .
Secondary Objectives:	Assess the effect of intensity of filarial infection on the frequency and severity of adverse events

	<p>Compare community acceptance of Mass Drug Administration with three drug vs two drug therapy To compare the efficacy of DA vs IDA on soil-transmitted helminthes (STH)</p>
DOLF Project	<p>This protocol is specific to Indonesia, but results will also be included in the larger DOLF project. Data will be available/reviewed at a country level and at the project level.</p>

STUDY DESIGN

General Flow Diagram:



DOLF_IDA_Indonesia Study	ARM 1	Sample Size: 2000	Triple Drug
	ARM 2	Sample Size: 2000	Two Drug

NOTE: A Study Flow Diagram specific for Indonesia is provided in [Appendix 1](#).

2 BACKGROUND INFORMATION AND RATIONALE

In 2000, the World Health Organization (WHO) launched the Global Programme to Eliminate Lymphatic Filariasis (GPELF) to eliminate lymphatic filariasis as a public health problem by 2020. To interrupt transmission, WHO recommends therapy using combinations of two medicines delivered to entire at-risk populations through a strategy known as mass drug administration (MDA). Ivermectin and albendazole are administered in areas where onchocerciasis is co-endemic; diethylcarbamazine and albendazole are administered in areas where onchocerciasis is not co-endemic.

Lymphatic filariasis (LF) is a parasitic worm infection caused by the filarial nematodes *Wuchereria bancrofti*, *Brugia malayi* and *Brugia timori*. Adult worms reside in the human lymphatic system and release immature forms (microfilariae) into the blood stream. These are taken up by mosquitoes that continue the cycle when they bite another person. Dying adult worms provoke disabling and disfiguring obstruction of the lymphatic vessels and can cause lymphedema leading to elephantiasis (known as “Kaki Gajah” in Indonesia). In addition, the species *W. bancrofti* causes hydrocele in men and breast/ vulva enlargement in women. In 2000, WHO launched the Global Programme to Eliminate Lymphatic Filariasis (GPELF) to eliminate LF as a public health problem by 2020. For Asia, WHO recommended the co-administration of diethylcarbamazine (DEC) and albendazole. The programme’s current strategy to interrupt transmission relies on the annual single dose mass drug administration (MDA) of these 2 drugs (DA) given to the entire eligible population in endemic districts. The program has made significant progress driving microfilaria (MF) prevalence (a measure of the distribution of infection) below 1% in many areas of the world as of 2015 [1]. Despite this success in some endemic countries, MF prevalence has remained >1% in a many areas within a number of countries, including Indonesia. Therefore, additional treatment strategies are needed to help interrupt transmission in these areas and ensure that the GPELF meets its goal by 2020 [2].

Results of a pilot study [3] in Papua New Guinea (PNG) showed that a single dose of three drugs [ivermectin, DEC, albendazole (IDA)] completely cleared *W. bancrofti* MF for at least 1 year in all participants, which was superior to the currently recommended two-drug regimen (DA). This observation was confirmed with results from a larger clinical trial in PNG where IDA completely cleared MF in 57 of 58 people with heavy LF infections while DA cleared only 33 of 112 participants (King et al. unpublished data). These results suggest that IDA effectively kills or permanently sterilizes adult filarial worms. Many people treated in these studies experienced transient systemic adverse events (AE) commonly associated with DEC or ivermectin treatment of filariasis, and AEs were more frequent after IDA than after DA. However, no serious adverse events (SAEs) were observed in these trials or in a trial that is currently in progress in the West African country of Côte d’Ivoire (King et al. personal communication). No information is available on the frequency or type of AEs following IDA treatment of uninfected persons, but this is expected to be low since most symptoms appear to be the response to dying or damaged worms. The dramatic reduction and sustained decrease of MF along with the safety profile seen in the PNG studies suggest that the triple drug therapy may be a useful tool for eliminating LF in

areas where MF rates have remained > 1% following MDA with the standard DA regimen. The addition of ivermectin in an MDA regimen would also provide additional public health benefits, since it complements the deworming effect of albendazole (a global initiative) and eliminates lice and scabies mites [4].

2.1 Country Specific Background

Indonesia is the only country in the world that is endemic for all three filarial species that cause LF, with *Brugia* causing the majority of infections. The country has one of the highest burdens of LF, and it is a key member of GPELF. Our team has shown that an MDA strategy can eliminate brugian LF [5]. But since achieving high MDA compliance for 5-6 years is a challenge in some areas in Indonesia [6], the country could benefit from the more rapid IDA MDA approach. Comparative trials between *Wuchereria* and *Brugia* using DEC with albendazole indicate a similar efficacy for both species, but adverse events may be more common in *Brugia* infection because of a more rapid killing of MF [7, 8]. IDA has not been previously studied for the treatment of brugian filariasis.

Although the studies mentioned above have clearly demonstrated the superiority of the triple drug therapy for clearing *W. bancrofti* microfilariae from the blood, more safety and efficacy data are needed before triple therapy can be rolled out on a large scale as a mass drug administration regimen in lymphatic filariasis endemic countries. WHO recommends a best practice called “cohort event monitoring” for demonstrating safety of new drug regimens for public health program use. Establishing safety through such methodology requires pre and post treatment assessments from at least 10,000 people treated with the triple therapy across multiple settings.

A consortium consisting of Washington University, Case Western Reserve University, the Universitas Indonesia, Jakarta, the Indonesian Ministry of Health, the Papua New Guinea Institute for Medical Research (PNG), the Papua New Guinea Department of Health (PNG), the National Vector-Borne Disease Control Programme (India), and The Centers for Disease Control (Haiti) was formed to test efficacy for brugian LF and to comparatively evaluate the AE and SAE profiles of DA and IDA. This IRB-approved protocol is being submitted specifically for WUSM and UI teams who will be in charge of the Indonesia study and actively coordinate with the other consortium members and sponsors to conduct this study.

3 POTENTIAL RISKS AND BENEFITS

3.1 Risks of Blood Draw

Blood collection via finger prick is considered to be minimal risk and little or no discomfort is anticipated. The risk of infection is minimized by the use of standard sterile techniques. On occasion a participant may faint during or after the finger prick. Study personnel will be alert to participant reactions after the blood collection and will provide aid as needed

3.2 Risks of Study Drugs

The combinations of ivermectin plus albendazole or DEC plus albendazole are widely used for MDA. There also have been clinical trials of DEC plus Ivermectin and for triple drug therapy that show no significant drug interactions [3]. Risks of each drug is summarized below:

Diethylcarbamazine (DEC): The most common side effects reported are itching and swelling of face, headache, joint pain, unusual tiredness or weakness. These are transient. Less common are dizziness, nausea or vomiting. Fever, painful and tender glands in groin, neck and armpits or skin rash can occur, and are usually associated with high burdens of infection as judged by the level of blood microfilaremia.

Albendazole (ALB): The most common side effects reported are headache, nausea, stomach pain and vomiting and are usually associated with heavy soil-transmitted helminths infections. Severe allergic reactions occur rarely, and include rash, hives, itching, difficulty breathing, tightness in the chest, swelling of the mouth, face, lips, or tongue, dark urine. Mild elevation in liver transaminases can occur, but normalize with cessation of treatment. These AEs are usually associated with prolonged ALB therapy.

Ivermectin (IVM): The most common side effects reported are diarrhea, dizziness and nausea. Rare side effects include rash, hives, itching, difficulty breathing, chest tightness, swelling of the mouth, face, lips, or tongue, eye pain, fainting, and fast heartbeat. Mild decrease in leukocyte counts, elevated liver function tests, and cardiovascular effects that included tachycardia and orthostatic hypotension have been described. Infrequently, treatment can exacerbate bronchial asthma. These AEs are usually also associated with prolonged therapy.

3.3 Potential Participant and Community Benefit

Infected individuals, who sign an informed consent, will be treated for the LF infection. LF transmission to the community will be reduced by participation in either treatment arm. A broader community benefit may be facilitated by the triple drug regimen as it is believed the triple drug regimen has the potential to markedly reduce the number of MDA treatments needed to achieve transmission interruption and elimination of LF.

Both regimens provide treatment for intestinal worms, and the triple drug treatment has the added benefit of providing an effective treatment for scabies.

If the triple drug intervention proves successful, the triple therapy is likely to be adopted in many LF endemic areas globally. In order to facilitate such an uptake of triple therapy into national treatment policies, the study will be performed by Dr. Taniawati Supali and Dr. Yenny Djuardi from Universitas Indonesia and local health districts. Results from this study will be combined and shared with the World Health Organization.

3.4 Participant Participation and Cost

Participation is voluntary and participants may decline participation without consequences. There will be no cost to the participant to participate in the study. Participants in the community-based study activities will not be paid for their participation. Participants in the hospital-based study will be compensated (Rp 300.000,00) to replace their lost income while staying in the hospital. The study will cover cost associated with laboratory test, study drugs, and clinical monitoring.

3.5 Compensation for Injury

The study drugs have been widely used for treatment of lymphatic filariasis and it is anticipated that injury resulting from treatment will be rare. In the event that a participant experiences a serious adverse event (SAE) attributable to study treatment, the project will help in supporting the medical treatment and/or hospitalization required.

4 STUDY DESIGN AND OBJECTIVES

4.1 Study Objectives

1. To determine the safety profile of triple-drug therapy by measuring the frequency, type and severity of adverse events following triple-drug therapy (IVM+DEC+ALB, IDA) compared to the standard two-drug treatment (DEC+ALB, DA) in *Brugia*-infected and uninfected individuals in a community.
2. To compare the efficacy of IDA vs. DA administered in communities for clearance of *Brugia* MF and filarial antibodies.

4.1.1 Secondary Objectives

1. To assess the effect of intensity of filarial infection on the frequency and severity of adverse events.
2. To compare community acceptance of MDA with IDA vs. DA.
3. To compare the efficacy of DA vs IDA on soil-transmitted helminthes (STH)

4.2 Study Design

This trial will be an open labeled two-armed study. The two arms are (1) MDA with IDA (triple drug therapy) and (2) MDA with the currently used combination of DA (two-drug regimen). An overview of the study flow is provided in [Appendix 1](#).

The primary endpoint will be the rate of AE(s) and SAE(s) among participants. The definitions of mild, moderate, severe, and serious AE are provided in [Appendix 4](#).

4.3 Study Screening and Enrollment

This study will provide treatment for 4000 people who are living in areas with *Brugia* MF prevalence rates >5%. Co-endemicity with bancroftian filariasis is not an exclusion criterion. Pilot surveys have identified suitable study villages in Flores (Flores Timur District, *B. timori* MF prevalence 8.6%) and Sumba (Sumba Barat Daya District, *B. timori* MF prevalence 6.5%) islands that are mainly endemic for *B. timori*. Anecdotal information from local doctors indicates relatively high scabies rates on Sumba, but low rates on Flores. Ojandetun village located in Flores Timur consist of 2 sub-villages with a total population of 600. Karang Inda, Kahale, and Rada Malando villages with a total of 4,000 people in Sumba Barat Daya district. Unfortunately, we were not able to find a suitable study population of sufficient size in a single area (island)

In the first part of the study, 60 *B. timori* MF positive individuals will be treated in a hospital to observe AEs in a controlled environment. Thirty adult participants will receive IDA and 30 adult participants will receive the standard treatment (DA). This pilot treatment trial requires a suitable hospital/health centre in the vicinity of the endemic villages. It is planned that the rest of the study population will be treated and monitored as outpatients in their home villages. A total

population of 4,000 eligible individuals (MF positive or negative) will be selected with 2,000 receiving IDA and 2,000 receiving DA.

4.4 Preparatory Activities

This study will be performed in two phases (1) A smaller hospital-based trial comparing the safety and efficacy of DA and IDA in MF positive individuals and (2) a large community-based trial comparing the safety and efficacy of DA and IDA in a population at risk of infection. This part of the study will include both MF positive and MF negative individuals and will be performed after phase 1 shows acceptable adverse events.

Nurses and community health workers will act as AE assessors, following standardized training, across both phases of the study. Individuals with basic medical training (nurses or community health workers) and who are able to complete and pass a training course will perform the AE evaluations and provide symptomatic relief as indicated by the protocol.

Prior to community-based treatment, medical teams will be located at strategic locations in the community. Both study participants and the drug administrators will be informed about the availability of these medical teams including their mobile phone numbers so that they can report directly to these teams if necessary. These medical teams will be available during the entire enrollment/treatment period. Each team will have a vehicle for transporting participants for AE evaluation and management. Teams will be comprised of a medical officer, a staff nurse, and a pharmacist, and they will have access to essential lifesaving drugs.

4.5 Hospital-Based Treatment

About 1,000 individuals who consent to participate in the study will be screened in the community for MF in peripheral blood by the examination of finger prick night blood (60 μ L, collected between 8 PM and 11 PM). Dried blood spots and plasma will be preserved for later analysis. The total amount of capillary blood collected will not exceed 300 μ L. Sixty MF positive adult individuals eligible for treatment will be recruited for hospital-based treatment. Participants will be brought to the hospital for treatment. Venous blood will be collected for filtration at three time points: before IDA or DA treatment, 24 hours, and 48 hours after. Approximately 12 mL of blood will be collected at each time point. 6 mL for immunological tests and PCR, 2 mL for filarial filtration diagnosis, 2 mL for microscopic tests, and 2 mL for reserve. Participants will be monitored for adverse events during their stay. Any adverse events that occurs during the observation period will be recorded in a patient medical record. At 24 and 48 hours the adverse events will be entered into the electronic data capture system. If an adverse event changes in severity during the reporting period the highest grade reported will be entered into the electronic data capture system. Seven days after being treated the participant will be visited at home to record any adverse events that presented late. Participants will be told to expect to be unable to work for 3 days to account for the hospitalization and travel to and from the hospital setting. Minors will not be selected for hospital based treatment, because they would require guardians during their stay.

4.6 Community-Based Treatment

The community-based study will follow the hospital-based study. The rest of the study population, including the participants screened and not included in the hospital-based study, will be treated and monitored as outpatients in their home villages. Monitoring teams will visit participants at 24 and 48 hours. Participants will be told to seek out designated passive monitors who will visit the communities through day 7 if they experience any adverse events.

4.7 Social Mobilization

Prior to the administration of the drugs, intense social mobilization activities will be conducted to ensure maximum community participation. This will include development and distribution of key messages that will emphasize the acceptance and swallowing of the drugs along with their benefits and safety.

4.8 Household Enumeration, Census and Geo-Referencing

Communities within areas known to be highly endemic for *brugian* filariasis will be selected on the basis of willingness to participate and ability to access the area. Furthermore, the area should have had no LF MDA during the last 10 months, because MF (microfilaremia) rates are likely to be too low following MDA.

Health workers with the research team and community drug distributors (CDD) will enumerate and record the GPS coordinates of each *Kampung* within the selected study areas (PHMs) (House Visit #1, [Appendix 1](#)). A census will be performed to collect name, age and sex of each household member greater than or equal to 5 years of age. Basic information on house structure that might affect mosquito exposure to lymphatic filariasis infection, e.g. type of structure, whether screened windows present, existence of a toilet, running water, electricity and/or insecticide treated bed nets will also be collected.

4.9 Pre-Treatment Assessment Team

The pre-treatment assessment (House visit #2, [Appendix 1](#)) team will be composed of people with basic medical training able to perform a medical history and a basic physical examination (local health workers, physicians, and nursing or medical students), laboratory technicians, and community drug distributors involved in previous MDA for LF and known by the local community.

4.10 Inclusion and Exclusion Criteria

Inclusion Criteria

1. Age \geq 5 years, for IDA and DA arms (males and females).

2. Able to provide informed consent or give parental consent for minors to participate in the trial
3. No evidence of severe or systemic co-morbidities except for features of filarial disease

Exclusion Criteria

1. Age < 5 years (ivermectin is not approved for use in children less than 5 years of age)
2. Unable to provide informed consent or give parental consent for minors to participate in the trial
3. Pregnant women (DEC, ivermectin and albendazole are not known to be safe for use during pregnancy)
4. Severe chronic illness (chronic renal insufficiency, severe chronic liver disease, or any illness that is severe enough to interfere with activities of daily living)
5. History of previous allergy to MDA drugs

4.11 Pregnant Females

Pregnant females will not be eligible to participate in this study because of the unknown effects of the drugs and drug combination used in this study. Females will be asked about the timing of the first day of their last menstrual period. Females who report that their last menstrual period started 4 weeks or longer before the interview will be excluded from the study. Females who do not recall the timing of their last menstrual period will have their urine tested for pregnancy.

4.12 Informed Consent

All participants will provide written informed consent before any study procedures are done. Participation of minors (less than 18 years of age) will require their assent and the written consent of at least one parent. Participants will sign a written, informed consent before the inclusion process ([Appendix 6](#)). In the event that a participant is unable to read or has insufficient level of knowledge to comprehend the consent form, another villager with sufficient reading and writing skills will act a witness to the consenting process. The witness should not be involved in the implementation of the study.

A waiver of consent is being requested for the Census and Geo-referencing portion of the study prior to receiving formal consent. The study team will be collecting information about the communities and residents. This portion of the study is not greater than minimal risk and the members of the study team who are conducting the Census and Geo-referencing portion of the study will explain what they are collecting to village residents.

4.13 Plan for Inclusion of Non-Bahasa Indonesia Speaking Individuals

Participants who do not speak or read Bahasa Indonesia are neither specifically included nor excluded from this study. There are many local languages in eastern Indonesia and a native-

speaking community worker who is knowledgeable about research and the study will translate the consent form from Bahasa into the local language.

4.14 Baseline Survey

B. timori is nocturnally periodic and MF are present in the blood stream only at night. A study team will visit each household or compound in the evening to interview each member for demography, treatment history and general health. Each study participant will be tested for MF in finger prick night blood. Dried blood spots and plasma will be preserved for later analysis. The total amount of capillary blood collected will not exceed 300µL. A subset of participants will be asked to provide a stool sample for assessment of STH. However, participants may choose not to provide a stool sample and will still be eligible for the rest of the study. Eligible individuals who were screened, but not selected for the hospital based trial, can be directly enrolled in the community-based treatment without repetition of the finger prick blood collection. Study participants will be given their assigned treatment (DA or IDA) under supervision of a study team member. No more than 50 participants will be enrolled and treated per team per night to ensure sufficient staff capacity for follow-up AE monitoring.

After consenting, and prior to evaluation for LF infection and treatment, all individuals will be assigned a unique ID and be enrolled using a participant enrollment form ([Appendix 2](#)). They will also get an information card with emergency contact so they would know whom to call in case of emergency. Questions will be asked to each participant about their general health and last menstrual period (to establish pregnancy for women of childbearing age). Female participants who fail to recall their last menstrual period will have their urine tested for pregnancy. Each individual will be asked if they have signs of LF complications (hydrocele, lymphedema, lymphangitis, and lymphadenitis), if they took treatment during the previous MDA for LF and if they recently took albendazole, diethylcarbamazine, or ivermectin for other conditions. Participants reporting lymphedema will be examined to identify the location of the lymphedema. A photo of each participants will be captured electronically and stored in a secure folder. The photo will be helpful in identifying participants in the future, considering there are numbers of villagers who share the same name and who are unable to recall their exact date of birth.

4.15 Screening for Filarial Antigenemia, Antibodies and Microfilaria

Approximately 75µl of capillary blood from each eligible individual will be collected via finger prick to be deposited on the rapid diagnostic test Filariasis Test Strip (FTS, Alere™, WHO approved) for LF antigen (*Wuchereria*) detection in the field. The BrugiaRapid (Rezon™, WHO approved) diagnostic test will be used in parallel to detect infection with *Brugia*. The BrugiaRapid test requires 35µl of capillary blood. All participants will undergo microfilaria testing (60 µl measured volume blood smear- 3 lines, prepared according to the project SOP) collected by the finger prick method.

Study participants will be informed that their blood samples may be stored in Department of Parasitology Universitas Indonesia. As many as 10% of the samples (approximately 300-400

samples) will be chosen randomly to be shipped to other laboratories for quality control of filarial diagnosis.

Universal precautions for individuals collecting and working with blood samples to include proper disposal of contaminated materials (test strips, lancets, capillary tubes, blood film slides) will be in accordance with the guidelines prescribed by the local health authorities.

4.16 Assessment of Efficacy of IDA vs DA on STH (including *Strongyloides* by qPCR)

Expected number of positive individuals per treatment arm: We assume that per treatment arm we will collect stool samples from a community of about 300 individuals (a total of 600 individuals for two arms). With a confidence level of 95% and a confidence interval of 5%, we would require testing at least 278 subjects. Assuming a sample size of 300 (~278) and a confidence level of 95% we expect to treat at a prevalence of 50% (ie any STH) between 133 and 167 infected individuals and at a prevalence of 10% (i.e. one STH species only) between 20-40 infected individuals. Based on previous data from eastern Indonesia and PNG we expect a minimum prevalence of any STH of 50%.

Study sites: It is sufficient to select the 300 individuals per treatment arm from one study area/village, because a more homogeneous distribution of STH compared to LF can be expected. Susceptibility to the drug treatment should not vary within the same region.

Collection of stool samples: We will follow the DOLF '*SOP for Stool Collection*'. A convenience sampling method will be used without special regard to sex and age, because drug efficacy is unlikely to depend on these parameters. A follow-up stool sample will be collected 2-4 weeks and one year after treatment from the same individuals that provided the baseline sample. We expect a compliance of 90% because of pre-selection of compliant individuals.

Assessment of STH eggs: We will use the Kato Katz method before and after treatment, because of its sufficient sensitivity in high prevalence areas, its simple performance in the field, and the standardized quantitative assessment. We will follow the DOLF '*SOP Kato Katz Procedure*'. Stool aliquots will be preserved for later examination by qPCR. This will enable us to archive STH DNA samples before and after IDA treatment and to test for efficacy of IDA for *Strongyloides*. We will follow the DOLF '*SOP Stool Sample Management*' (version 2016). (Some samples may randomly be picked and shipped to other laboratories for quality control). These samples may be stored for a longer time after the intended testing. No HIV or human genetic testing will be performed.

4.17 Randomization

A randomization scheme will be prepared for the hospital-based study. Individuals will be assigned to one of two treatment arms using a random number generator; 50% will be assigned to DA therapy and 50% to IDA. The randomization scheme will be maintained in a locked file at all times with limited access. However, should it be necessary to link participants to their

assigned treatment, the randomization will be available to the DSMB and a copy will be maintained in a locked cabinet at the coordinating site.

Communities will be assigned treatment either by randomization in the level of dusun or by purposively matching communities based on population and prevalence of LF. If the prevalence is homogenous across the communities each site may be randomly assigned to one of the two treatment arms. If the prevalence is heterogeneous, communities will be selected into each arm so that the population and prevalence between the two treatment arms is similar.

4.18 Withdrawal

Participation in this project is completely voluntary, and participants may terminate participation at any time. Also if the well-being of the participant is compromised in any way, based on the opinion of the investigator, the participant can also be withdrawn from the study. Even if the participant leaves the project early, we will encourage them to contact us at any time within the month after treatment to report any possible study-related AEs.

All participants that sign the informed consent and receive study drug will be included in the analysis.

4.19 Efficacy and Effectiveness of IDA vs DA

One year post MDA all participants who were positive for microfilariae, filarial antigenemia (FTS), or antibody (Brugia Rapid) during the baseline visit will be tested for nocturnal microfilariae. Finger prick blood will be collected at night from the community participants to be tested for microfilaremia by thick blood smear. Venous blood will be collected from hospital-based study participants for filtration membrane test. Serological tests using FTS and Brugia Rapid, will also be used to assess their responses to treatment and compare the efficacy of the two treatment regimens.

We will also collect stool samples from all treated individuals who were positive for helminth infections in order to describe the long term effect of both treatment regimens on STH.

4.20 Retreatment

Any individual who tests positive for lymphatic filariasis at 12 months (by microscopy or antigen test) will be re-treated with the standard MDA regimen (single dose of DEC with Albendazole). If triple drug therapy (IDA) is recommended by the WHO or by national regulatory agencies for lymphatic filariasis and if investigators have adequate supply of ivermectin, infected individuals may be offered IDA. This practice is meant to ensure that all participants who participated in the study may get the most beneficial treatment.

4.21 Guidelines for Stopping the Trial

There are no pre-specified criteria for terminating the study early.

Upon review of the data for the trial, the DSMB will make decisions regarding the continuation of the trial. The final decision to stop the trial is left to the recommendation of the DSMB. If the DSMB recommends discontinuation or modification of the study, the Chair of the DSMB will meet or talk with the DOLF Project Team at the earliest opportunity to review the basis for the recommendation. The study should be stopped if a treatment arm shows a significant increase in unacceptable side effects that would include, death, fever, and nausea that persist more than a day and would require hospitalization.

4.22 Triple Drug Regimen Acceptability

A survey to assess the treatment acceptability in the community is planned to follow the safety trial. The overall aim is to understand the community's acceptance of the 3-drug regimen as well as gain insight into the feasibility of administering this new therapy in the future. Part of the investigation will include assessing community member's perception of the possible side effects experienced as a result of the 3-drug therapy compared to the 2-drug therapy, and how that might affect future rounds of mass drug administration (MDA) at the community level.

Community acceptance will be measured using a survey to community members receiving both the 2-drug and 3-drug treatments during the safety trial. The survey participants will be identified from the roster of individuals enrolled in the safety trial. To complement this survey, a series of focus group discussions in the community as well as key informant interviews are proposed with community leaders, health personnel and drug distributors in the same communities to assess perceptions about the 3-drug versus the 2-drug regimen. The community acceptability study will be carried out within one month of the completion of the safety trial. The protocol for the acceptability survey is included in [Appendix 7](#) of this protocol. The community questionnaire and topic guides will be submitted to the EC for approval as an amendment prior to implementation of the survey.

5 INVESTIGATIONAL PRODUCT

Each of the drugs used in this study is approved for human use and has a prior history of use in the treatment of Lymphatic Filariasis.

5.1 Study Drug Background

Albendazole (ALB) has been known to cause degenerative alterations in the tegument and intestinal cells of the worm by binding to the colchicine-sensitive site of tubulin, thus inhibiting its polymerization or assembly into microtubules [10]. The loss of cytoplasmic microtubules leads to impaired uptake of glucose by larval and adult stages of the parasite, and depletes glycogen stores. Degenerative changes in endoplasmic reticulum and mitochondria of the germinal layer, and the subsequent release of lysosomal enzymes result in decreased production of adenosine triphosphate, which is the source of energy required for survival of the helminth. Due to diminished energy production, the parasite is immobilized and eventually dies. Adverse events are uncommon in persons who are treated with a single dose of albendazole (apart from AEs that result from parasite death). Some patients report mild gastrointestinal AEs such as nausea after ingesting the tablet.

Ivermectin (IVM) is an avermectin compound of macrocyclic lactones derived from the bacterium *Streptomyces avermitilis* [11]. The mechanism by which IVM kills LF microfilariae is not known with certainty, but the drug interferes with glutamate gated ion channels that can affect parasite contractility and release of immunomodulatory molecules by the parasite [12]. IVM also has a direct effect on the central nervous system and muscle function of worms as it enhances strength of inhibitory neurotransmission pathways. The main concern with the use of IVM in animals and humans is neurotoxicity, which can be manifest as ataxia. Neurotoxicity has not been observed in humans given single dose IVM for LF or other parasitic infections [13]. IVM has been used to treat millions of people with LF and onchocerciasis. Peak IVM serum concentrations are reached approximately 4-5 hours after administration. The half-life of IVM in various populations ranges from 12 to 56 hours [14]. There is no evidence for pharmacokinetic drug to drug interaction between ALB and IVM [14]. IVM can cause nausea, dizziness and occasionally pruritus, but these are infrequent, transient and usually mild. Serious adverse events have occurred in patients with heavy *Loa loa* infections.

DEC (diethylcarbamazine citrate) is an anthelmintic drug that is structurally distinct from ALB and IVM [15]. DEC inhibits arachidonic acid metabolism by LF, and inducible nitric oxide synthase and the cyclooxygenase pathway may be essential for activity *in vivo* [16]. DEC also has anti-inflammatory properties. The mechanisms of action of DEC remain poorly understood. Its ability to kill MF and adult worm depends on the host immune responses since the drug has little direct activity on parasites *in vitro*. The drug has potent activity against LF microfilaria. DEC has about 50-70% efficacy in killing or sterilization of adult worms [17]. The drug is rapidly absorbed from the gastrointestinal tract, has a serum half-life of 12 to 14 hours, and is excreted in the urine with

little modification by liver metabolism. Adverse events from DEC are unusual apart from those that result from killing filarial worms.

5.2 Product Supply and Storage

Only WHO approved drugs will be used in this study. DEC and albendazole will be provided by the Indonesian Lymphatic Filariasis Elimination Program and the WHO. A request will be submitted to the manufacturer Merck to provide ivermectin for the present study. Alternatively WHO approved generic ivermectin may be purchased..

Albendazole and DEC are approved for use and commonly used in Indonesia. Ivermectin (Mectizan) is registered in numerous countries around the world for use in humans, but not in Indonesia. Approval for its use in the present study will be sought from the government of Indonesia together with the Ethical Review of this proposal.

All three study drugs are approved and distributed globally by WHO as part of GPELF. Detailed information for each drug is available from the pharmaceutical manufacturer. All products should be maintained at ambient temperature, and if possible <30 °C.

6 STUDY PROCEDURES/EVALUATIONS/SCHEDULE

6.1 Triple Drug Therapy (IDA) and Two-Drug Therapy (DA)

The triple-drug combination will consist of a single dose of ivermectin (200 µg /kg), DEC (6mg/kg) and albendazole (flat dose of 400 mg). The two-drug combination will consist of a single dose of DEC (6 mg/kg) and albendazole (flat dose of 400 mg). Study personnel will directly observe oral administration of drugs. Drugs will be given after the informed consent has been obtained. The study population will be encouraged to eat before swallowing the medicine (without chewing the tablets) with a glass of water. Vomited doses will be replaced. Drug administration will be supervised (directly observed treatment or DOT) to ensure that all enrolled individuals swallow the drugs. There will be one supervisor per study team.

6.2 Overall Study Schedule and Timeline

A flow diagram illustrating the study events schedule is presented in [Appendix 1](#).

7 SAFETY REPORTING AND SAFETY MONITORING

The post-treatment assessment team will be composed of individuals with basic medical training who are able to perform a medical history and a basic physical examination (Physicians, local health workers, nursing and/or medical students). Physicians from the area will be available to assist in the evaluation and management of adverse events.

7.1 Definitions

Adverse Event (AE)

Any untoward medical occurrence in a clinical investigation participant who has received a study product intervention and that does not necessarily have to have a causal relationship with the study product. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a study medicinal product, whether or not considered related to the study medicinal product.

An AE does not include:

- Medical or surgical procedures (e.g. surgery, tooth extraction, transfusion). The condition that leads to the procedure is an adverse event
- Pre-existing diseases or conditions or laboratory abnormalities present or detected prior to the screening visit that do not worsen.

Serious Adverse Event (SAE)

An SAE is any adverse event that results in any of the following outcomes:

- Death;
- Life-threatening (immediate risk of death);
- Inpatient hospitalization or prolongation of existing hospitalization;
- Persistent or significant disability or incapacity;
- Congenital anomaly/birth defect;
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Unexpected

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Package Insert).

Expedited Safety Report

Documentation in appropriate form and format summarizing an SAE that meets expedited safety reporting criteria, submitted within the required reporting time frame of applicable regulatory authorities and/or IRBs/IECs of participating countries.

7.2 Assessment of Adverse Events

Adverse event monitoring will be performed approximately 24 and 48 hours following drug administration (late afternoon and evenings following treatment, house visit #3 and 4, [Appendix 1](#)). All those participants will be followed for adverse events through Day 7.

Evaluations will be documented on pre-printed Patient Monitoring forms ([Appendix 3](#)) using the scoring instructions for AEs ([Appendix 4](#)) or entered directly into an electronic form using tablet computers.

Most adverse events after mass drug administration are associated with killing of MF and are seen in the first 12-24h following treatment. However, occasional adverse events related to adult worm death may be delayed by several days.

To capture these adverse events and to assure that any systemic adverse events that occurred earlier have resolved, study personnel will also visit study villages daily on days 3 through 7 after treatment (passive AE monitoring). Individuals with AEs that interfere with activities of daily living (grade 2 or higher) will have more detailed assessments that will include a brief physical examination (including measurement of temperature, blood pressure and pulse).

7.3 Serious Adverse Event (SAE) Assessment and Management

Study participants with definite or suspected serious AEs (any event \geq grade 3) will be referred to a physician or appropriate health care professional for evaluation. These evaluations will be documented with special adverse event evaluation forms ([Appendix 5](#)), following the instructions ([Appendix 5a](#)).

An SAE may qualify for reporting to regulatory authorities if the SAE is possibly attributable to one or more of the study drugs, and is unexpected based on the Company Core Safety Information.

A Data Safety Review Board will monitor the type and frequency of AEs and SAEs recorded by the teams and provide guidance to the PIs and the teams in the field.

The investigator should notify the Institutional Review Board (IRB) or Ethics Committee (EC) as soon as is practical, of serious events in writing where this is required by local regulatory authorities, and in accordance with the local institutional policy.

7.4 Country Specific SAE Reporting Requirements

All local SAEs will be reported to the PI of the study and sponsor within 24 hours:

- Peter U Fischer PhD, Pufische@dom.wustl.edu
- Taniawati Supali PhD, taniawati@yahoo.com, phone +6221-310 2135 (office), +62 812 8400 5628
- Yenny Djuardi MD PhD yenny_djuardi@yahoo.com, phone +62 812 8852 7832).

In parallel, all SAEs will be reported to the ethics committee and District Health Authority via the head of the local Primary Health Center (Puskesmas) within three days.

Serious Adverse Drug Reactions (SADRs) will be reported to the Badan Pengawas Obat dan Makanan (BPOM). All SADRs will be reported to BPOM within 15 days since the first day of discovery by sponsor or within 7 days if the SADR is life- threatening or results in death. If there is any subsequent event following the initial event, it will be reported as soon as possible.

7.5 Reporting of Pregnancy

Pregnancy is an exclusion criteria for this study. Although not AEs, pregnancies are reportable events. In the event that a pregnant woman is inadvertently dosed efforts will be made to follow-up and ascertain and report the pregnancy outcome (e.g., any premature terminations, elective or therapeutic, and any spontaneous abortions or stillbirths, as well as the health status of the mother and child including date of delivery and infant's gender and weight). Any pregnant woman inadvertently dosed who has a miscarriage or spontaneous abortion within the week of follow-up will be reported as an SAE.

7.6 Safety Monitoring by the Oversight Committee

A Data Safety Monitoring Board consisting of 4 experts (including 3 physicians) knowledgeable in neglected tropical diseases will be in place to monitor the safety data per country and across countries participating in the DOLF project.

8 CLINICAL MANAGEMENT OF EVENTS

Individuals who have basic medical training (physicians and/or nursing or medical students) who are able to complete and pass a training course will be responsible for the initial adverse event evaluations.

In the case of mild symptomatic reactions local health workers/study personnel will provide antipyretics/analgesics and anti-allergic agents at the time of follow-up. It is anticipated that the majority of adverse events will resolve within a day or two and will not require treatment. In the initial adverse event monitoring if any of the following are noted a physician will be notified to evaluate the participant for a potential serious adverse event:

- Participant reports they are unable to participate in their normal daily activities
- Participant has or reports a temperature >39°C
- Participant has or reports a significant drop in blood pressure
- Participant has other significant objective findings that should be referred to a physician

All grade 3, 4 or 5 events or overnight hospitalization will require completion of the Adverse Event Evaluation and Report Form ([Appendix 5](#)). The physician will provide any required immediate treatment and facilitate admission into the hospital or health center as deemed appropriate.

8.1 Adverse Event Monitoring and Management

Adverse event monitoring and management will follow or exceed WHO guidelines. Participants will be visited on the two days following treatment by study personnel with medical training. Formal assessment of adverse events (with a standard form) will take place on days 1 and 2 and later if symptoms persist or start late.

Study personnel will use the toxicity table ([Appendix 4](#)) to score adverse events for severity. Serious adverse events will be followed until resolution. Study personnel will visit each study area daily for 7 days following MDA treatment to manage any adverse events as follows:

8.1.1 Mild Localized Symptoms

Participants who develop painful lymphadenopathy, scrotal pain or painful swelling or nodules along lymphatic vessels will be treated with acetaminophen or ibuprofen.

8.1.2 Moderate to Severe Localized Adverse Events

Participants with more severe local adverse effects (Grade 3, [Appendix 4](#)) like acute swelling or severe scrotal pain that is not relieved by acetaminophen will be transported by study personnel to the medical facility identified for the study for evaluation by one of the physicians or other qualified medical personnel involved in the study. If necessary, participants will be transferred (after stabilization) to the Departmental Hospital or primary health center.

8.1.3 Moderate to Severe Systemic Adverse Events

Participants with more severe systemic adverse effects (fever over 39 C > 72 hours, other adverse events ≥ Grade 3, syncope, jaundice, or any condition that might require hospitalization) will be transported by study personnel for physician or other qualified medical personnel for evaluation at the medical facility identified for the study. If necessary, participants will be transferred (after stabilization) to a local hospital.

8.2 Rapid Response Teams for Management of Adverse Events

Medical teams will be located at strategic places close to the study sites. Participants, and persons involved in the study (inclusion process and AE monitoring) will be informed about the location and phone numbers of these teams so that they can report directly to these teams if necessary. These teams will be in position from the day of drug administration until the completion of operations.

9 STATISTICAL CONSIDERATIONS

All participants receiving study drug will be included in both the safety and efficacy analysis

9.1 Safety

The sample size of 2000 participants in each arm will contribute to the total sample size for the project. The WHO requires a total of 10,000 participants to detect an SAE rate of 0.1% for each of the treatment regimens and recruitment in other countries (e.g., Haiti, India, Papua New Guinea, and Sri Lanka) is planned to contribute to the overall sample size required. It is well known that systemic AEs are related to killing of MF and that the severity of AEs is related to MF counts.

WHO recommends a best practice called “cohort event monitoring” for demonstrating safety of new drug regimens for public health program use. Establishing safety through such methodology requires pre and post treatment assessments from at least 10,000 people treated with the triple therapy across multiple settings. The Triple Drug Therapy for LF study is a multi-center study with 5 sites that together will reach the 10,000 target. The Indonesia sites will contribute 2,000 individuals *treated with triple drug therapy* to the overall 10,000.

The primary endpoint for safety studies will be the rates of SAEs that occur in infected and in uninfected participants within the first 7 days post MDA. Total AEs will be a secondary endpoint for the study.

9.2 Efficacy

Assuming an average MF-prevalence of 5% in the study population at baseline, the survey is expected to detect at least 100 MF positive participants in each arm. A minimum of 70 (70%) of all these MF-positive participants in each arm will be retested at 12 months post-treatment for microfilaraemia, antigenemia (for Wuchereria) and IgG 4 (Brugia Rapid for Brugia), assuming there will be participants lost to follow up due to urbanization or transmigration and those who choose to end their participation in the study. This sample size is adequate to demonstrate superiority of the IDA regimen (assumptions: 90% reduction in MF prevalence after IDA and 60% reduction after DA, 80% power for detecting an effect size of 30%). The primary endpoint for efficacy will be complete clearance of MF 12 months post MDA.

9.3 Enrolling Additional Participants

It is possible that recruitment in other countries may be less than anticipated. In this case the number of participants enrolled in this study may need to be increased to make up for the loss in another country. The number of additional people enrolled will be no more than is necessary to reach the total of 10,000 participants treated with IDA. In this situation the principal investigators will inform the ethics review committees of the expanded enrollment.

10 DATA HANDLING/RECORD KEEPING/SOURCE DOCUMENTS

Data will be collected using a tablet based system, pre-loaded with study templates. Field teams will be trained in the use of the instruments and data will be uploaded as entries are completed.

10.1 Types of Data Collected

Enrollment Data will include ([Appendix 2](#)):

- Site Identification
- Participant Identifier
- Informed Consent Date
- Demographic Information
- Digital photo
- Pregnancy/last menstrual period
- Medical History
- Presence of hydrocele and lymphedema
- Bed Net and Window Screen Use
- History of prior MDA treatment
- Pre-treatment adverse event assessment
- Limited Physical Exam

Laboratory Results

- FTS (filarial antigen test)
- FTS score
- BrugiaRapid (filarial antibody test)
- MF slide (including MF count)
- Soil Transmitted Helminthes egg counts and qPCR diagnostics

Participant Monitoring Forms (24 & 48 hour post treatment):

- Adverse Event Assessment
- Physical Examination, as appropriate

Adverse Event Evaluation and Report ([Appendix 5](#))

- Participant Identification
- MDA Treatment
- Concomitant Medication taken at the time of the MDA
- AE Description,
- Start and Stop Date
- Outcome
- SAE Evaluation and causality to MDA (definite, probable, possible, or unrelated)

10.2 Study Records Retention

Study documents will be retained for a minimum of three (3) years after the last participant has completed the study. These documents will be retained for a longer period, however, if required by local regulations. No record will be destroyed without the written consent of DOLF.

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6, Section 4.9, regulatory and institutional requirements for the protection of confidentiality of participants. Each site participating in this study will permit authorized representatives of the sponsor and regulatory agencies to examine (and when required by applicable law, copy) clinical records for the purposes of clinical site monitoring, quality assurance reviews, audits, and evaluation of the study safety and progress.

10.3 Source Documents

This study will use both paper and electronic source and this may vary by location due to local availability. All sites will be provided with hard copy data collection forms derived from the eCRFs. If data is first entered on paper the study staff will enter the data into the electronic capture system.

11 RESPONSIBILITIES

11.1 Investigator Responsibilities

11.1.1 Good Clinical Practice

The investigator will ensure that the basic principles of Good Clinical Practice are followed along with the appropriate laws and regulations of the country in which the research is conducted.

11.2 Institutional Review Board (IRB)/Ethics Committee (EC)

The protocol and any accompanying material to be provided to the participants such as the informed consent will be submitted to the EC for review and approval. Approval from the committee must be obtained before starting the study and should be documented in correspondence to the investigator.

Any modifications to the protocol after receipt of the IRB or EC approval must be submitted to the committee for approval prior to implementation.

11.3 Informed Consent

It is the responsibility of the investigator to obtain written informed consent from each individual participating in the study after adequate explanation of the aims, methods, objectives and potential risk of any study related procedures. The investigator must use an IRB/EC approved informed consent. The investigators will accept either signed (cursive) or printed signatures or a witnessed mark in the case of illiterate study participants on the consent form.

Only the principal investigators or study staff authorized and certified to obtain consent will consent participants for this study. Only individuals who have signed the consent form and meet eligibility criteria will be enrolled in the study.

Entry into the study and participation will be strictly voluntary. It will be made clear that refusal to participate or a decision to withdraw can occur at any time throughout the course of the study and will not influence their rights or the care they receive at local health facilities. Potential participants will be told that all of their health information will be confidential and that records will be coded without personal identifiers before they are shared with statisticians or project scientists outside of the village/region/country. They will also be told that no monetary or other gains are offered in exchange for participation apart from compensation for time and reimbursement of travel expenses as described above.

11.3.1 Informed Consent Training

Each step of the study will be explained in detail to the local study personnel. The basic principles of informed consent process, documentation of informed consent, protection of participants' rights, confidentiality, and handling of data will be covered in these training sessions. Study personnel will be monitored by the on-site project coordinator on a regular basis to ensure compliance with the principles of informed consent. The investigators and study

personnel who will obtain consent from study participants will also receive training in the informed consent process and good clinical practices (GCP).

11.3.2 Country Specific ICF Information

The Informed Consent for the hospital based trial will include the collection of venous blood and additional testing.

11.4 Participant Privacy

Privacy of the study participants will be maintained by assigning study participants a unique study identification number (UNID). All data, blood samples and laboratory results will be recorded and analyzed by UNID with no personal identifiers. All information collected, including demographic information about enrolled participants and their photos will be kept confidential and available only to the investigators and authorized study personnel such as the data manager.

Though most data will be collected on tablets, all written forms (i.e., consent and any paper data collection forms) will be stored in a designated locked area with limited control. All forms will be labeled and filed in cabinets with the study protocol number, PI's names and collection dates. These cabinets will be metal and have functioning locks. Keys will be kept with the Project Coordinator. All electronic devices on which data are entered will be password protected. PIs and/or Project Coordinator will authorize access. The paper forms will be stored for the duration of the study plus three years per IRB protocol for primary data storage.

11.5 Data Ownership

The data are the property of UI. The Principal Investigators, Co-investigators and key personnel may use the results of this study for publications, presentations at scientific meetings or as preliminary data for subsequent grant applications. Confidentiality of study participants will be maintained by not using names or personal identifiers. UI will provide de-identified data from the study to DOLF for use in publications and presentations that present results across different study sites. At least one Indonesian researcher will be included as an author for any publications with data from Indonesia.

The study site Project Coordinator will permit access to all documents and records that may require inspection by the funding agencies, governmental regulatory agencies, institutional review boards or its authorized representatives.

12 PUBLICATION POLICY

Manuscripts should be submitted for publication no later than one year following the date of the “last patient/last visit”. This study includes follow-up data collection past the primary end point, including acceptability and efficacy results. It is not necessary to wait for the follow-up studies to be completed in order to publish the primary safety data.

Endemic country investigators have an obligation to publish the results of DOLF studies conducted in their country. These results benefit the national NTD programs and the citizens of the country where the study was completed. DOLF collaborating institutions are willing to help their endemic country partners with the data analysis, manuscript preparation, publication fees, etc. However, the lead author should be an investigator from the country where the study was performed.

DOLF scientists will be responsible for publishing the results from the aggregated data that combines the results from multiple study sites. The purpose of these manuscripts is to consider the similarities and differences in results obtained in different countries. These publications will not include as much detailed data or analyses as the country specific publications. Publications that report multi-country results will have at least one co-author from each country included in the manuscript.

13 LITERATURE REFERENCES

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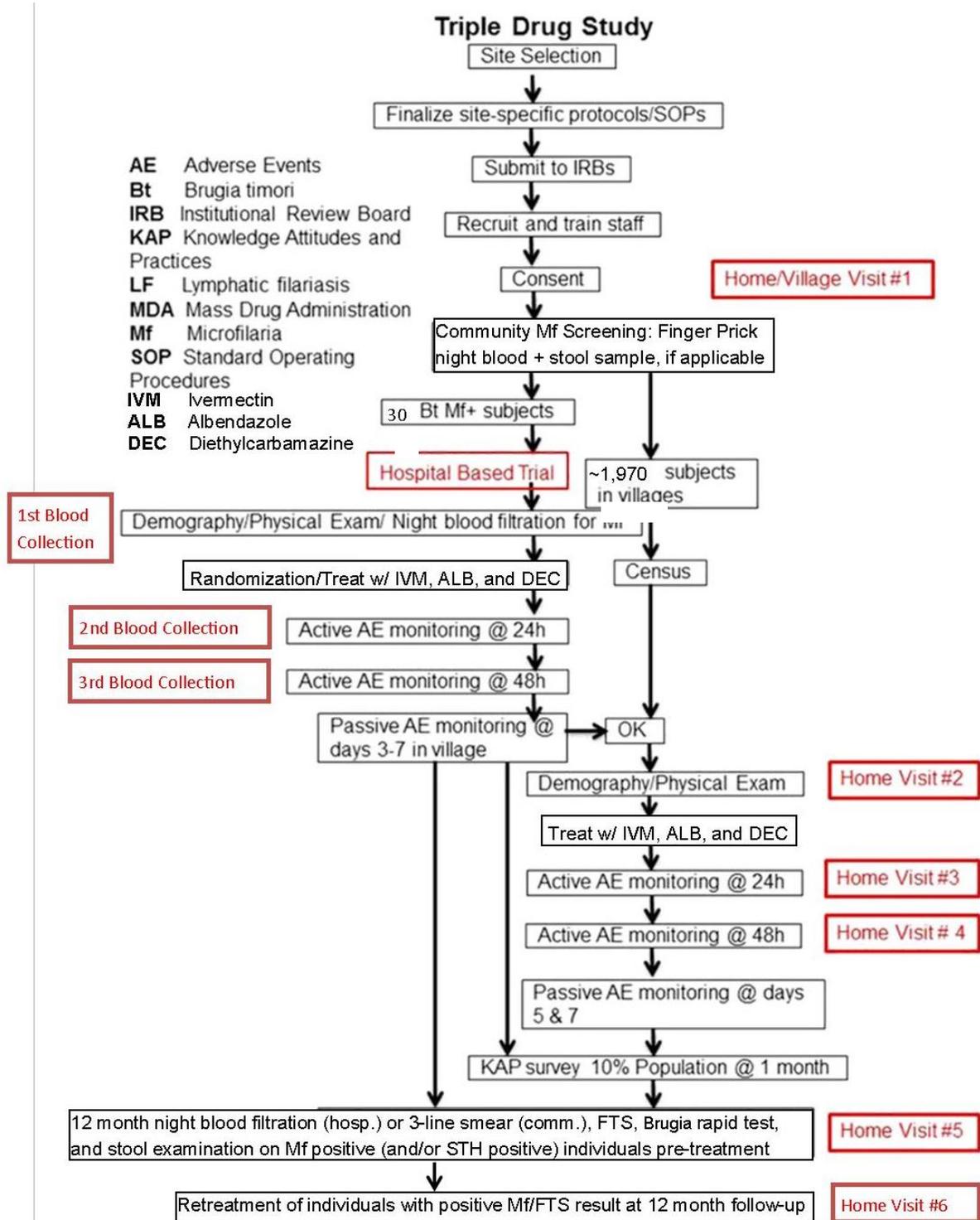
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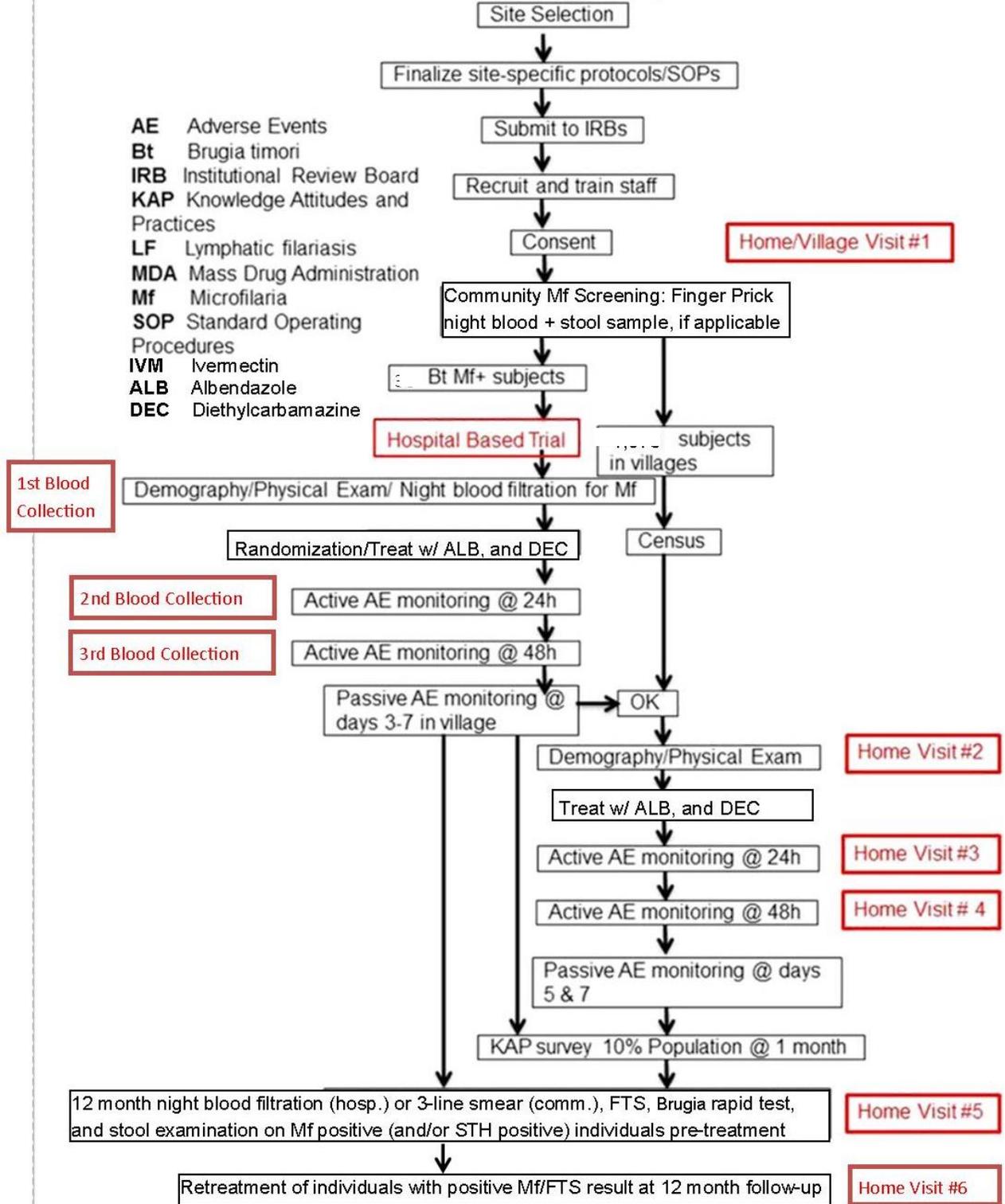
Appendix 11: Visitation Matri

APPENDIX 1: STUDY FLOW DIAGRAM (COUNTRY SPECIFIC)

Study Flow Diagram: Triple Drug



Study Flow Diagram: Two Drug Triple Drug Study



APPENDIX 2: PARTICIPANT ENROLLMENT FORM

Participant ID (Barcode):

1. DEMOGRAPHICS

Team (required):	Data Entry Clerk ID (required):			
Informed Consent Date (required) (DD-MM-YYYY): _____-_____-_____				
Site Location (required)				
<input type="checkbox"/> Site 1	<input type="checkbox"/> Site 6			
<input type="checkbox"/> Site 2	<input type="checkbox"/> Site 7			
<input type="checkbox"/> Site 3	<input type="checkbox"/> Site 8			
<input type="checkbox"/> Site 4	<input type="checkbox"/> Site 9			
<input type="checkbox"/> Site 5	<input type="checkbox"/> Site 10			
<input type="checkbox"/> Site 6	<input type="checkbox"/> Site 11			
Gender: <input type="checkbox"/> M <input type="checkbox"/> F <input type="checkbox"/> Unknown	<i>Note: if exact date is not known, birth year is sufficient</i>			Age (Years):
Birth Day (DD):	Birth Month (MM):	Birth Year (YYYY):		
Weight (in kg):				
Height (in cm):				
BMI Calculation [(weight/height*0.01)²]:				

2. PRE-TREATMENT MEDICAL HISTORY

Do you feel well today? <input type="checkbox"/> Yes <input type="checkbox"/> No				
Symptoms/Signs <ul style="list-style-type: none"> • Grade 2 requires Vital Signs • Grade 3 and higher requires physical examination by medical personnel or refer out to local health clinic. Do not enroll. 				
NOTES: <i>If participant does not feel well today, please mark the symptoms they describe and identify the grade.</i>				
Sign/Symptom	1 - Mild	2 -Moderate	3 - Severe	4 - Life-threatening
Fever				
Dizziness, lightheaded				
Headache				
Fatigue				

APPENDIX 2: PARTICIPANT ENROLLMENT FORM [EXAMPLE]

Participant ID (Barcode): _____

Difficulty breathing (wheezing or dyspnea)				
Cough				
Joint pain				
Muscle pain				
Muscle Weakness				
Rash				
Itchy skin				
Swelling in armpit				
Swelling in groin				
Pain in armpit				
Pain in groin				
Men only: pain in your scrotum				
Nausea				
Vomiting				
Diarrhea				
Stomach Pain				
Other illness or symptoms (specify):				
Other Grade:				
<p>Did the participant report any symptoms that are Grade 2 or greater?</p> <p><input type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> Not Applicable</p> <p>If YES, you must notify a member of the medical team to conduct vital signs.</p> <p>Any Grade 3 symptom requires physical examination by medical personnel or refer out to local health clinic. Do not enroll.</p>				
<p>Subject can be enrolled</p> <p><input type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p>				

3. Special Interest Events - LF

<p>Do you have swelling in your arms or legs (lymphedema)? <input type="checkbox"/> Yes <input type="checkbox"/> No</p>	
<p>If lymphedema: Confirm and indicate which limbs are affected</p> <p><input type="checkbox"/> Left Arm</p>	<p>Severity of lymphedema:</p> <p><input type="checkbox"/> Mild</p> <p><input type="checkbox"/> Moderate</p>

APPENDIX 2: PARTICIPANT ENROLLMENT FORM [EXAMPLE]

Participant ID (Barcode): _____

<input type="checkbox"/> Right Arm <input type="checkbox"/> Left Leg <input type="checkbox"/> Right Arm	<input type="checkbox"/> Severe - Elephantiasis <input type="checkbox"/> Severe - Disabled
Males only: Are your testicles swollen? <input type="checkbox"/> Yes <input type="checkbox"/> No	
Males only: Are your testicles swollen all the time or only when carrying heavy things? <input type="checkbox"/> All the time <input type="checkbox"/> Only when carrying heavy things	

5. Pre Treatment Vital Signs (Grade 2 and higher Pre-Tx Medical History only)

Measurements	Values / status
Systolic blood pressure, sitting	_____ (mm HG) <input type="checkbox"/> Not done
Diastolic blood pressure, sitting	_____ (mm HG) <input type="checkbox"/> Not done
Blood pressure: Systolic under 100 and/or Diastolic under 60?	<input type="checkbox"/> Yes <input type="checkbox"/> No <i>If Yes, send home to eat and return tomorrow</i>
Was individual orthostatic? <i>Note: Systolic BP at least 20 points lower and diastolic BP at least 10 points lower when standing.</i>	
	<input type="checkbox"/> Yes <input type="checkbox"/> No
Pulse rate	_____ (bpm) <input type="checkbox"/> Not done
Temperature	_____ (Celsius) <input type="checkbox"/> Not done

6. Filarial Antigen test (FTS) results

FTS Results: <input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Undetermined	FTS Score: <input type="checkbox"/> Weak <input type="checkbox"/> Medium <input type="checkbox"/> Strong <input type="checkbox"/> Not Done
If FTS is Positive , Night Blood Collection is required. MDA will be administered after night blood has been collected. If Negative , continue form and administer MDA If Undetermined , repeat the test – if 2nd test is undetermined, then treat this as positive	
Indonesia Only:	
BrugiaRapid date (DD-MM-YYYY): _____ - _____ - _____	BrugiaRapid Results: <input type="checkbox"/> Positive <input type="checkbox"/> Negative

APPENDIX 2: PARTICIPANT ENROLLMENT FORM [EXAMPLE]

Participant ID (Barcode): _____

	<input type="checkbox"/> Undetermined
--	---------------------------------------

7. Pregnancy Test Results

Indonesia Only:	
Pregnancy test date (DD-MM-YYYY): _____ - _____ - _____	Pregnancy Test Results: <input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Undetermined

8. Inclusion/Exclusion Criteria

Inclusion Criteria:	
Able to provide informed consent or parental consent to participate in the study (Forms to be attached)	<input type="checkbox"/> No <input type="checkbox"/> Yes
Exclusion Criteria:	
FEMALE ONLY: Pregnant women (DEC, ivermectin and albendazole are contraindicated in pregnancy)	<input type="checkbox"/> No <input type="checkbox"/> Yes
FEMALE ONLY: Childbearing age (between age 12 -50) who has not had a menstrual period in the last 4 weeks	<input type="checkbox"/> No <input type="checkbox"/> Yes or Do not Recall <input type="checkbox"/> Not Applicable
FEMALE ONLY: Breastfeeding in first 7 days following delivery	<input type="checkbox"/> No <input type="checkbox"/> Yes
Severe acute or chronic illness (for example: chronic renal failure, inability to care for oneself with activities of daily living) except for features of filarial disease	<input type="checkbox"/> No <input type="checkbox"/> Yes
History of previous allergy to MDA drugs	<input type="checkbox"/> No <input type="checkbox"/> Yes

APPENDIX 2: PARTICIPANT ENROLLMENT FORM [EXAMPLE]

Participant ID (Barcode): _____

9. MDA Treatment

Please calculate dose using Dosage according to Below Chart		
Weight (kg): _____		
Drug Regimen:	<input type="checkbox"/> Double drug therapy (ALB, DEC) <input type="checkbox"/> Triple drug therapy (ALB, DEC, IVM)	
MDA Treatment Date (DD-MM-YYYY):	_____ - _____ - _____	
Albendazole (ALB) dose (400 mg)	<input type="checkbox"/> 1 tablet (400 mg) Not done	
Diethylcarbamazine citrate (DEC) dose (6mg/kg)	<input type="checkbox"/> 1 tablet (100 mg) <input type="checkbox"/> 2 tablets (200 mg) <input type="checkbox"/> 3 tablets (300 mg)	<input type="checkbox"/> 4 tablet (400 mg) <input type="checkbox"/> 5 tablets (500 mg) <input type="checkbox"/> 6 tablets (600 mg)
Ivermectin (IVM) dose (200 ug /kg)	<input type="checkbox"/> 1 tablet (3 mg) <input type="checkbox"/> 2 tablets (6 mg) <input type="checkbox"/> 3 tablets (9 mg) <input type="checkbox"/> 4 tablets (12 mg) <input type="checkbox"/> 5 tablet (15 mg) <input type="checkbox"/> 6 tablets (18 mg) <input type="checkbox"/> 7 tablets (21 mg)	
Did Patient vomit or spit out the pills?	<input type="checkbox"/> Yes <input type="checkbox"/> No	
2 nd MDA Treatment Date (DD-MM-YYYY):	_____ - _____ - _____	
2 nd Albendazole (ALB) dose (400 mg)	<input type="checkbox"/> 1 tablet (400 mg) Not done	
2 nd Diethylcarbamazine citrate (DEC) dose (6mg/kg)	<input type="checkbox"/> 1 tablet (100 mg) <input type="checkbox"/> 2 tablets (200 mg) <input type="checkbox"/> 3 tablets (300 mg)	<input type="checkbox"/> 4 tablet (400 mg) <input type="checkbox"/> 5 tablets (500 mg) <input type="checkbox"/> 6 tablets (600 mg)

APPENDIX 2: PARTICIPANT ENROLLMENT FORM [EXAMPLE]

Participant ID (Barcode): _____

2 nd Ivermectin (IVM) dose (200 ug /kg)	<input type="checkbox"/> 1 tablet (3 mg)	<input type="checkbox"/> 5 tablet (15 mg)
	<input type="checkbox"/> 2 tablets (6 mg)	<input type="checkbox"/> 6 tablets (18 mg)
	<input type="checkbox"/> 3 tablets (9 mg)	<input type="checkbox"/> 7 tablets (21 mg)
	<input type="checkbox"/> 4 tablets (12 mg)	

DOLF IDA MDA DOSING CHART (by weight)					
<u>Albendazole (ALB)</u>	dosing (400 mg)	Diethylcarbamazine citrate (DEC)	dosing 6mg/kg	Ivermectin (IVM)	(dosing 200 ug /kg)
15 kg-120kg	1 tablet (400 mg)	15-25kg	1 tablet (100 mg)	15-23kg	1 tablet (3 mg)
		26-41kg	2 tablets (200 mg)	24-38kg	2 tablets (6 mg)
		42-58kg	3 tablets (300 mg)	39-53kg	3 tablets (9 mg)
		59-75kg	4 tablets (400 mg)	54-68kg	4 tablets (12 mg)
		76-92kg	5 tablets (500 mg)	69-83kg	5 tablets (15 mg)
		93-100kg	6 tablets (600 mg)	84-98kg	6 tablets (18 mg)
				99-100kg	7 tablets (21 mg)

APPENDIX 3: PARTICIPANT MONITORING FORM [EXAMPLE]

Team (required):	Clinician (required):
Data Entry Clerk ID (required):	

1. PARTICIPANT INFORMATION

Site #:	Treatment Date (DD-MM-YYYY): ____-____-____					
Monitoring Start Date (DD-MM-YYYY): ____-____-____						
Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Was Participant found during Active Monitoring?				Day 1		<input type="checkbox"/> Yes <input type="checkbox"/> No
				Day 2		<input type="checkbox"/> Yes <input type="checkbox"/> No

Team (required):	Clinician (required):
Data Entry Clerk ID (required):	

1. PARTICIPANT INFORMATION

Site #:	Treatment Date (DD-MM-YYYY): ____-____-____					
Monitoring Start Date (DD-MM-YYYY): ____-____-____						
Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Was Participant found during Active Monitoring?				Day 1		<input type="checkbox"/> Yes <input type="checkbox"/> No
				Day 2		<input type="checkbox"/> Yes <input type="checkbox"/> No

2. ASSESSMENT INFORMATION

Were any adverse events experienced? <input type="checkbox"/> Yes <input type="checkbox"/> No	<p style="text-align: center;">AE Identifier</p> <p>Record unique identifier for each adverse event for this subject.</p> <p>Number sequence for all following forms should not duplicate existing numbers for the subject.</p>
Symptoms/Signs • Grade 2 requires Vital Signs	

APPENDIX 3: PARTICIPANT MONITORING FORM [EXAMPLE]

Participant ID (Barcode): _____

- Grade 3 requires Vital Signs AND Physical Exam by Medical Personnel

Day 1 and 2: All participants should be asked all the questions in Table 1.

Days 3-7: Any participant who presents with a complaint should have their AEs graded below in Table 1.

Table 1: Reported Symptoms

- *Record a symptom grade from 0-5 for each day on which the participant experienced symptoms.*
- *Refer to the Guide for Assigning Adverse Event Severity for symptom-specific scoring criteria.*
- *Report Start and Stop dates for each Adverse Events*
- *If Participant has an Adverse Event and is lost to follow-up, please indicate*

Symptom Grading

0 = No adverse event or within normal limits

1 = Mild adverse event, does not interfere with work or school

2 = Moderate adverse event, interferes with work or school at least 1 day

3 = Severe and undesirable adverse event; interferes with ADL, requires medical assessment

4 = Potentially life-threatening or disabling adverse event; requires transfer to medical facility

5 = Death

APPENDIX 3: PARTICIPANT MONITORING FORM [EXAMPLE]

Participant ID (Barcode): _____

Symptoms /Signs Were any adverse events experienced by participant?	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Continuing?	Lost To Follow-up?	Is the Adverse Event Serious?
Neurologic-										
Fever - Grade								<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Dizziness, lightheaded - Grade								<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Headache - Grade								<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Fatigue - Grade								<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Respiratory										
Difficulty breathing (wheezing or dyspnea) - Grade								<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Cough - Grade								<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Musculoskeletal										
Joint pain - Grade								<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Muscle pain - Grade								<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Muscle Weakness - Grade								<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Skin										
Rash - Grade								<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Itchy Skin - Grade								<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Lymphatic										
Swelling in armpit - Grade								<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

APPENDIX 3: PARTICIPANT MONITORING FORM [EXAMPLE]

Participant ID (Barcode): _____

Swelling in groin - Grade										
Pain in armpit - Grade								<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Pain in groin - Grade										
Genital										
Men only: pain in your scrotum - Grade								<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Gastrointestinal										
Nausea - Grade								<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Vomiting - Grade								<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Diarrhea - Grade								<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Stomach Pain - Grade								<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
New Swelling - Grade								<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Specify the location of the unusual swelling										
Other										
Other illness or symptoms - Grade								<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other (please specify):										

- If there are any symptoms Grade ≥ 2, participant's vital signs must be taken by a Health Worker.
- If there are any symptoms Grade ≥ 3, you must notify the supervising medical officer and the participant must be evaluated by the medical team.

Table 2: Special Interest Events – Lymphatic Filariasis

APPENDIX 3: PARTICIPANT MONITORING FORM [EXAMPLE]

Participant ID (Barcode): _____

<ul style="list-style-type: none"> • Record the result under the column that corresponds to the day the assessment was taken. • Results for individual questions are listed under question • These questions only are answered if the corresponding AE above is recorded <ul style="list-style-type: none"> • “Swelling in armpit or groin” and/or “New Swelling” • “Men only: pain in your testicles or scrotum” 								
Special Interest Events - LF	Post-treatment day(s)							
	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 12.5%;">Day 1</th> <th style="width: 12.5%;">Day 2</th> <th style="width: 12.5%;">Day 3</th> <th style="width: 12.5%;">Day 4</th> <th style="width: 12.5%;">Day 5</th> <th style="width: 12.5%;">Day 6</th> <th style="width: 12.5%;">Day 7</th> </tr> </table>	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7		
Lymphedema (Swelling in arms or legs) <i>Results: Yes, No</i>								
Confirm and indicate which limbs are affected <i>Results: 1- Left arm, 2- Right arm, 3 - Left leg, 4- Right arm</i>								
Severity of lymphedema <i>Results: 1- Mild, 2 – Moderate, 3 – Severe Elephantiasis, 4 – Severe Disabling</i>								
Hydrocele (testicle swollen) <i>Results: Yes, No</i>								
Testicle swelling <i>Results: 1 – all the time; 2- only when carrying large objects</i>								

Table 3: Vital Signs														
<ul style="list-style-type: none"> • You must complete this table for any participant reporting any symptom Grade ≥2 • Record the result under the column that corresponds to the day the assessment was taken. 														
Measurements	Post-treatment day(s)													
	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 12.5%;">Day 1</th> <th style="width: 12.5%;">Day 2</th> <th style="width: 12.5%;">Day 3</th> <th style="width: 12.5%;">Day 4</th> <th style="width: 12.5%;">Day 5</th> <th style="width: 12.5%;">Day 6</th> <th style="width: 12.5%;">Day 7</th> </tr> </table>							Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7								
Systolic blood pressure, sitting (mm Hg)														
Diastolic blood pressure, sitting (mm Hg)														
Orthostatic? Results: Yes, No														
Pulse rate (beats per minute)														

APPENDIX 3: PARTICIPANT MONITORING FORM [EXAMPLE]

Participant ID (Barcode): _____

Temperature (in Celsius)							
--------------------------	--	--	--	--	--	--	--

Table 4: Abnormal Physical Findings							
<ul style="list-style-type: none"> You must complete this table for any participant reporting any symptom Grade ≥ 3 Record the result under the column that corresponds to the day the assessment was taken. 							
	Post-treatment day(s)						
	D a y 1	D a y 2	D a y 3	D a y 4	D a y 5	D a y 6	D a y 7
Was participant referred for further assessment? <u>Results:</u> Yes, No							
Tender Lymph node locations <u>Results:</u> 1 - Axilla, 2 - Inguinal, 3 - Scrotal							
For participants with GI symptoms, record the following <u>Results:</u> 1 - Abdominal tenderness, 2 - Enlarged spleen, 3- Enlarged liver							
Post-Exam Adverse Event Grade (Assign grade of 0-5 for the adverse reactions below based on physical exam. See "post-exam assessment" for specific grading criteria)							
Allergic reaction							
Lung Wheezing							
Lymphangitis (streaks of redness, warmth, and swelling in arms or legs)							
Are there any abnormal physical findings? <u>Results:</u> Yes, No							
Additional notes or comments:							

APPENDIX 3: PARTICIPANT MONITORING FORM [EXAMPLE]

Participant ID (Barcode): _____

Table 5: Body Systems Physical Exam							
<ul style="list-style-type: none"> Everyone with Grade ≥ 3 AE will have a Physical Exam by a Medical Examiner. Not all body systems need to be examined as these are directed physical exams; review body systems related to reported AEs. 							
Body Systems	Post-treatment day(s)						
	Da y 1	Da y 2	Da y 3	Da y 4	Da y 5	Da y 6	Da y 7
Has anything changed since the last physical exam? Results: Yes, No							
Exam performed: Results: Yes, No							
Reason Not Performed:							
Review of Body Systems Record whether: 1 – Normal, 2- Abnormal, 3 – Not Done	Post-treatment day(s)						
	Da y 1	Da y 2	Da y 3	Da y 4	Da y 5	Da y 6	Da y 7
Cardiac							
Ear and Labyrinth							
Endocrine and Lymph							
Eye							
Hepatobiliary, Renal and Urinary							
Mouth, Throat and Gastrointestinal							
Musculoskeletal and Connective Tissue							
Nervous System							
Reproductive System and Breast							
Respiratory, Thoracic and Mediastinal							
Skin and Subcutaneous Tissue							
Vascular							
Other							

APPENDIX 3: PARTICIPANT MONITORING FORM [EXAMPLE]

Participant ID (Barcode): _____

Abnormal Findings:									
RESULTS									
		D a y 1	D a y 2	D a y 3	D a y 4	D a y 5	D a y 6	D a y 7	PE Identi fier
Clinically significant Results: Yes, No									
Reporting Clinician Name		Day 4							
Day 1		Day 5							
Day 2		Day 6							
Day 3		Day 7							

Symptoms /Signs Were any adverse events experienced by participant?	Post-treatment day(s) on which symptoms or signs were present								Con- tin- uin- g?	Lost To Foll- ow- up?	Is the Adve- rse Even- t Serio- us?
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7				
____-____- ____	____- ____-____	____- ____- ____	____- ____- ____	____- ____- ____	____- ____- ____	____- ____- ____	____- ____- ____				

APPENDIX 3: PARTICIPANT MONITORING FORM [EXAMPLE]

Participant ID (Barcode): _____

Neurologic-										
Fever - Grade								<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Dizziness, lightheaded - Grade								<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Headache - Grade								<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Fatigue - Grade								<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Respiratory										
Difficulty breathing (wheezing or dyspnea) - Grade								<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Cough - Grade								<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Musculoskeletal										
Joint pain - Grade								<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Muscle pain - Grade								<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Muscle Weakness - Grade								<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Skin										
Rash - Grade								<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Itchy Skin - Grade								<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Lymphatic										
Swelling in armpit - Grade								<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Swelling in groin - Grade										
Pain in armpit - Grade								<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Pain in groin - Grade										
Genital										

APPENDIX 3: PARTICIPANT MONITORING FORM [EXAMPLE]

Participant ID (Barcode): _____

Men only: pain in your scrotum - Grade									<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Gastrointestinal</i>											
Nausea - Grade									<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Vomiting - Grade									<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Diarrhea - Grade									<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Stomach Pain - Grade									<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
New Swelling - Grade									<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Specify the location of the unusual swelling											
<i>Other</i>											
Other illness or symptoms - Grade									<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other (please specify):											

- If there are any symptoms Grade \geq 2, participant's vital signs must be taken by a Health Worker.
- If there are any symptoms Grade \geq 3, you must notify the supervising medical officer and the participant must be evaluated by the medical team.

Table 2: Special Interest Events – Lymphatic Filariasis

APPENDIX 3: PARTICIPANT MONITORING FORM [EXAMPLE]

Participant ID (Barcode): _____

<ul style="list-style-type: none"> Record the result under the column that corresponds to the day the assessment was taken. Results for individual questions are listed under question These questions only are answered if the corresponding AE above is recorded <ul style="list-style-type: none"> “Swelling in armpit or groin” and/or “New Swelling” “Men only: pain in your testicles or scrotum” 								
Special Interest Events - LF	Post-treatment day(s)							
	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 12.5%;">Day 1</th> <th style="width: 12.5%;">Day 2</th> <th style="width: 12.5%;">Day 3</th> <th style="width: 12.5%;">Day 4</th> <th style="width: 12.5%;">Day 5</th> <th style="width: 12.5%;">Day 6</th> <th style="width: 12.5%;">Day 7</th> </tr> </table>	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7		
Lymphedema (Swelling in arms or legs) <i>Results: Yes, No</i>								
Confirm and indicate which limbs are affected <i>Results: 1- Left arm, 2- Right arm, 3 - Left leg, 4- Right arm</i>								
Severity of lymphedema <i>Results: 1- Mild, 2 – Moderate, 3 – Severe Elephantiasis, 4 – Severe Disabling</i>								
Hydrocele (testicle swollen) <i>Results: Yes, No</i>								
Testicle swelling <i>Results: 1 – all the time; 2- only when carrying large objects</i>								

Table 3: Vital Signs														
<ul style="list-style-type: none"> You must complete this table for any participant reporting any symptom Grade ≥2 Record the result under the column that corresponds to the day the assessment was taken. 														
Measurements	Post-treatment day(s)													
	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 12.5%;">Day 1</th> <th style="width: 12.5%;">Day 2</th> <th style="width: 12.5%;">Day 3</th> <th style="width: 12.5%;">Day 4</th> <th style="width: 12.5%;">Day 5</th> <th style="width: 12.5%;">Day 6</th> <th style="width: 12.5%;">Day 7</th> </tr> </table>							Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7								
Systolic blood pressure, sitting (mm Hg)														
Diastolic blood pressure, sitting (mm Hg)														
Orthostatic? Results: Yes, No														
Pulse rate (beats per minute)														

APPENDIX 3: PARTICIPANT MONITORING FORM [EXAMPLE]

Participant ID (Barcode): _____

Temperature (in Celsius)							
--------------------------	--	--	--	--	--	--	--

Table 4: Abnormal Physical Findings							
<ul style="list-style-type: none"> You must complete this table for any participant reporting any symptom Grade ≥ 3 Record the result under the column that corresponds to the day the assessment was taken. 							
	Post-treatment day(s)						
	D a y 1	D a y 2	D a y 3	D a y 4	D a y 5	D a y 6	D a y 7
Was participant referred for further assessment? <u>Results:</u> Yes, No							
Tender Lymph node locations <u>Results:</u> 1 - Axilla, 2 - Inguinal, 3 - Scrotal							
For participants with GI symptoms, record the following <u>Results:</u> 1 - Abdominal tenderness, 2 - Enlarged spleen, 3- Enlarged liver							
Post-Exam Adverse Event Grade (Assign grade of 0-5 for the adverse reactions below based on physical exam. See “post-exam assessment” for specific grading criteria)							
Allergic reaction							
Lung Wheezing							
Lymphangitis (streaks of redness, warmth, and swelling in arms or legs)							
Are there any abnormal physical findings? <u>Results:</u> Yes, No							
Additional notes or comments:							

APPENDIX 3: PARTICIPANT MONITORING FORM [EXAMPLE]

Participant ID (Barcode): _____

Table 5: Body Systems Physical Exam							
<ul style="list-style-type: none"> Everyone with Grade ≥ 3 AE will have a Physical Exam by a Medical Examiner. Not all body systems need to be examined as these are directed physical exams; review body systems related to reported AEs. 							
Body Systems	Post-treatment day(s)						
	Da y 1	Da y 2	Da y 3	Da y 4	Da y 5	Da y 6	Da y 7
Has anything changed since the last physical exam? <u>Results:</u> Yes, No							
Exam performed: <u>Results:</u> Yes, No							
Reason Not Performed:							
Review of Body Systems Record whether: 1 – Normal, 2- Abnormal, 3 – Not Done	Post-treatment day(s)						
	Da y 1	Da y 2	Da y 3	Da y 4	Da y 5	Da y 6	Da y 7
Cardiac							
Ear and Labyrinth							
Endocrine and Lymph							
Eye							
Hepatobiliary, Renal and Urinary							
Mouth, Throat and Gastrointestinal							
Musculoskeletal and Connective Tissue							
Nervous System							
Reproductive System and Breast							
Respiratory, Thoracic and Mediastinal							
Skin and Subcutaneous Tissue							
Vascular							
Other							

APPENDIX 3: PARTICIPANT MONITORING FORM [EXAMPLE]

Participant ID (Barcode): _____

Abnormal Findings:																									
RESULTS																									
	<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 12.5%;">D a y 1</th> <th style="width: 12.5%;">D a y 2</th> <th style="width: 12.5%;">D a y 3</th> <th style="width: 12.5%;">D a y 4</th> <th style="width: 12.5%;">D a y 5</th> <th style="width: 12.5%;">D a y 6</th> <th style="width: 12.5%;">D a y 7</th> <th style="width: 12.5%;">PE Identi fier</th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">Clinically significant Results: Yes, No</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> </tbody> </table>	D a y 1	D a y 2	D a y 3	D a y 4	D a y 5	D a y 6	D a y 7	PE Identi fier	Clinically significant Results: Yes, No															
D a y 1	D a y 2	D a y 3	D a y 4	D a y 5	D a y 6	D a y 7	PE Identi fier																		
Clinically significant Results: Yes, No																									
Reporting Clinician Name		Day 4																							
Day 1		Day 5																							
Day 2		Day 6																							
Day 3		Day 7																							

APPENDIX 4: GUIDE TO ASSIGNING ADVERSE EVENT SEVERITY

(Grade 0 = no symptoms; grade 5 = death from adverse event)

Symptoms/Signs	Grades			
	1. Mild	2. Moderate	3. Severe	4. Life-threatening
Fever (non-axillary temperatures only)	38.0 – 39.0°C	39.1 – 40.0°C	> 40.0°C	> 40.0°C for > 48 hrs
Dizziness, giddiness, or fainting	Mild, not interfering with work or school	Moderate, unable to work or attend school for 1 day, but no fainting	Any loss of consciousness (fainting)	-
Confusion or excess drowsiness*	Mild, not interfering with work or school	Moderate; confusion or drowsiness interfering with ability to work	Confusion, loss of memory, or sleepiness interfering with activities of daily living	Delerium, inability rouse, or coma
Fatigue	Mild, not interfering with work or school	Moderate, unable to work or attend school at least 1 day	Unable to perform activities of daily living, > 1day	Required hospitalization
Headache	Mild pain not interfering with work or school	Moderate pain; pain or analgesics interfering with ability to work or attend school	Severe pain; pain or analgesics interfering with activities of daily living	Disabling, duration > 48 hr
Cough	Mild, relieved by non-prescription medication	Requiring narcotic antitussive	Severe cough or coughing spasms, poorly controlled by treatment	Hospitalization or respiratory failure requiring mechanical ventilation

APPENDIX 4: GUIDE TO ASSIGNING ADVERSE EVENT SEVERITY

(Grade 0 = no symptoms; grade 5 = death from adverse event)

Symptoms/Signs	Grades			
	1. Mild	2. Moderate	3. Severe	4. Life-threatening
Difficulty breathing (wheezing or dyspnea)	Mild, not interfering with work or school	Moderate, unable to work or attend school for 1 day	Severe, more than 1 day and required transfer to clinic or hospital	Hospitalization or respiratory failure requiring mechanical ventilation
Nausea	Able to eat	Oral intake significantly decreased	No significant intake, requiring IV fluids	-
Vomiting	1 episode in 24 hours over pretreatment	2-5 episodes in 24 hours over pretreatment	≥ 6 episodes in 24 hours, or need for IV fluids (Outpatient)	Hemodynamic collapse or overnight hospitalization
Diarrhea	Increase of < 4 stools/day over pre-treatment	Increase of 4-6 stools/ day, or nocturnal stools	Increase of ≥ 7 stools/ day or need for outpatient parenteral support for dehydration	Physiologic consequences with hemodynamic collapse or requiring hospitalization
Abdominal pain	Mild pain not interfering with work or school	Moderate pain; pain or analgesics interfering with ability to work or attend school	Severe pain; pain or analgesics interfering with activities of daily living	Disabling, duration > 48 hr
Unusual swelling (beyond baseline lymphedema)	Mild, not interfering with work or school	Moderate, unable to work or attend school 1 day	Severe, unable to work/school >1 day	Severe, limiting activities of daily living (unable to walk) > 2 days
Joint or muscle pain	Mild pain not interfering with work or school	Moderate pain; pain or analgesics interfering with ability to work or attend school	Severe pain; pain or analgesics interfering with activities of daily living	Disabling, duration > 48 hr

APPENDIX 4: GUIDE TO ASSIGNING ADVERSE EVENT SEVERITY

(Grade 0 = no symptoms; grade 5 = death from adverse event)

Symptoms/Signs	Grades			
	1. Mild	2. Moderate	3. Severe	4. Life-threatening
Swelling or pain in your armpit or groin*	Mild, not interfering with work or school	Moderate, unable to work or attend school 1 day	Severe, unable to work/school >1 day	Severe, limiting activities of daily living (unable to walk) > 2 days
Men only: testicular or scrotal pain	Mild, not interfering with work or school	Moderate, unable to work or attend school 1 day	Severe, unable to work/school >1 day	Severe, limiting activities of daily living (unable to walk) > 2 days
Itching skin	Mild, not interfering with work or school	Moderate, unable to work or attend school 1 day	Severe, unable to work/school >1 day	
Rash	Localized rash (covers only one part of the body)	Diffuse rash (covers multiple parts of the body)	Diffuse rash (covers multiple parts of the body) AND has any blisters or ulcers or mouth sores	Extensive areas with blisters or ulcers OR peeling or blackening of skin
Other illness or symptoms	Mild, not interfering with work or school	Moderate, unable to work or attend school at least 1 day	Unable to perform activities of daily living, > 1day	Required hospitalization

APPENDIX 4: GUIDE TO ASSIGNING ADVERSE EVENT SEVERITY

(Grade 0 = no symptoms; grade 5 = death from adverse event)

Post-Exam Assessment	Grades			
	1. Mild	2. Moderate	3. Severe	4. Life-threatening
Acute allergic reaction	Transient rash, drug Fever <38°C (<100.4°F)	Urticaria, drug fever ≥38°C (≥100.4°F) and/or asymptomatic bronchospasm	Symptomatic bronchospasm, requiring parenteral medication(s) with or without urticaria	Anaphylaxis with hypotension required hospitalization
Hypotension (low blood pressure)	Changes, but not requiring therapy (including transient orthostatic hypotension)	Requiring brief fluid replacement (such as oral rehydration) but not hospitalization	Requiring i.v. fluids without overnight hospitalization. No sequelae.	Required overnight hospitalization for i.v. fluids, or Shock (acidemia and impaired vital organ function due to tissue hypoperfusion)
Lymphangitis	Mild, not interfering with work or school	Moderate, unable to work or attend school 1 day	Severe, unable to work/school >1 day	Severe, limiting activities of daily living (unable to walk) > 2 days

Note on general aspects of grading

0 = No adverse event or within normal limits

1 = Mild adverse event, does not interfere with work or school

2 = Moderate adverse event, interferes with work or school at least 1 day

3 = Severe and undesirable adverse event; interferes with ADL, requires medical assessment

4 = Potentially life-threatening or disabling adverse event; requires transfer to medical facility

5 = Death

Note: Any event ≥ grade 2 requires a medical evaluation and notification of the medical officer.

APPENDIX 5: ADVERSE EVENT EVALUATION AND REPORT FORM (AEERF) [EXAMPLE]

Instructions: Complete this form **AFTER** completing the Participant Monitoring Form for anyone with symptoms or signs of **grade 3 or higher** (unable to perform activities of daily living without assistance for at least one day) and determined by a physician or health care worker to be a potential Serious Adverse Event (SAE). The purpose of this form is to provide additional information on more severe adverse events and to assist the medical monitor in determining whether a Serious Adverse Event (SAE) has occurred.

PROTOCOL: DOLF IDA	Country: _____	Site#: _____	Participant Barcode:
SECTION 1: REPORT TYPE			
<input type="checkbox"/> Initial - Date: <u> - - </u> DD-MMM-YYYY		<input type="checkbox"/> Follow-up # _____ - Date: <u> - - </u> DD-MMM-YYYY	
SECTION 2: DEMOGRAPHICS			
Gender: <input type="checkbox"/> Female <input type="checkbox"/> Male		Date of Birth: <u> - - </u> MMM-YYYY	
SECTION 3: ADVERSE EVENT INFORMATION			
SAE Term (concise medical diagnosis): _____			
Start Date: <u> - - </u> DD-MMM-YYYY		End Date: <u> - - </u> DD-MMM-YYYY	
Serious Criteria (check all that apply): <input type="checkbox"/> Inpatient or Prolonged Hospitalization - If yes, Date of Admission: <u> - - </u> DD-MMM-YYYY Date of Discharge: <u> - - </u> DD-MMM-YYYY <input type="checkbox"/> Life-threatening (immediate risk of death) <input type="checkbox"/> A persistent or significant disability/incapacity <input type="checkbox"/> Congenital Anomaly or Birth Defect <input type="checkbox"/> Other Serious or Important Medical Event <input type="checkbox"/> Death - If yes, Cause of Death: _____ Date of Death: <u> - - </u> DD-MMM-YYYY Was autopsy completed? <input type="checkbox"/> No <input type="checkbox"/> Yes - <i>If yes, please forward report</i> Is death certificate available? <input type="checkbox"/> No <input type="checkbox"/> Yes - <i>If yes, please forward</i>			Outcome (check one): <input type="checkbox"/> Recovered/Resolved <input type="checkbox"/> Recovered/Resolved with sequelae (<i>describe sequelae in narrative</i>) <input type="checkbox"/> Recovering/Resolving <input type="checkbox"/> Not Recovered/Not Resolved <input type="checkbox"/> Fatal <input type="checkbox"/> Unknown
CTCAE Grade Version 4.03 / Severity (check one): <input type="checkbox"/> Grade 1/Mild <input type="checkbox"/> Grade 2/Moderate <input type="checkbox"/> Grade 3/Severe <input type="checkbox"/> Grade 4/Life-threatening <input type="checkbox"/> Grade 5/Death			

APPENDIX 5: ADVERSE EVENT EVALUATION AND REPORT FORM (AEERF) [EXAMPLE]

Participant ID (Barcode): _____

PROTOCOL: DOLF IDA	Country: _____	Site#: _____	Participant Barcode:
--------------------	----------------	--------------	----------------------

SECTION 4: STUDY DRUG INFORMATION

MDA Treatment Date	Albendazole (400 mg tablets)	DEC (100 mg tablets)	Ivermectin (3 mg tablets)	Relationship of SAE to MDA <i>(check one)</i>
____ - ____ - ____ DD-MMM-YYYY	# Tabs <input type="checkbox"/>	# Tabs <input type="checkbox"/>	# Tabs <input type="checkbox"/> NA <input type="checkbox"/>	<input type="checkbox"/> Not Related <input type="checkbox"/> Possibly Related <input type="checkbox"/> Probably Related <input type="checkbox"/> Related

Possible alternate cause other than Study Drug *(select all that apply)*:

- | | |
|--|--|
| <input type="checkbox"/> Study Disease-related | <input type="checkbox"/> Pre-existing condition - Specify: _____ |
| <input type="checkbox"/> Concomitant medication - Specify: _____ | <input type="checkbox"/> Other - Specify: _____ |

SECTION 5: RELEVANT LABORATORY/DIAGNOSTIC TESTS None

Test Name	Date	Result	Unit	Normal Range
	____ - ____ - ____ DD-MMM-YYYY			
	____ - ____ - ____ DD-MMM-YYYY			
	____ - ____ - ____ DD-MMM-YYYY			
	____ - ____ - ____ DD-MMM-YYYY			
	____ - ____ - ____ DD-MMM-YYYY			

SECTION 6: RELEVANT CONCOMITANT MEDICATIONS None

Medication	Start Date	Stop Date or Ongoing	Dose & Unit	Frequency	Route	Indication
	____ - ____ - ____ DD-MMM-YYYY	____ - ____ - ____ OR <input type="checkbox"/> Ongoing DD-MMM-YYYY				
	____ - ____ - ____ DD-MMM-YYYY	____ - ____ - ____ OR <input type="checkbox"/> Ongoing DD-MMM-YYYY				
	____ - ____ - ____ DD-MMM-YYYY	____ - ____ - ____ OR <input type="checkbox"/> Ongoing DD-MMM-YYYY				
	____ - ____ - ____ DD-MMM-YYYY	____ - ____ - ____ OR <input type="checkbox"/> Ongoing DD-MMM-YYYY				
	____ - ____ - ____ DD-MMM-YYYY	____ - ____ - ____ OR <input type="checkbox"/> Ongoing DD-MMM-YYYY				

SECTION 7: RELEVANT MEDICAL HISTORY None

Diagnosis	Start Date	Stop Date or Ongoing
	____ - ____ - ____ DD-MMM-YYYY	____ - ____ - ____ OR <input type="checkbox"/> Ongoing DD-MMM-YYYY
	____ - ____ - ____ DD-MMM-YYYY	____ - ____ - ____ OR <input type="checkbox"/> Ongoing DD-MMM-YYYY

APPENDIX 5: ADVERSE EVENT EVALUATION AND REPORT FORM (AEERF) [EXAMPLE]

Participant ID (Barcode): _____

PROTOCOL: DOLF IDA	Country: _____	Site#: _____	Participant Barcode:
	- - DD-MMM-YYYY	- - DD-MMM-YYYY	OR <input type="checkbox"/> Ongoing
	- - DD-MMM-YYYY	- - DD-MMM-YYYY	OR <input type="checkbox"/> Ongoing
	- - DD-MMM-YYYY	- - DD-MMM-YYYY	OR <input type="checkbox"/> Ongoing
SECTION 8: NARRATIVE SUMMARY			
<i>Describe the event in detail from onset through resolution. Include rationale for causality and any interventions given.</i>			
SECTION 9: REPORTER INFORMATION			
Reporter Name (if not Investigator): _____		Location: _____	
<i>I, the undersigned investigator, attest that I have reviewed this SAE Report and agree with the content.</i>			
Investigator Name:			
Investigator Signature:			Date: - - DD-MMM-YYYY

APPENDIX 5A: REQUIRED REPORTING & GUIDELINES FOR SAE(S)

An Adverse Event Evaluation and Report Form (AEERF) should be completed for every severe adverse event (those scoring grade 3 or higher, see [Appendix 4](#)). However, a grade 3 or severe adverse event is NOT the same as a Serious Adverse Events (SAE) and the majority of grade 3 adverse events will not be classified as SAE. The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

The AEERF should guide the medical monitor or health care provider evaluating the patient experiencing a severe AE to determine whether a SAE has occurred. All SAE must be reported promptly. (See Safety Reporting Plan for SAE Reporting Timeline)

Required Reporting

A written report or case report form (CRF—in this study, the AEERF) must be sent from the local physician and local medical monitor by email (scanned records) in the stated timeframes to the Country PI, Global Medical Monitor including the Project PI for the events listed below.

Guidelines for Reporting - Standard Reporting Information

The following information should be included in the **initial** report/CRF (additional information may be requested):

Minimum Criteria for Reporting

Information for final description and evaluation of a case report may not be available within the required time frames for reporting outlined below. Initial reports should be submitted within the prescribed time as long as the following minimum criteria are met: an **identifiable patient**; an **identifiable reporting source**; and an **event or outcome that can be identified as serious**. Follow-up information should be actively sought and submitted as it becomes available.

Complete the following information if available on the initial report and complete a follow-up report as new or additional information becomes available as noted below:

- Description of the event
Date, time of onset
Clinical history
Associated signs and symptoms
Temporal association with study agent
Medical management, including rationale

APPENDIX 5A: REQUIRED REPORTING & GUIDELINES FOR SAE(S)

Pertinent laboratory tests
Severity – see *definitions or toxicity score*
Causal relationship to the study drug/vaccine

- Other information
Relevant past medical history
Concomitant medications
Autopsy report or expectation of an autopsy in the case of death
- Outcome of event
Date, time of resolution, if resolved
- Plans for study participant
Follow-up
Treatment of event
Return to treatment/Contraindicate
- Location/Study Centre
- Reporting Physician
- Verification of notification to IRB and Safety Monitor or DSMB

Definitions

- Adverse Event [Experience] (AE):

Any untoward medical occurrence, including dosing errors, that may arise during administration of study agent, and which may or may not have a causal relationship with the study agent.
- Unexpected Adverse Event [Experience]:

Any adverse experience that has not been previously observed (i.e., included in the labelling), whether or not the event is anticipated because of the pharmacologic properties of the study agent.

APPENDIX 5A: REQUIRED REPORTING & GUIDELINES FOR SAE(S)

- Serious Adverse Event (SAE):

Any adverse event occurring at any dose that results in any of the following outcomes:

- a. Death
- b. Life threatening – defined as an experience that places the patient or participant, in the view of the Investigator, at *immediate risk* of death from the reaction as it occurred. (Note; this does not include a reaction that, had it occurred in a more severe form, might have caused death.)
- c. Requires inpatient hospitalization or prolongation of existing hospitalization
- d. Results in a congenital anomaly or birth defect
- e. Results in a persistent or significant disability or incapacity
- f. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (*The event might be defined as serious based on progression of grade if Toxicity Tables are being used.*)

Severity

Adverse experience/events should be assessed by the on-site investigator as to their severity and/or intensity.

- a. Life threatening
- b. Severe: incapacitating with inability to work or do usual activity
- c. Moderate: enough discomfort to cause interference with usual activity
- d. Mild: awareness of sign or symptom, but easily tolerated

Relationship or Association with Use of Study Agent or Participation in the Study

Causal relationship with the investigational study treatment must be assessed by the on-site investigator using the following or similar terms:

- **Definite** – clear-cut temporal association, with a positive re-challenge test or laboratory confirmation.

APPENDIX 5A: REQUIRED REPORTING & GUIDELINES FOR SAE(S)

- **Probable** – clear-cut temporal association, with improvement upon drug withdrawal, and not reasonably explained by the participant’s known clinical state.
- **Possible** – less clear temporal association; other aetiologies are possible.
- **None** – no temporal association with the study drug; related to other aetiologies such as concomitant medications or conditions, or participant’s known clinical state.

Other Reporting

Investigators are reminded that they may have other reporting obligations:

- For all studies, there must be compliance with the clinical site Ethics/IRB’s policy for reporting adverse events. (As soon as possible for SAEs and as required for AEs.)

APPENDIX 6A: INFORMED CONSENT FORM (V.3, 30 AUGUST 2016)

INFORMED CONSENT FORM (Version 3, 30 August 2016)

Community Based Safety Study of 2-drug versus 3-drug Therapy for Lymphatic Filariasis in Indonesia

Principal Investigators: Peter U. Fischer, Ph.D. (USA), Taniawati Supali, Ph.D. (Indonesia)

Lymphatic filariasis, commonly called Elephant foot is a problem in this village. This disease is caused by infection of worms that live in the blood, left untreated for a long time. If this disease has gotten to a stage elephant foot which cause your limbs to swell, then the swollen parts cannot go back to normal. This disease might make it difficult for you to work and to perform daily activities.

Elephant foot is commonly treated in Indonesia with two drugs. These two drugs need to be taken by most people in the community every year for five years in order to get rid of the disease. We, the team of Department of Parasitology Faculty of Medicine Universitas Indonesia together with Washington University and the local health district are doing a new MDA approach along with research study to see if there is a better and faster treatment for elephant foot. We will study the effect of two different drug combinations given to men, women, and children aged 5 years or more in this village. The study will look at the effects of the drugs in treating gut worms since each drug is known to kill gut worms.

Aim of the study and the reason you are asked to participate

Two drugs are currently used to treat elephant foot. They are called Diethylcarbamazine (DEC) and Albendazole. There is another drug called Ivermectin that has been used safely to treat elephant foot in Africa. The purpose of this research is to learn if three drugs (DEC, Albendazole and Ivermectin) work better than the two drugs (DEC and Albendazole). We will also look at the side effects of these drugs used together to get rid of elephant foot and to treat gut worms. This research will be done in four villages in two districts. The villages are Karang Inda, Kahale and Rada Malando in Southwest Sumba District and Ojandetun village in East Flores District.

The reason why that we are asking you to be in this study is because your village is in an area with a high risk of elephant foot. In order to get rid of this disease your village like every village in Indonesia needs to get treatment. In addition to comparing how the treatment with two or three drugs work to get rid of elephant foot we also want to know if the drugs will be accepted by you and your community, so it is important that you participate in this study.

APPENDIX 6A: INFORMED CONSENT FORM (V.3, 30 AUGUST 2016)

Drug administration and Drug Reaction

In this study, you will take either two drugs (albendazole and DEC) or three drugs (albendazole, DEC, and ivermectin). The number of pills you take depend on how much you weigh. The pills must be swallowed in front of the study officer in charge. The first 60 adults in this study will take the drug at the hospital in the city (RSUD Waikabubak). Everyone else will take the drug in their villages where they live.

You may have drug reaction after taking the drugs. The side effects that might include things like headache, nausea, vomiting, stomach pain, tiredness, difficulty in breathing, faint, itching, rash, or swelling in some parts of your body. However those drug reaction do not occur so often. There may be some side effects we do not know about yet.

Hospital- Based Treatment (Procedure, Potential risk, and Compensation)

We will come to your village to take blood from your finger at night. If we find the elephant foot worm in your blood you may be chosen to be one of the 60 people who will take the drug at the hospital. If you are selected, you will be asked to stay at the hospital for three nights and four days. The reason you have to be hospitalized is that we want to carefully see if you have any side effects and to make sure the drugs are working. The drug is supposed to kill the worms. The dead worms may cause reactions in your body, causing symptoms like fever, drowsiness, and weariness which generally happens in people who have elephant foot. There is a small chance that you are allergic to one or more of the drugs. We want to monitor all of these possible effects, either by a doctor's examination or laboratory test, to make sure you are safe and that the drug is working. You will be given the medicine to treat the effect, if you experience any reaction.

The blood collection in the hospital will be done by drawing blood from your vein which may cause slightly more discomfort compared to finger prick blood collection. Infection, bruising and bleeding might also occur but this is very unlikely to happen. The amount of blood collected is approximately as much as two table spoons. The blood collected will be tested for worms.

Four days after you leave the hospital, we will visit your home to ask if you have had any other side effects since leaving the hospital. You will not be charged any fee during the hospitalization. All transportation to and from your home to the hospital, as well as your treatment and meals will be free. To replace the lost income that you might get from working, we will give you compensation in amount of IDR 300,000. You are free to quit the study any time for any reason or no reason. If you leave the hospital early you will still receive partial payment for the time you stayed at the hospital. If you leave the study there will be no impact on your medical care. We will provide full insurance if you get sick, have an accident or get injured because of the study.

Community- Based Treatment (Procedure, Potential Risk, and Compensation)

APPENDIX 6A: INFORMED CONSENT FORM (V.3, 30 AUGUST 2016)

Everyone who was not chosen to be treated at the hospital will be treated in their community where they live.

Basically, the same steps will be done. You will be given medication, then we will visit you to see how the medicine worked and look at any side effects caused by the medicine. If you have side effects we will record it and give you treatment to help you. We will visit you twice, once on the first day after you have taken the medicine and again on the second day. If you have any side effects during the next five days (7 days after you took the medicine) you should tell the head of your Dusun about it. Someone from our research team will visit the head of your Dusun to ask if anyone has a side effect and will find you. Health workers from the Faculty of Medicine, Department of Health, or the primary health care will accompany you during your treatment. In order to see if the medicines are working we will take blood samples from you finger. Blood collection might cause some pain. Infection and bleeding might also occur but this is very unlikely to happen.

In addition to taking blood, some of you will be asked to collect your poo in a special container which we have provided. We will ask for your poo before and after you take the drug. We will use your poo to see if you have gut worms and also to see if the drug works to kill gut worms.

You will not be charged to participate in this study. You will also not be compensated in this community-based study. We will provide full insurance if you get sick, have an accident or get injured because of the study. You may quit the study at any time for any reason or no reason with no impact on your medical care.

Acceptability Study

After all treatment is over, we will do a survey to learn what the community thinks about the three drug treatment compared to the standard two drug therapy. In this survey you will be asked questions about how you felt about taking the drug, your opinion on the side effects, and your opinion about taking three drugs again in the future.

Sample Size and Study Participants' Criteria

We expect 4,000 participants in total to take part in this study. This includes male and female adults, and children aged 5 years old or older. People will be picked from these villages: Karang Inda, Kahale, Rada Malando and Ojandetun. Sixty people with high infection of worms will be picked to take the drug at the hospital. We will ask for poo from 600 participants to see the effect on gut worms.

To be in the study you must be 5 years old or older, you must not have severe disease at the moment (which may cause problems for the study or cause harm to yourself), you must not have an allergy or bad reaction to drugs used to treat elephant foot, if you are a woman you must not

APPENDIX 6A: INFORMED CONSENT FORM (V.3, 30 AUGUST 2016)

be pregnant or be breastfeeding at the moment. If you are not sure if you are pregnant or forget when you had your last menstrual period, we will give you a pregnancy test to tell whether you are pregnant or not.

If you meet this criteria, you can be in this study. To be in the study, you have to provide written consent for yourself or for your children (as a parent or legal guardian).

Duration and Term and Condition of Participation

If you decide to be in this study, you will be part of the study for one year. This starts from the day you are given treatment. You will be visited on the first and second day after taking the drug. If you tell the head of the dusun that you have side effects, you may be visited again. Within four months after you took the drug, you may be asked to participate in acceptability study. After that, one year later we may visit you again. You will be asked to give finger prick blood to see how the drug worked.

Your participation in this study is voluntary. You are free to decide if you or your children want to be involved. You are also free to decide to quit the study at any time. If you move away outside of the study villages during the study you can be taken out of the study. If you are taken out of the study there will be no impact on your medical care. If you do not want to be part of this study, you will still be given medication for elephant foot (DEC and ALB given once a year for five years). The two drugs are part of a mass treatment program for elephant foot given to people by the Health Ministry of Indonesia.

Confidentiality

For long term follow up purpose, we will take your photo and store it in our data. This data can be seen only by study team. We will keep your identity secret. A code using only numbers will be used to identify your blood and stool. You will be given an identification card which you might write your name on it. This card will be kept by yourself. There will be an emergency contact on the card which you can call if you have an emergency situation within 7 days after taking the drug. Your name or any other information about you will not be put on your blood or stool. Your information will be kept secret even if you are taken out of the study or decide to quit the study.

Sample Storage and Usage

All blood and stool sample will be stored in Department of Parasitology Universitas Indonesia. The blood collected from you will only be used for the study described above related to elephant foot and gut worms. Some blood and stool may be picked at random (like rolling dice) to be sent to other laboratory to check that the tests for worms are done correctly.

APPENDIX 6A: INFORMED CONSENT FORM (V.3, 30 AUGUST 2016)

WHOM TO CALL IF I HAVE QUESTIONS OR PROBLEM RELATED TO THE STUDY?

If in the future you have a question or problem related to your participation in the study, you may call the field coordinator, dr. Michael Christian (081237587120) or study coordinator, Dr. Yenny Djuardi at this number: +62812 8852 7832.

ASSESSMENT OF CONSENT

Point to be confirmed	Yes	No
Do you understand the explanation?		
Do you have any question?		
If yes:		
Are you voluntarily willing to be involved in this study?		
If yes, in which part of the study would you participate?		
<input type="checkbox"/> Hospital- based treatment		
<input type="checkbox"/> Community- based treatment		
Will we draw blood from you?		
Will we ask you to collect your stool in a container we provide?		
Are you free to decide to quit the study anytime?		
Are you charged for participating in this study?		
Are you going to receive a compensation by taking part in this study?		
Do you know whom to call if in future you have questions or problems related to your participation?		

By signing this document you agree that:

1. _____ has explained what we are going to do, the risk, and the benefit of participating in this study.
2. You have understood the explanation given to you about your involvement and you have been given time to ask questions.
3. We (the study team) have checked that you understand this study by asking you questions about the study.

By signing this page, you confirm that you or your children whom you represent has agreed to participate in this study voluntarily.

APPENDIX 6A: INFORMED CONSENT FORM (V.3, 30 AUGUST 2016)

Participant's name: Consent date: <i>(For participant aged < 18 years old, please fill out the assent form next page)</i>	Signature/thumbprint
Explainer's name: Date:	Signature
Investigator's name: Date:	Signature
Witness' name: Date:	Signature

ASSENT FORM

, My name is _____ and I am the child of my parent whose name is: _____. I confirm that I am voluntarily willing to be in this study and that my parents/legal guardian agree that I can participate. I understand that I will be given medication, have my blood drawn and tested, and might have side effects that were explained to me by the study researchers. I also understand that I may decide to quit the study at any time.

Participant's name:	
Consent giver's name: Relation to participant: (Parent/ Legal guardian)	Signature/thumbprint

APPENDIX 6B: INFORMED RE-CONSENT FORM (V.1, 24 MAY 2017)

STUDY NAME: Community Based Safety and Efficacy Study of 2-drug versus 3-drug Therapy for Lymphatic Filariasis in Indonesia

PRINCIPLE INVESTIGATORS: Prof. Dr. Taniawati Supali

Approximately one year ago, you volunteered to be a part of a research study about lymphatic filariasis, which is caused by worms that live in your blood. You may also hear people calling this disease filaria or Kapola.

Researchers from Universitas Indonesia and Washington University in the United States talked to you about the study and when you agreed to be in the study they gave you the study medicine. The study team came back to see you to see if you had any side effects from the medicine and we told you that we would come back in one year to see how well the medicine killed the worms. **We are now visiting you to see if the worms are still inside your blood. Beside collecting your blood, we will also collect your poo to see if there is any worm in your gut, since the study medicine also have effect on gut worm.**

Today you are being asked to continue participating in the study to see how well the medicine killed the worms. If you agree, you will be tested for the worms with the test listed in the table below. If we find worms we will give you medicine to treat the worms.

Type of Test	What Will Happen
Filaria Test Strip, Brugia Rapid & Thick Blood Smear	We will ask for a small amount of blood from your finger. It will only take 2 to 5 minutes for us to collect this blood. The blood collection might cause some pain. Infection and bleeding may also occur, but this is VERY UNLIKELY to happen. If you have history of prolonged bleeding, please REPORT this to study team. We will test your blood to see if you have worms in your blood. This procedure will be done for COMMUNITY BASED STUDY participants, who were treated in the village in the previous study stage.
Filarial Test Strip, Brugia Rapid, and Venous Blood Draw	This procedure will be done for HOSPITAL BASED STUDY participants who were treated in the hospital in the previous study stage. We will draw blood from your vein in your arm. It will take about 5 to 10 minutes to collect this blood. This may cause pain. Infection, bruising and bleeding may occur, but this is VERY UNLIKELY. If you have history of prolonged bleeding, please REPORT this to study team. The amount of blood collected is approximately two tablespoons. We will test your blood to see if you have worms in your blood.
Stool Sample	We will ask for a small amount of your poo <i>or po'e</i> in a special container that we will give you. We will test your poo to see if you have worms in your gut.

You will not be charged to be in the study. You will not be given any gifts to be in the study. If you are injured or get sick because of this study we will pay for your care.

Your participation is voluntary. You will not be punished if you do not want to volunteer. Your worms can still be treated during the government's regular community treatment program. You may stop the study at any time and you do not have to give a reason. If you stop the study you will not be changed for any of the medicines you took.

APPENDIX 6B: INFORMED RE-CONSENT FORM (V.1, 24 MAY 2017)

We will keep your identity secret. Your name and information about you will be kept in a safe place and can only be seen by the study team. A code using only numbers will be used to identify your blood and stool samples. Your information will be kept secret even if you stop the study.

All blood and stool samples will be stored in Department of Parasitology Universitas Indonesia. Some samples may be sent to other laboratories to check that the tests for worms were done correctly. The blood and stool samples we collect from you will only be used in this study.

If you have questions about your participation in this study you may call dr. Michael Christian on 081237587120

By signing this page, you confirm that you and/or your children have voluntarily agreed to be in this study.

Participant's name: Consent date: <i>(For participant aged < 18 years old, please fill out the assent form)</i>	Signature/thumbprint
Explainer's name: Date:	Signature
Witness' name (if necessary): Date:	Signature

ASSENT FORM (To Be Signed For All Children Less Than Age 18 yo)

My name is _____

My parent's/legal guardian name is: _____

I agree that I am volunteering to be in this study and that my parents/legal guardian agree that I can participate. I understand that I will be given medication, have my blood drawn and tested, and might have side effects that were explained to me by the study researchers. I also understand that I may decide to quit the study at any time.

Participant's name:	
Consent giver's name: Relation to participant: (Parent/ Legal guardian)	Signature/thumbprint

APPENDIX 7: PROTOCOL FOR A TREATMENT ACCEPTABILITY STUDY FOLLOWING THE TRIPLE DRUG COMMUNITY SAFETY TRIALS

Version 29 June 2016

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APPENDIX 7: PROTOCOL FOR A TREATMENT ACCEPTABILITY STUDY FOLLOWING THE TRIPLE DRUG COMMUNITY SAFETY TRIALS

A. Summary

As part of the larger “Community Based Safety Study of 2-drug versus 3-drug Therapy for Lymphatic Filariasis” a study to assess treatment acceptability in the community is planned in each research site: Papua New Guinea, Indonesia, Haiti, Sri Lanka and India. The overall aim of this research is to understand the community’s acceptance of the 3-drug regimen as well as gain insight into the feasibility of administering this new therapy in the future. Part of the investigation will include assessing community member’s perception of the possible adverse events experienced as a result of the 3-drug therapy, and how that might affect future rounds of mass drug administration (MDA) at the community level. Community acceptance will be measured using a survey to community members receiving treatment during the trial. In addition, focus group discussions (FGD) will be carried out with community members and community health workers to further investigate acceptability of the new therapy. To complement the community survey and focus group discussions, a series of key informant interviews are proposed with community leaders and health personnel in the same communities to assess perceptions about the 3-drug *versus* the 2-drug regimen as well as gain insight into the feasibility of distributing the new regimen as well as perceptions about managing adverse events.

B. Rationale for the study

With the introduction of a new treatment regimen for the elimination of lymphatic filariasis (LF), understanding community perceptions about the treatment, its adverse events (AE) as well as its efficacy will be an important component of assessing the acceptability of the 3-drug therapy. In particular, perceptions about the severity of experienced or observed AE, the efficacy of the treatment in killing the worms and understanding the positive presence of AE will be important to investigate.

Research has demonstrated the important impact that AE can have on individuals’ acceptance of LF treatment using the 2-drug regimen [1, 2]. In some areas where MDA has been ongoing for many years, we might expect these AE to be objectively of minimal clinical significance, yet subjectively community members continue to report “fear of AE” as a deterrent to comply with MDA. In recent research in a low prevalence area in Indonesia, 33% of individuals interviewed reported experiencing some form of side effect or AE as a result of taking the LF treatment (A. Krentel personal experience). Thomsen et al (2016) reported a higher rate of AE in those who were administered the 3-drug regimen versus those who received the 2-drug therapy [3]. As the wider application of this new therapy is considered, it will be important to understand if the perception of these AE is different in between the two treatment arms.

Another important deterrent to compliance with MDA is a lack of understanding of the benefit of treatment [4, 5]. The 3-drug regimen has been shown to be highly effective in the reduction of microfilariae [3]; therefore communicating this message to participants will be of crucial importance. Measuring participants’ understanding of this message will be essential in determining their acceptance of AE associated with the treatment. In PNG and in neighboring

APPENDIX 7: PROTOCOL FOR A TREATMENT ACCEPTABILITY STUDY FOLLOWING THE TRIPLE DRUG COMMUNITY SAFETY TRIALS

Indonesia when communities understand the reasons AE occur, they welcome them as a sign that the drugs are working [6, 7]. Knowing if this message also works with the 3-drug therapy where more AE are expected to occur is important in the future promotion of this treatment.

For the purposes of this research, a mixed method approach is recommended, combining the use of a community survey, focus group discussions and in depth interviews with key informants. The community survey will allow a robust comparison of treatment acceptability between those receiving the 2-drug regimen and those receiving the 3-drug regimen. A composite score will measure acceptability, combining outcomes like the respondents' intention to take the treatment again and willingness to recommend it to other family members. Acceptability will be analyzed by the impact of some of the known factors that impact compliance: perception of AE, knowledge about AE, perceptions about the drug characteristics (safe, number of pills, taste), knowledge of vector, belief that the treatment is associated with health, and others. In order to assess the difference between the two treatment arms, the sampling frame for the community survey will take into account which regimen the individual received.

To complement the community surveys and provide further in depth analysis, focus group discussions (FGD) are planned with specific groups in the community, namely men, women, young people and community health workers. The FGDs will provide further insight and depth for some of the questions asked in the community survey. Specifically FGDs will investigate issues expected to relate to the 3-drug regimen: number of pills, perception of AE, how to ensure directly observed treatment and proposed messages to encourage compliance.

These results will be further substantiated by interviews with key community leaders, as well as community and professional health workers working in LF elimination at the village level. These interviews will provide an understanding of the macro level issues that key informants perceive as critical to consider with the use of the 3-drug therapy. With this, interview respondents will be asked what advantages and concerns they have with regards to the 3-drug regimen based on their participation in and understanding of the safety trial.

The outcome of this research will provide operational recommendations to accompany the safety study. These will inform additional acceptability research if the 3-drug regimen is adopted as global policy. An important outcome will be to determine if there are any real differences in community acceptance of the 3-drug regimen when compared to the standard treatment. If there are any differences, then further investigation may be recommended. In addition, the global programme will need to consider how to adjust the delivery protocols and recommended messages used by community drug distributors giving out the 3-drug regimen. The acceptability study will provide a preliminary understanding of these issues and will provide important insights into the use of this regimen on a wider scale.

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C. Study objectives

- 1) Measure the perception of AE reported by safety trial participants, comparing those in the 2-drug *versus* 3-drug arms
- 2) Assess the overall acceptability in the community of the 3-drug regimen, as compared to the 2-drug regimen
- 3) Assess the overall acceptability in the community of those individuals who are mf positive, as compared to those who are mf negative
- 4) Investigate the acceptability and feasibility of delivering the 3-drug regimen

D. Community survey

Community surveys are often called Knowledge, Attitudes and Practice (KAP) surveys because they use a cross sectional survey design to understand what community members *know* about disease, treatment and prevention; how they *perceive* factors related to the disease and finally what they *do* about it (e.g. take a drug, hang a bednet, use a condom). For the purposes of this survey, it is recommended to use a cross sectional survey design. However the terminology and format of the KAP may not be the most appropriate questionnaire design for the study proposed. Specific knowledge about LF disease is not a strong predictor for compliance in MDA for LF, with the exception of knowing that mosquitoes transmit LF [8, 9]. For the purposes of this research, focusing on knowledge of LF disease may not inform community acceptability of the 3-drug regimen as compared to the 2-drug regimen. Furthermore research has shown that there are important intrinsic reasons that affect people's decisions to take or not to take the LF treatment during MDA. Social norms of compliance, emotional cues, altruism and an individual's personal situation have all been shown to be associated with taking the LF drug [5, 10-12]. Understanding some of these intrinsic factors associated with taking the 3-drug regimen as opposed to the 2-drug regimen will be important in building a picture of community acceptability. As a result, although there may be similarities in some of the questions asked, it is recommended to call the community survey a "treatment acceptability survey" as opposed to a "KAP survey."

1. Timing

Coverage surveys are recommended to occur as soon as possible after MDA occurs in order to reduce recall bias in respondents [13]. In order to allow some space between the clinical assessment and monitoring of AE in the community trial as well as some time for the effects of ivermectin to become apparent, individuals approached for enrollment in the community survey will be approached at least two weeks after the completion of their drug administration and adverse events monitoring.

2. Questionnaire development

Questionnaire development is based on previous LF surveys carried out in Indonesia and in Papua New Guinea. In addition, known influences based on the most recent literature on compliance will be included in the acceptability survey, where appropriate. Validated questions from acceptability research as well as quality of life indicators for scabies will be included in the questionnaire.

APPENDIX 7: **PROTOCOL FOR A TREATMENT ACCEPTABILITY STUDY FOLLOWING THE TRIPLE DRUG COMMUNITY SAFETY TRIALS**

Questionnaires will be written in English and translated into the local language. In order to test the understandability of the questionnaire with the local population, the enumerators will give advice on the vocabulary used during the training and a small sample of individuals will be administered the questionnaire prior to survey implementation. At the end of this testing, these respondents will be asked to comment on the questions themselves, whether they were clear and the language was appropriate. Changes will be made if needed. The questionnaire will then be translated back into English.

3. Sampling frame

In estimating the sample size for the acceptability survey, one of the challenges we have is that we do not know the estimated acceptability rates in people who have received the 3-drug regimen. From recent research in Indonesia (A. Krentel, personal experience) in low (mf rate=1%) and high prevalence (mf=8%) areas, we know that acceptability with DEC+ALB, as measured in the intent to take the LF drugs again, was measured as 79% and 82% respectively.

Because we do not have a 3-drug acceptability rate, we cannot estimate the difference we might expect in between the regimen groups. As a result, this survey will create preliminary data, estimating the difference in acceptability rates between those individuals receiving the 2 and 3 drug regimens as well as the difference in rates between those with positive mf rates at the start of the safety trial and those who are mf negative. This survey will provide insight into possible trends in acceptability and will inform if further investigation is needed.

The range of mf prevalence is expected to be wide in between the study sites. As such, we will oversample those areas where it will be higher. The target samples for the acceptability survey are as follows:

- 400 individuals in Papua New Guinea
- 400 individuals in Indonesia
- 400 individuals in Haiti
- 400 individuals in Fiji

Within each country, equal numbers of subjects will be enrolled in the two drug and the three drug intervention arms. In PNG, we will oversample those villages where LF prevalence is expected to be higher. With a projected 50% infection rate, this is the only participating country that is expected to have an infection rate in excess of 10%. It is therefore the only country that will provide a universe of infected subjects that is sufficiently large to provide accurate measures of the acceptability of study medications in subjects who are infected. Specifically, if we add the 50 subjects who are expected to be infected in Indonesia, Haiti, and Fiji combined to the 200 anticipated infected subjects in PNG, we anticipate that this acceptability study will enroll 250 infected subjects, or 125 in each intervention arm. With a total of 125 infected subjects in each arm, a dichotomous measure (yes or no) of the acceptability of a particular drug combination will, with 95% certainty, differ by no more than 9% from the true acceptability rate.

APPENDIX 7: PROTOCOL FOR A TREATMENT ACCEPTABILITY STUDY FOLLOWING THE TRIPLE DRUG COMMUNITY SAFETY TRIALS

Because we expect the acceptability of a particular drug combination to be highly correlated within families, our protocol permits the enrollment of precisely one subject from each participating family. Eligible family members will have to be at least 14 years of age. As chronic manifestations of the disease begin to show at adolescence, so personal experience with LF may also begin at this age [14]. Both men and women will be included in the sample.

Enrollment procedures are as follows. Our goal will be to interview acceptability study participants beginning at least two weeks after the AE monitoring has been completed within a given village. The reason for waiting at least two weeks is that we want to minimize the likelihood that we will interview individuals who are still experiencing the symptoms of any adverse events that may have occurred in the parent study. If we were to conduct acceptability interviews while subjects were still experiencing adverse effect symptoms, the immediacy of those symptoms might bias subjects' perceptions of acceptability.

All families within a village that participated in the parent safety study will be eligible to participate in this acceptability study, with consent for such participation having been a part of the consent form of the parent study. Within each country, we will enter villages sequentially in the order that they were entered in the parent study. We will continue to interview subjects in a particular country until the target number within a given study arm has been reached. When the target number has been reached in one study arm, we will stop enrolling subjects in that arm and will continue enrolling in the other study arm until the target has been reached.

The family member to be interviewed for this study will be selected using the following procedures. A list of family members over the age of 14 who have been enrolled in the parent study will be compiled as soon as possible after the parent study has been concluded in a village. From this list, a random family member will be selected as the target participant in the acceptability study. When we approach a household, we will seek to interview the randomly selected family member. If that family member is not immediately available, we will discuss whether the logistics of conducting the interview with that family member at a different time are feasible. If we conclude that waiting for that alternative time is not reasonable or if the selected family member does not wish to participate, we will conduct the interview in whatever family member is available, independent of which individual has been randomly selected.

Enumerators will travel to the house to interview the identified individual. Data will be collected using the REDCap system.

4. Outcome of interest:

Acceptability of the 3-drug therapy will be measured in a composite score from the following questions¹:

- Intention to take LF drugs in the future measured on a 5-point scale ranging from "I will never take this drug again" to "I will definitely take this drug again." (Adapted from Liau and Zimet 2001)

¹ Scoring concept amended from Treatment Acceptability Research (see Carter SL (2007) "Review of Recent Treatment Acceptability Research" *Education and Training in Developmental Disabilities* 42(3): 301-316.

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- Willingness to encourage other family members to take the LF drug, if offered in the future measured as a 5-point scale ranging from “I will never encourage my family to take the LF drugs” to “I will definitely encourage my family to take the LF drugs.”
- Overall feeling about the LF elimination program as a 5-point scale ranging from “Very negative” to “Very positive”
- Perception of health since taking the LF drugs as a 5-point scale ranging from “Considerably worse” to “greatly improved”
- In addition to the scoring, each outcome can be converted to a binary variable for multivariate modeling.

4.

5. Inputs / Exposure variables:

- SES data
- Data from safety trial (clinical presence of AE, mf rate, household information)
- Treatment arm (2-drug versus 3-drug)
- Informed about the treatment before receiving the drug (e.g. did they receive any information)
- Belief in the efficacy of the treatment to eliminate / prevent LF (e.g. believe that the drugs work to prevent / treat LF)
- Belief in the efficacy of the treatment to treat scabies (e.g. believe that the drugs work to treat scabies)
- Belief in the efficacy of the treatment to treat other intestinal worms (e.g. believe that the drugs work to treat worms)
- Knowledge of the ‘positive’ component of AE (e.g. occur because the medicine is working)
- Perception of AE (e.g. none, mild, moderate, severe)
- Understanding that taking LF medicine is good for promoting health
- Knowledge that mosquitoes transmit LF
- Perception that the rest of the family/ household would take the LF drugs, if offered in the future (yes/no)
- Belief that the drug distributors are doing a good job (using a 10-point scale)
- Perceptions of the drugs (e.g. safe, neutral, dangerous)
- Components of the drugs (e.g. number, size, taste of pills)
- Emotions surrounding LF treatment (e.g. how does taking LF treatment make you feel?)

6. Analysis

For the data cleaning and data reduction, the following steps will be performed:

- Check response bias
- Clean the raw data set (range check, consistency checks)
- Transfer corrected data set to STATA statistical software (Stata Corporation, College Station, Texas).
- Group continuous variables into categorical variables, namely age. Recode certain variables where needed.

For the analysis, a descriptive analysis of the whole dataset will be prepared. The data from the community survey will be linked to the safety trial within the REDCap system.

Likert scales will be analyzed as both dichotomous and as continuous variables.

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For both of the predictors of acceptability (drug regimen and presence of mf) logistic regression models will be created. Presence of AE as measured in the clinical surveys will be considered in the analysis, as will subjective perceptions of AE.

E. Focus Group Discussion

H. Timing

The focus group discussions will take place at the same time as the community survey, in the same communities.

2. Sampling frame

For the focus group discussions, we will identify persons from specific groups of people: women of reproductive age, young people, men and community health workers. The rationale behind the selection of each of these groups is related to the prevailing evidence of their participation in MDA in the literature. Women of reproductive age often do not comply with treatment because they are either pregnant or breastfeeding, however they are often the gatekeepers for health in the household and ensure members of their household takes the treatment when offered. Men and young people have been known to be less compliant with MDA and so understanding their perceptions about the 3-drug regimen, MDA in general and soliciting their advice about how best to promote and reach their communities will be informative. Finally, as community health workers are usually the persons responsible for distributing the drug at the community level, understanding their perspectives on DOT, AE and messaging for the 3-drug regimen is important.

For the FGD, women, young men and men will be selected from the cohort of individuals receiving the 3-drug regimen.

3. Range of issues to explore include:

- How is LF elimination different / similar from the other health programs in their village?
- What are the health benefits from taking the treatment?
- What are the social benefits from taking the treatment?
- Do people like to take the pills in front of the distributor? Why or why not?
- How do you feel about the number of pills that you have to take?
- Why don't people want to take it?
- Did you have any side effects after you took the drugs (positive or negative)? How did you feel about them?
- What suggestions do you have to promote MDA to their community? Household?
- Are there any specific messages you would recommend to us?

4. Analysis

Recorded focus group discussions will be transcribed word for word in the local language. They will be translated into English. A second researcher with knowledge of English and the local

APPENDIX 7: PROTOCOL FOR A TREATMENT ACCEPTABILITY STUDY FOLLOWING THE TRIPLE DRUG COMMUNITY SAFETY TRIALS

language will check translation, sampling portions of each transcript and back translating them from English to the local language to check the reliability of the translation. The researchers will read through each transcript, recording emergent themes in an Excel matrix. NVivo will be used to assess trends and patterns in the interview transcripts.

F. In depth interviews with key informants

H. Timing

The key informant interviews will take place at the same time as the community survey, in the same communities.

2. Sampling frame

A purposive sampling frame will be used, with individuals identified based on their leadership and cultural position with the village as well as their involvement with LF elimination and with the community trial. With this in mind, a range of 8-10 individuals will be included in the sample. In order to understand the acceptability of administering the 3-drug regimen, individuals to be interviewed would need to be those persons who are either directly involved with LF activities in the village or who *would be* involved in MDA in the future. Suggestions include community and/or religious leaders, community health workers, teachers.

3. Range of issues to explore include:

- What are the advantages of the 3-drug therapy in MDA? Disadvantages?
- What opportunities do they see in the administration of the 3-drug therapy, versus the 2-drug therapy?
- What concerns or challenges do they see in the administration of the 3-drug therapy, versus the 2-drug therapy?
- How do they feel about the number of pills that the community is asked to take?
- How do they feel about the side effects people might have / have?
- What suggestions do they have to promote MDA in this village? This province? The country? What messages would they recommend using?
- Which groups of people do they think will be difficult to reach with future MDA? Why? Any advice to approach them?

4. Analysis

Recorded interviews will be transcribed word for word in the local language. They will be translated into English. A second researcher with knowledge of English and the local language will check translation, sampling portions of each transcript and back translating them from English to the local language to check the reliability of the translation. The researcher will read through each transcript, recording emergent themes in an Excel matrix. Nvivo will be used to assess trends and patterns in the interview transcripts.

G. Ethical Considerations

APPENDIX 7: **PROTOCOL FOR A TREATMENT ACCEPTABILITY STUDY FOLLOWING THE TRIPLE DRUG COMMUNITY SAFETY TRIALS**

H. Community survey

Ethical approval will be obtained from the local national research institution in each country as well as Washington University in St. Louis, Case Western University and Bruyère Research Institute.

Prior to giving consent to participate, the enumerator will read out the information sheet in the local language containing the aim of the survey, the length of time it is expected to take (15 minutes) as well as the protection of confidentiality for each respondent. Following this, each respondent will be asked to sign the informed consent form and where respondents are illiterate, a mark can be made. The enumerator will indicate that informed consent has been given. Age of eligible respondents is 14 years of age and older. For those aged 14 – 18 years, parental consent will be sought and provided on the informed consent form before the interview can begin. All forms will remain with the research team and will not contain any personal information other than the individual's signature.

At the end of the interview, each respondent will be given an information sheet with the principal investigator's contact details, should there be any questions. With this sheet, the respondent will also receive a brief information sheet on lymphatic filariasis, the mass drug administration and who is eligible for treatment.

The data will be stored on Washington University servers during the duration of the study. After the study ends, electronic copies of the de-identified datasets will be kept by the PI indefinitely.

2. Focus Group discussions

Ethical approval will be obtained from the local national research institution in each country as well as Washington University in St. Louis, Case Western University and Bruyère Research Institute.

The interviewer will read the informed consent form to each person participating in the focus group discussion. The respondents will be asked to each sign an informed consent form for their participation. All interviews will be recorded with the permission of the respondent. Where permission is not granted, the interviewer will ask to take notes throughout the interview.

Any identifying information (name, address) will not be recorded. Individuals will not be identified in the transcripts or in the recordings and their anonymity will be maintained in all reporting and in the manuscripts. Transcripts of the interviews will remain with the research team.

The data will be stored with the PI, under password protection. After the study ends, electronic copies of the de-identified datasets will be kept by the PI indefinitely.

3. In depth interviews with key informants

APPENDIX 7: PROTOCOL FOR A TREATMENT ACCEPTABILITY STUDY FOLLOWING THE TRIPLE DRUG COMMUNITY SAFETY TRIALS

Ethical approval will be obtained from the local national research institution in each country as well as Washington University in St. Louis, Case Western University and Bruyère Research Institute.

The interviewer will read the informed consent form to each person participating in the interview. The respondents will be asked to sign an informed consent form for their participation. All interviews will be recorded with the permission of the respondent. Where permission is not granted, the interviewer will ask to take notes throughout the interview.

Any identifying information (name, address) will not be recorded and the identity of the respondent will be kept confidential in reporting. Transcripts of the interviews will remain with the research team. The data will be stored with the PI under password protection. After the study ends, electronic copies of the de-identified datasets will be kept by the PI indefinitely.

APPENDIX 7: PROTOCOL FOR A TREATMENT ACCEPTABILITY STUDY FOLLOWING THE TRIPLE DRUG COMMUNITY SAFETY TRIALS

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APPENDIX 7: PROTOCOL FOR A TREATMENT ACCEPTABILITY STUDY FOLLOWING THE TRIPLE DRUG COMMUNITY SAFETY TRIALS

Information sheet and informed consent for community survey

As part of the “Community Based Safety Study of 2-drug versus 3-drug Therapy for Lymphatic Filariasis” that just happened in your area last month, we are asking some people who participated in that study to take part in a short survey so that we can understand more about lymphatic filariasis [or local name], the drugs used in the safety trial and health in general. Your name was selected randomly from the list of people who participated in that safety trial.

It is important that you understand why we are doing this survey, so please read this information sheet carefully. If you have any more questions, ask the interviewer and they will try to answer them for you.

We are interested in the experiences people had participating in the safety trial and what they understand about lymphatic filariasis [or local name]. We would like to talk to about 400 people in this area so that we can understand better how people felt about taking the LF drugs. Your participation is entirely voluntary and you are under no obligation to participate. Whether or not you choose to participate, your status and access to health care will not be affected in any way.

If you do choose to help with this study, we will only need about 15 minutes of your time to ask you some questions. At any time during this discussion, you are free to stop and withdraw from the study. You do not have to give the interviewer a reason.

The information that you provide during our discussion will be completely confidential. We will record your answers on a tablet. All digital files will remain with the main investigator and will be password protected.

I have read the information sheet provided or it has been read to me concerning this study and I understand what will be required of me if I participate in this study, which will be a verbal interview and discussion.

My questions regarding this study have been answered by: _____.

I understand that at any time I may withdraw from this study without giving a reason and without having any effect on my access to health care.

I agree to take part in this study.

Signature of the respondent: _____

Signature of a witness: _____

Signature of the enumerator to indicate that the informed consent has been read and the information sheet given to the respondent: _____

APPENDIX 7: PROTOCOL FOR A TREATMENT ACCEPTABILITY STUDY FOLLOWING THE TRIPLE DRUG COMMUNITY SAFETY TRIALS

Information sheet and informed consent for in depth interviews with key informant

As part of the “Community Based Safety Study of 2-drug versus 3-drug Therapy for Lymphatic Filariasis” that just happened in your area last month, we are asking some people who participated in that study to take part in a verbal discussion so that we can understand more about lymphatic filariasis [or local name], the drugs used in the safety trial and health in general. It is important that you understand why we are doing this survey, so please read this information sheet carefully. If you have any more questions, ask the interviewer and they will try to answer them for you.

We are interested in the experiences people had participating in the safety trial and what they understand about lymphatic filariasis [or local name]. We would like to talk to about 8 people in this area so that we can understand better how people felt about taking the LF drugs. Your participation is entirely voluntary and you are under no obligation to participate. Whether or not you choose to participate, your status and access to health care will not be affected in any way.

If you do choose to help with this study, we will only need about one hour of your time to ask you some questions and to discuss informally. At any time during this discussion, you are free to stop and withdraw from the study. You do not have to give the interviewer a reason.

The information that you provide during our discussion will be completely confidential and we will not even write down your name or address. We will take some written notes during our discussion and if you agree, we may also record the interview using a digital recorder so that it will be easier to remember what we discussed. All digital files will remain with the main investigator and your name and address will not be recorded. We will write down the conversation and store it safely, with a password. Other researchers may ask to look at our discussion together, and we may share it with them, provided that they respect the same rules of confidentiality.

I have read the information sheet provided or it has been read to me concerning this study and I understand what will be required of me if I participate in this study, which will be a verbal interview and discussion.

My questions regarding this study have been answered by: _____.

I understand that at any time I may withdraw from this study without giving a reason and without having any effect on my access to health care.

I agree to take part in this study.

Signature of the respondent: _____

Signature of a witness: _____

Signature of the enumerator to indicate that the informed consent has been read and the information sheet given to the respondent: _____

Information sheet and informed consent for focus group discussion participants

APPENDIX 7: PROTOCOL FOR A TREATMENT ACCEPTABILITY STUDY FOLLOWING THE TRIPLE DRUG COMMUNITY SAFETY TRIALS

As part of the “Community Based Safety Study of 2-drug versus 3-drug Therapy for Lymphatic Filariasis” that just happened in your area last month, we are asking some people who participated in that study to take part in a focus group discussion so that we can understand more about lymphatic filariasis [or local name], the drugs used in the safety trial and health in general. It is important that you understand why we are doing this survey, so please read this information sheet carefully. If you have any more questions, ask the interviewer and they will try to answer them for you.

We are interested in the experiences people had participating in the safety trial and what they understand about lymphatic filariasis [or local name]. We would like to talk to about 4 groups of people in this area so that we can understand better how people felt about taking the LF drugs. Your participation is entirely voluntary and you are under no obligation to participate. Whether or not you choose to participate, your status and access to health care will not be affected in any way.

If you do choose to help with this study, we will only need about one hour of your time to ask you some questions and to discuss informally. At any time during this discussion, you are free to stop and withdraw from the study. You do not have to give the interviewer a reason.

The information that you provide during our discussion will be completely confidential and we will not even write down your name or address. We will take some written notes during our discussion and if you agree, we may also record the interview using a digital recorder so that it will be easier to remember what we discussed. All digital files will remain with the main investigator and your name and address will not be recorded. We will write down the conversation and store it safely, with a password. Other researchers may ask to look at our discussion together, and we may share it with them, provided that they respect the same rules of confidentiality.

I have read the information sheet provided or it has been read to me concerning this study and I understand what will be required of me if I participate in this study, which will be a verbal interview and group discussion.

My questions regarding this study have been answered by: _____.

I understand that at any time I may withdraw from this study without giving a reason and without having any effect on my access to health care.

I agree to take part in this study.

Signature of the respondent: _____

Signature of a witness: _____

Signature of the enumerator to indicate that the informed consent has been read and the information sheet given to the respondent: _____

APPENDIX 9: TOPIC GUIDE – FOCUS GROUP DISCUSSION ON THE ACCEPTABILITY OF IDA [EXAMPLE]

MAIN RESEARCH QUESTION: UNDERSTANDING THE FEASIBILITY OF ADMINISTERING IDA: WHAT ARE THE FACTORS AND CONSIDERATIONS FOR THE INTRODUCTION OF TRIPLE DRUG THERAPY FOR LF ELIMINATION INTO THIS COMMUNITY?

RATIONALE

REFER TO THE INFORMATION SHEET

CONFIDENTIALITY

REFER TO THE INFORMED CONSENT SHEET

WARM-UP QUESTIONS

AS YOU'VE READ THE INFORMATION SHEET, YOU WILL REMEMBER THAT WE ARE HERE TO COLLECT SOME INFORMATION THAT WILL HELP THE GOVERNMENT TO MAKE YOUR HEALTH AND THE HEALTH OF PEOPLE IN YOUR VILLAGE BETTER. SO MAYBE YOU COULD TELL ME A LITTLE BIT ABOUT THE HEALTH OF PEOPLE IN YOUR VILLAGE...

(IF NO RESPONSE... THEN PROMPT WITH: ARE THERE MANY SICK PEOPLE IN YOUR VILLAGE? WHAT DO PEOPLE GET SICK FROM IN YOUR VILLAGE?)

LEAD IN TO DISCUSSION

AS I MENTIONED IN THE BEGINNING OF THE INTERVIEW, WE ARE INTERESTED IN THE DISEASE FILARIA AND ITS TREATMENT. IS THAT SOMETHING THAT YOU'VE TAKEN MEDICINE FOR? AND WHAT DID YOU TAKE?

(INTERVIEWER: OH, THAT'S INTERESTING... MAYBE WE CAN TALK ABOUT THAT A BIT MORE LATER...)

KNOWLEDGE ABOUT LF

ASK THEM TO TELL YOU WHAT THEY KNOW ABOUT THE DISEASE LF:

DEPENDING ON THE IDENTITY OF THE RESPONDENT (MEDICAL V NON-MEDICAL) PROMPT WITH THE FOLLOWING:

- LOCAL NAMES
- HOW DO YOU GET IT?
 - o PROMPT: WOULD YOU LIKE TO DRAW HERE FOR ME HOW THE DISEASE ENTERS THE BODY?
- TELL ME WHAT HAPPENS TO YOU WHEN YOU GET IT.
- WHERE DID YOU HEAR ABOUT FILARIA?
- WHO DO YOU THINK GETS IT MOST? (PROMPT: MEN? WOMEN? CHILDREN?)
- DO YOU KNOW ANYONE WHO HAS FILARIA? CAN YOU TELL ME ABOUT THEM?

APPENDIX 9: TOPIC GUIDE – FOCUS GROUP DISCUSSION ON THE ACCEPTABILITY OF IDA [EXAMPLE]

PAST PARTICIPATION IN MDA ACTIVITIES

RESPONDENTS' COMMENTS ABOUT PAST PARTICIPATION WITH MDA

YOU'VE ALREADY TOLD ME ABOUT YOUR EXPERIENCE WITH THE DRUGS FOR FILARIA.

[FOR FGD WITH CDDs] COULD YOU TELL ME ABOUT YOUR ROLE IN THE DISTRIBUTION FOR LF DRUGS IN YOUR AREA?

IF NECESSARY PROMPT THE STORY WITH:

- *ANY PART YOU PLAYED IN THE PROMOTION AND/OR DISTRIBUTION OF THE DRUGS*
- *HOW DID YOU TELL PEOPLE ABOUT THE TREATMENT DAY?*
- *WHAT WAS THE ROLE OF COMMUNITY LEADERS: VILLAGE LEADER, SCHOOL TEACHERS, CHURCH OR MOSQUE LEADERS, NEIGHBOURS, HEALTH STAFF*

CAN WE TALK ABOUT THE PEOPLE AROUND YOU AND HOW THEY FELT ABOUT THE TREATMENT?

IF NECESSARY PROMPT WITH:

- *FAMILY/HOUSEHOLD: ANY DISCUSSION? FEELINGS OR VIEWS ABOUT THE TREATMENT? DID THEY TAKE IT?*
- *NEIGHBOURS? FEELINGS OR VIEWS ABOUT THE TREATMENT? DID THE NEIGHBOURS TAKE IT?*
- *OTHER PARTS OF THE VILLAGE? DID THEY TAKE IT?*
- *ANYONE WHO DIDN'T TAKE IT? WHAT HAPPENED TO THEM?*
- *HOW DID YOU KNOW WHO TOOK IT AND WHO DIDN'T?*

LET'S TALK A LITTLE MORE ABOUT THE PEOPLE WHO DIDN'T TAKE THE LF PILLS IN THE PAST. WHAT CAN YOU TELL ME ABOUT THEM?

IF NECESSARY PROMPT WITH:

- *WHY DO YOU THINK THEY DIDN'T TAKE THE LF PILLS?*
- *WHAT SUGGESTIONS DO YOU HAVE TO BETTER REACH THIS GROUP OF PEOPLE?*

I'D LIKE US TO TALK A BIT MORE ABOUT THE GOOD AND BAD PARTS ABOUT TAKING THE LF PILLS?

IF NECESSARY PROMPT WITH:

- *WHO DO YOU THINK GAINS THE MOST FROM TAKING FILARIA TREATMENT?*
- *WHO DO YOU THINK IS HURT BY THE TREATMENT / WHO LOSES MOST?*

APPENDIX 9: TOPIC GUIDE – FOCUS GROUP DISCUSSION ON THE ACCEPTABILITY OF IDA [EXAMPLE]

LET’S THINK ABOUT THE GOOD THINGS FIRST, AND FOR YOU,

IF NECESSARY PROMPT WITH:

- WHAT DO YOU THINK IS GOOD ABOUT THE TREATMENT?
- HOW DID IT HELP YOU?
- WHAT DID YOU GAIN FROM TAKING THE TREATMENT?

STILL THINKING ABOUT THE GOOD THINGS, BUT NOW FOR OTHERS,

IF NECESSARY PROMPT WITH:

- WHAT IS GOOD ABOUT THE TREATMENT FOR OTHERS?

LET’S DO THE SAME FOR THE BAD THINGS, STARTING WITH YOU,

IF NECESSARY PROMPT WITH:

- WHAT DO YOU THINK IS BAD ABOUT THE TREATMENT?
- HOW DID IT HURT YOU?

AND THEN FOR OTHERS?

IF NECESSARY PROMPT WITH:

- DO YOU KNOW ANYONE WHO SUFFERED IN SOME WAY AFTER TAKING THE TREATMENT?
- HOW DID IT HURT THEM?

IN ORDER TO MAKE SURE THAT PEOPLE ACTUALLY TAKE THE PILLS THAT ARE GIVEN TO THEM, IT IS RECOMMENDED THAT COMMUNITY MEMBERS TAKE THE PILLS IN FRONT OF THE DISTRIBUTOR. I’D LIKE TO TALK A BIT MORE ABOUT THAT.

- CAN YOU TELL ME HOW THIS HAPPENED IN YOUR COMMUNITY?
- HOW DO YOU THINK PEOPLE FEEL ABOUT TAKING PILLS IN FRONT OF THE DISTRIBUTOR?
- WHAT RECOMMENDATIONS DO YOU HAVE TO IMPROVE THE FREQUENCY OF PEOPLE TAKING PILLS IN FRONT OF THE DISTRIBUTOR?

HOW DO YOU THINK THE DISTRIBUTION OF LF PILLS DIFFERS FROM OTHER HEALTH ACTIVITIES IN YOUR COMMUNITY?

[RECENT SAFETY TRIAL FOR IDA](#)

APPENDIX 9: TOPIC GUIDE – FOCUS GROUP DISCUSSION ON THE ACCEPTABILITY OF IDA [EXAMPLE]

AS YOU KNOW, THERE WAS A SAFETY TRIAL IN YOUR COMMUNITY RECENTLY TO ASSESS THE SAFETY OF A NEW DRUG COMBINATION FOR LF TREATMENT THAT HAS BEEN SHOWN TO BE VERY GOOD AT KILLING THE LF WORMS. NOW, I WOULD LIKE TO TALK ABOUT THAT RECENT LF DRUG DISTRIBUTION A BIT MORE AND THE FUTURE PROSPECTS OF DELIVERING THE THREE DRUGS IN YOUR COMMUNITY.

CAN YOU TELL ME ABOUT THE SPECIAL LF DRUG DISTRIBUTION THAT TOOK PLACE RECENTLY?

IF NECESSARY PROMPT WITH:

- HOW WAS IT DIFFERENT FROM PAST MDA ACTIVITIES?
- WHAT WERE PEOPLE TALKING ABOUT IN THE COMMUNITY WHEN THE SAFETY TRIAL TOOK PLACE?

LET’S TALK ABOUT THE PILLS THEMSELVES A BIT. ADULTS IN YOUR COMMUNITY RECEIVED # [FILL IN FOR THE SPECIFIC COUNTRY] OF PILLS. CAN YOU TELL ME ABOUT THAT?

IF NECESSARY PROMPT WITH:

- WHAT MESSAGES OR INFORMATION DID YOU TELL PEOPLE ABOUT TAKING THE PILLS?
- HOW DID PEOPLE FEEL ABOUT TAKING # OF PILLS?
- CAN YOU GIVE US ANY ADVICE ABOUT WHAT MESSAGES OR INFORMATION WE COULD USE IN THE FUTURE TO ENCOURAGE PEOPLE IN YOUR COMMUNITY TO TAKE ALL OF THESE PILLS?

SOMETIMES PEOPLE HAVE SIDE EFFECTS AFTER THEY TAKE THE LF PILLS. I’D LIKE TO ASK YOU ABOUT ANY SIDE EFFECTS THAT OCCURRED HERE AFTER THE SPECIAL LF DISTRIBUTION.

IF NECESSARY PROMPT WITH:

- TELL ME ABOUT THE SIDE EFFECTS THAT YOU WITNESSED OR HEARD ABOUT IN YOUR COMMUNITY
- TELL ME ABOUT THE REACTION IN THE COMMUNITY TO THESE SIDE EFFECTS
- WERE THERE ANY MORE SIDE EFFECTS THAN IN PREVIOUS YEARS?
- WHAT ADVICE DO YOU HAVE FOR THE PROGRAMME TO ENSURE PEOPLE UNDERSTAND WHY THESE SIDE EFFECTS OCCUR?
- WHAT ADVICE DO YOU HAVE FOR THE PROGRAMME TO ENSURE PEOPLE FEEL REASSURED IF THERE ARE ANY SIDE EFFECTS?

SOME OF THE SIDE EFFECTS FROM THE LF PILLS CAN BE ALSO CONSIDERED AS ‘GOOD’. PLEASE TELL ME ABOUT ANY ‘GOOD’ SIDE EFFECTS THAT OCCURRED IN YOUR COMMUNITY?

IF NECESSARY PROMPT WITH:

- WHAT ADVICE DO YOU HAVE FOR THE PROGRAMME TO PROMOTE THESE ‘GOOD’ SIDE EFFECTS IN YOUR COMMUNITY?

APPENDIX 9: TOPIC GUIDE – FOCUS GROUP DISCUSSION ON THE ACCEPTABILITY OF IDA [EXAMPLE]

WHAT SUGGESTIONS DO YOU HAVE FOR THE MESSAGES WE MIGHT USE TO PROMOTE THE 3-DRUGS IN THE COMMUNITY IN THE FUTURE?

IF NECESSARY PROMPT WITH:

- WHAT WOULD MOTIVATE / ENCOURAGE PEOPLE TO SWALLOW THE PILLS?
- WHO SHOULD DELIVER THOSE MESSAGES?
- IN YOUR OPINION, DO WE NEED TO MAKE A NEW MESSAGE?

[FOR FGD WITH CDDs] IF THE NEW TREATMENT WERE INTRODUCED HERE, WHAT WOULD YOU NEED TO HELP YOU TO DISTRIBUTE IT?

IF NECESSARY PROMPT WITH:

- *SPECIFIC TOOLS (MATERIALS)?*
- *TRAINING?*
- *CAN YOU TELL ME ABOUT ANY SPECIFIC CHALLENGES THAT WE NEED TO CONSIDER?*
- *WHAT OPPORTUNITIES DOES THE 3-DRUG COMBINATION OFFER THE COMMUNITY?*

PLEASE PROBE CONTINUALLY THROUGHOUT WITH THINGS LIKE:

- WHY DID YOU SAY THAT?
- WHAT DO YOU MEAN BY THAT?
- COULD YOU TELL ME A BIT MORE?
- CAN YOU SAY WHAT YOU MEAN BY THAT?
- SO THEN WHAT HAPPENED?
- OH, THAT MAKES SENSE...
- THAT'S INTERESTING...

THANK YOU FOR YOUR TIME!

MAKE SURE THEY KNOW WHERE TO GET FURTHER INFORMATION.

APPENDIX 10: TOPIC GUIDE – IN DEPTH INTERVIEWS WITH KEY INFORMANTS FOR ACCEPTABILITY OF IDA [EXAMPLE]

MAIN RESEARCH QUESTION: UNDERSTANDING THE FEASIBILITY OF ADMINISTERING IDA: WHAT ARE THE FACTORS AND CONSIDERATIONS FOR THE INTRODUCTION OF TRIPLE DRUG THERAPY FOR LF ELIMINATION INTO THIS COMMUNITY?

RATIONALE

REFER TO THE INFORMATION SHEET

CONFIDENTIALITY

REFER TO THE INFORMED CONSENT SHEET

WARM-UP QUESTIONS

AS YOU'VE READ THE INFORMATION SHEET, YOU WILL REMEMBER THAT WE ARE HERE TO COLLECT SOME INFORMATION THAT WILL HELP THE GOVERNMENT TO MAKE YOUR HEALTH AND THE HEALTH OF PEOPLE IN YOUR VILLAGE BETTER. SO MAYBE YOU COULD TELL ME A LITTLE BIT ABOUT THE HEALTH OF PEOPLE IN YOUR VILLAGE...

(IF NO RESPONSE... THEN PROMPT WITH: ARE THERE MANY SICK PEOPLE IN YOUR VILLAGE? WHAT DO PEOPLE GET SICK FROM IN YOUR VILLAGE?)

LEAD IN TO INTERVIEW

AS I MENTIONED IN THE BEGINNING OF THE INTERVIEW, WE ARE INTERESTED IN THE DISEASE FILARIA AND ITS TREATMENT. IS THAT SOMETHING THAT YOU'VE TAKEN MEDICINE FOR? AND WHAT DID YOU TAKE?

(INTERVIEWER: OH, THAT'S INTERESTING... MAYBE WE CAN TALK ABOUT THAT A BIT MORE LATER...)

KNOWLEDGE ABOUT LF

ASK THEM TO TELL YOU WHAT THEY KNOW ABOUT THE DISEASE LF:

DEPENDING ON THE IDENTITY OF THE RESPONDENT (MEDICAL V NON-MEDICAL) PROMPT WITH THE FOLLOWING:

- LOCAL NAMES
- HOW DO YOU GET IT?
 - o PROMPT: WOULD YOU LIKE TO DRAW HERE FOR ME HOW THE DISEASE ENTERS THE BODY?
- TELL ME WHAT HAPPENS TO YOU WHEN YOU GET IT.
- WHERE DID YOU HEAR ABOUT FILARIA?
- WHO DO YOU THINK GETS IT MOST? (PROMPT: MEN? WOMEN? CHILDREN?)
- DO YOU KNOW ANYONE WHO HAS FILARIA? CAN YOU TELL ME ABOUT THEM?

APPENDIX 10: TOPIC GUIDE – IN DEPTH INTERVIEWS WITH KEY INFORMANTS FOR ACCEPTABILITY OF IDA [EXAMPLE]

PAST PARTICIPATION IN MDA ACTIVITIES

RESPONDENTS' COMMENTS ABOUT PAST PARTICIPATION WITH MDA

YOU'VE ALREADY TOLD ME ABOUT YOUR EXPERIENCE WITH THE DRUGS FOR FILARIA. COULD YOU TELL ME ABOUT YOUR ROLE IN THE DISTRIBUTION FOR LF DRUGS IN YOUR AREA?

IF NECESSARY PROMPT THE STORY WITH:

- ANY PART YOU PLAYED IN THE PROMOTION AND/OR DISTRIBUTION OF THE DRUGS
- HOW DID YOU TELL PEOPLE ABOUT THE TREATMENT DAY?
- WHAT WAS THE ROLE OF OTHER LEADERS: VILLAGE LEADER, SCHOOL TEACHERS, CHURCH OR MOSQUE LEADERS, NEIGHBOURS, HEALTH STAFF

CAN WE TALK ABOUT THE PEOPLE AROUND YOU AND HOW THEY FELT ABOUT THE TREATMENT?

IF NECESSARY PROMPT WITH:

- FAMILY/HOUSEHOLD: ANY DISCUSSION? FEELINGS OR VIEWS ABOUT THE TREATMENT? DID THEY TAKE IT?
- NEIGHBOURS? FEELINGS OR VIEWS ABOUT THE TREATMENT? DID THE NEIGHBOURS TAKE IT?
- OTHER PARTS OF THE VILLAGE? DID THEY TAKE IT?
- ANYONE WHO DIDN'T TAKE IT? WHAT HAPPENED TO THEM?
- HOW DID RESPONDENT KNOW WHO TOOK IT AND WHO DIDN'T?

I'D LIKE US TO TALK A BIT MORE ABOUT THE GOOD AND BAD PARTS ABOUT TAKING THE LF PILLS?

IF NECESSARY PROMPT WITH:

- WHO DO YOU THINK GAINS THE MOST FROM TAKING FILARIA TREATMENT?
- WHO DO YOU THINK IS HURT BY THE TREATMENT / WHO LOSES MOST?

LET'S THINK ABOUT THE GOOD THINGS FIRST, AND FOR YOU,

IF NECESSARY PROMPT WITH:

- WHAT DO YOU THINK IS GOOD ABOUT THE TREATMENT?
- HOW DID IT HELP YOU?
- WHAT DID YOU GAIN FROM TAKING THE TREATMENT?

STILL THINKING ABOUT THE GOOD THINGS, BUT NOW FOR OTHERS,

APPENDIX 10: TOPIC GUIDE – IN DEPTH INTERVIEWS WITH KEY INFORMANTS FOR ACCEPTABILITY OF IDA [EXAMPLE]

IF NECESSARY PROMPT WITH:

- WHAT IS GOOD ABOUT THE TREATMENT FOR OTHERS?

LET’S DO THE SAME FOR THE BAD THINGS, STARTING WITH YOU,

IF NECESSARY PROMPT WITH:

- WHAT DO YOU THINK IS BAD ABOUT THE TREATMENT?
- HOW DID IT HURT YOU?

AND THEN FOR OTHERS?

IF NECESSARY PROMPT WITH:

- DO YOU KNOW ANYONE WHO SUFFERED IN SOME WAY AFTER TAKING THE TREATMENT?
- HOW DID IT HURT THEM?

IN ORDER TO MAKE SURE THAT PEOPLE ACTUALLY TAKE THE PILLS THAT ARE GIVEN TO THEM, IT IS RECOMMENDED THAT COMMUNITY MEMBERS TAKE THE PILLS IN FRONT OF THE DISTRIBUTOR. I’D LIKE TO TALK A BIT MORE ABOUT THAT.

- CAN YOU TELL ME HOW THIS HAPPENED IN YOUR COMMUNITY?
- HOW DO YOU THINK PEOPLE FEEL ABOUT TAKING PILLS IN FRONT OF THE DISTRIBUTOR?
- WHAT RECOMMENDATIONS DO YOU HAVE TO IMPROVE THE FREQUENCY OF PEOPLE TAKING PILLS IN FRONT OF THE DISTRIBUTOR?

HOW DO YOU THINK THE DISTRIBUTION OF LF PILLS DIFFERS FROM OTHER HEALTH ACTIVITIES IN YOUR COMMUNITY?

RECENT SAFETY TRIAL FOR IDA

AS YOU KNOW, THERE WAS A SAFETY TRIAL IN YOUR COMMUNITY RECENTLY TO ASSESS THE SAFETY OF A NEW DRUG COMBINATION FOR LF TREATMENT THAT HAS BEEN SHOWN TO BE VERY EFFECTIVE AT KILLING THE LF WORMS. NOW, I WOULD LIKE TO TALK ABOUT THAT RECENT LF DRUG DISTRIBUTION A BIT MORE AND THE FUTURE PROSPECTS OF DELIVERING THE THREE DRUGS IN YOUR COMMUNITY.

CAN YOU TELL ME ABOUT THE SPECIAL LF DRUG DISTRIBUTION THAT TOOK PLACE RECENTLY?

IF NECESSARY PROMPT WITH:

- HOW WAS IT DIFFERENT FROM PAST MDA ACTIVITIES?
- WHAT WERE PEOPLE TALKING ABOUT IN THE COMMUNITY WHEN THE SAFETY TRIAL TOOK PLACE?

APPENDIX 10: TOPIC GUIDE – IN DEPTH INTERVIEWS WITH KEY INFORMANTS FOR ACCEPTABILITY OF IDA [EXAMPLE]

LET’S TALK ABOUT THE PILLS THEMSELVES A BIT. ADULTS IN YOUR COMMUNITY RECEIVED # [FILL IN FOR THE SPECIFIC COUNTRY] OF PILLS. CAN YOU TELL ME ABOUT THAT?

IF NECESSARY PROMPT WITH:

- WHAT MESSAGES OR INFORMATION DID YOU TELL PEOPLE ABOUT TAKING THE PILLS?
- HOW DID PEOPLE FEEL ABOUT TAKING # OF PILLS?
- CAN YOU GIVE US ANY ADVICE ABOUT WHAT MESSAGES OR INFORMATION WE COULD USE IN THE FUTURE TO ENCOURAGE PEOPLE IN YOUR COMMUNITY TO TAKE ALL OF THESE PILLS?

SOMETIMES PEOPLE HAVE SIDE EFFECTS AFTER THEY TAKE THE LF PILLS. I’D LIKE TO ASK YOU ABOUT ANY SIDE EFFECTS THAT OCCURRED HERE AFTER THE SPECIAL LF DISTRIBUTION.

IF NECESSARY PROMPT WITH:

- TELL ME ABOUT THE SIDE EFFECTS THAT YOU WITNESSED OR HEARD ABOUT IN YOUR COMMUNITY
- TELL ME ABOUT THE REACTION IN THE COMMUNITY TO THESE SIDE EFFECTS
- WERE THERE ANY MORE SIDE EFFECTS THAN IN PREVIOUS YEARS?
- WHAT ADVICE DO YOU HAVE FOR THE PROGRAMME TO ENSURE PEOPLE UNDERSTAND WHY THESE SIDE EFFECTS OCCUR?
- WHAT ADVICE DO YOU HAVE FOR THE PROGRAMME TO ENSURE PEOPLE FEEL REASSURED IF THERE ARE ANY SIDE EFFECTS?

SOME OF THE SIDE EFFECTS FROM THE LF PILLS CAN BE ALSO CONSIDERED AS ‘GOOD’. PLEASE TELL ME ABOUT ANY ‘GOOD’ SIDE EFFECTS THAT OCCURRED IN YOUR COMMUNITY?

IF NECESSARY PROMPT WITH:

- WHAT ADVICE DO YOU HAVE FOR THE PROGRAMME TO PROMOTE THESE ‘GOOD’ SIDE EFFECTS IN YOUR COMMUNITY?

WHAT SUGGESTIONS DO YOU HAVE FOR THE MESSAGES WE MIGHT USE TO PROMOTE THE 3-DRUGS IN THE COMMUNITY IN THE FUTURE?

IF NECESSARY PROMPT WITH:

- WHAT WOULD MOTIVATE / ENCOURAGE PEOPLE TO SWALLOW THE PILLS?
- WHO SHOULD DELIVER THOSE MESSAGES?
- IN YOUR OPINION, DO WE NEED TO MAKE A NEW MESSAGE?
- HOW SHOULD THIS NEW TREATMENT BE PROMOTED TO THE DISTRIBUTORS? THE LOCAL LEADERS?

RESPONDENT ORDERS STATEMENTS:

APPENDIX 10: TOPIC GUIDE – IN DEPTH INTERVIEWS WITH KEY INFORMANTS FOR ACCEPTABILITY OF IDA [EXAMPLE]

IN THIS LAST PART OF THE INTERVIEW, WE WILL BE LOOKING AT 5 STATEMENTS. LET'S READ THEM TOGETHER.

1. TAKE THE PILLS SO YOU WON'T GET FILARIA.
2. TAKE THE PILLS SO YOUR CHILDREN WON'T GET FILARIA.
3. TAKE THE PILLS SO OUR COMMUNITY WILL NOT GET FILARIA.
4. TAKE THE PILLS SO THE [DISTRICT / DEPARTMENT NAME] DOESN'T GET FILARIA.
5. TAKE THE PILLS SO [COUNTRY NAME] DOESN'T GET FILARIA.

CAN YOU PUT THEM IN ORDER OF IMPORTANCE? WHY DID YOU ARRANGE THEM THIS WAY?

PLEASE PROBE CONTINUALLY THROUGHOUT WITH THINGS LIKE:

- WHY DID YOU SAY THAT?
- WHAT DO YOU MEAN BY THAT?
- COULD YOU TELL ME A BIT MORE?
- CAN YOU SAY WHAT YOU MEAN BY THAT?
- SO THEN WHAT HAPPENED?
- OH, THAT MAKES SENSE...
- THAT'S INTERESTING...

THANK YOU FOR YOUR TIME!

MAKE SURE THEY KNOW WHERE TO GET FURTHER INFORMATION.

APPENDIX 11: VISITATION MATRIX

Activity	Pre-Treatment		Active Adverse Event Monitoring			Passive Adverse Event Monitoring					STH Efficacy	Acceptability Study	FTS/MF on FTS (+) individuals before treatment
	Before Dosing		Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	1 Month	2-4 Months	Day 365 (± 30 days)
Census	x												
Informed Consent		x											
Demographics		x											
Physical Exam		x											
Baseline Stool		x											
MDA Treatment			x										
AE Assessment*				x	x	x*	x*	x*	x*	x*			
Stool collection											x		
Acceptability Survey												x	
Efficacy Survey													x

* During passive follow-up participants reporting AEs grade 2 or higher will be followed until AE resolves. Participants with grade 1 should be told to seek out passive monitors if symptoms persist or get worse